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Title

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Permalink
https://escholarship.org/uc/item/2rr82304

Journal
Journal of Pediatric Urology, 17(4)

ISSN
1477-5131

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Publication Date
2021-08-01

DOI
10.1016/j.jpurol.2021.04.020

Peer reviewed

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HHS Public Access
Author manuscript
J Pediatr Urol. Author manuscript; available in PMC 2022 August 01.

Published in final edited form as:
J Pediatr Urol. 2021 August ; 17(4): 452–462. doi:10.1016/j.jpurol.2021.04.020.

Non-invasive bladder function measures in healthy, asymptomatic female children and adolescents: a systematic review and meta-analysis

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Conflict of Interest Statement: The authors report no conflicts of interest

Ethical approval was not required for this manuscript

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Prevention of Lower Urinary Tract Symptoms (PLUS) Research Consortium

SUMMARY

Background: Lower urinary tract symptoms (LUTS) are common in children and adolescents. Non-invasive tests evaluating bladder function are generally preferred over invasive tests, yet few studies have explored the range of normative values for these tests in healthy, asymptomatic children.

Objective: To define normative reference ranges for non-invasive tests of bladder function in healthy, asymptomatic girls and adolescents.

Study design: A comprehensive search strategy was performed in seven electronic databases through October 2019. English-language studies reporting data on voiding frequency, voided and postvoid residual volumes (PVR) and uroflowmetry results in healthy, asymptomatic girls (mean age ≥ 5 years) were included. Two independent reviewers performed study review, data extraction, and quality assessment. Overall mean estimates and 95% confidence intervals for each bladder function parameter were calculated using random effects models, and 95% normative reference values were estimated.

Results: Ten studies met eligibility criteria for the meta-analysis (n=2,143 girls, age range: 3–18). Mean estimates of maximum voided volume and PVR were 233.4 ml (95% CI 204.3–262.6; n=1 study) and 8.6 ml (95% CI 4.8–12.4; n=2 studies) respectively. Pooled mean estimates for uroflowmetry parameters were: 21.5 ml/sec (95% CI 20.5–2.5) for maximum flow rate (n=6 studies), 12.5 ml/sec (95% CI 11.2–13.8) for mean flow rate (n=6 studies), 6.8 sec (95% CI 4.4–9.3) for time to maximum flow (n=3 studies), 15.7 sec (95% CI 13.0–18.5) for flow time (n=3 studies), and 198.7 ml (95% CI 154.2–234.2) for voided volume (n=9 studies). No studies reported estimates of voiding frequency. Between-study heterogeneity was high (89.0–99.6%).

Conclusions: Although we were able to calculate pooled mean estimates for several parameters, the small number of included studies and the wide age ranges of participants preclude generalization of reference values to all healthy girls. Further research is needed to determine normative reference values within specific age groups.

Keywords

voiding; urinary volume; voided volume; uroflowmetry; reference values; children

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INTRODUCTION

Lower urinary tract symptoms (LUTS) are common in children and adolescents with prevalence estimates as high as 22% in some populations [1, 2]. Women with a history of LUTS in childhood are more likely to suffer from LUTS as adults, and the individual and societal impact is substantial[3]. Efforts to promote bladder health and prevent onset of LUTS in girls and women may effectively reduce this impact.

The Prevention of Lower Urinary Tract Symptoms (PLUS) Research Consortium was established in 2015 with the mission of bladder health promotion and lower urinary tract symptom (LUTS) prevention in adolescent and adult women through transdisciplinary research [4]. The Consortium recognized the need to develop terminology and definitions of healthy bladder function [5], as well as to identify normative reference values for healthy bladder function in girls and women. Normative reference values are useful clinically to better understand whether results from tests of bladder function indicate “normal” function or suggest an underlying disorder necessitating further evaluation. In girls and adolescents, in particular, test results that fall outside of these normative parameters may signify risk for developing LUTS in the future.

Non-invasive measures that can capture bladder storage and emptying functions include voiding frequency, voided volumes, non-instrumented urine flow rate parameters and ultrasound assessment of postvoid residual urine (PVR). In children, these are generally preferred over invasive tests [6], yet few studies have explored the range of normative

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values for non-invasive tests of bladder function in healthy, asymptomatic children. In 2014, Martinez-Garcia et al published a systematic review and meta-analysis on maximum voided volume in children, but the majority of included studies utilized invasive measures of bladder volume or obtained measurements under general anesthesia, and data were not presented separately for boys and girls[7]. Other literature reviews describe normative reference values for non-invasive tests of bladder function in healthy, asymptomatic adult women [8–11], but these values are not applicable to children or adolescents as LUT function is known to mature with age [6, 12, 13]. The objective of this systematic review and meta-analysis was to define normal reference ranges for non-invasive tests of bladder function that evaluate storage and emptying phase parameters in healthy, asymptomatic, community-dwelling school-age girls.

MATERIALS AND METHODS

Protocol and Registration

This systematic review and meta-analysis conformed to the Preferred Reported Items for Systematic Reviews and Meta-analyses (PRISMA) Guidelines[14] and reporting of Meta-analysis of Observational Studies in Epidemiology (MOOSE)[15]. The protocol was prospectively registered in The International Prospective Register of Systematic Reviews (PROSPERO; CRD420160498528).

Search Strategy

Informed by an initial scoping search of PubMed, a medical librarian searched published literature for records discussing bladder function measurements and reference values in healthy females. The librarian created search strategies using a combination of keywords and controlled vocabulary in seven electronic databases: Ovid Medline 1946-, Embase 1947-, Scopus 1923-, EbscoHost CINAHL Plus 1937-, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (EED), and Clinicaltrials.gov 1997- (see Appendix 1). Animal studies were excluded using the human filter recommended in the Cochrane Handbook for Systematic Reviews of Interventions. [16][8] No additional limits or restrictions were used for the search.

Search strategies were executed in February 2017, December 2018, and most recently in October 2019. Search results were exported to EndNote and duplicates were removed using the automatic duplicate finder in EndNote. Reference lists from relevant articles and systematic reviews were manually searched to identify additional studies. Number of records returned, deleted following deduplication, and added after manual search of reference lists for each execution of the search can be found in the supplementary materials with fully reproducible search strategies for each database.

Eligibility Criteria

Studies were required to meet the following inclusion criteria in this systematic review and meta-analysis: 1) healthy, community-dwelling girls and adolescents with a mean age ≥ 5 – 18 years; 2) non-invasive bladder function tests; 3) observational studies (cross-

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sectional, case-control, or longitudinal studies); 4) randomized controlled trials (if at least one study arm met all inclusion criteria); and 5) full-text article published in English or English translation available. Age 5 was selected as the lower limit for inclusion based on recommendations from the International Children's Continence Society (ICCS) and is consistent with age limits used to characterize urinary incontinence disorders by the DSM-5 and ICD-10[12]. Studies were excluded if participants had known LUTS, urinary incontinence, nocturnal enuresis, overactive bladder, or current or recurrent urinary tract infections, current nephrolithiasis, or congenital urinary tract anomalies. Studies were also excluded if participants had known cognitive or developmental disabilities, spinal cord or neurologic conditions (e.g., spina bifida, spinal cord tethering), or selected medical conditions (kidney disease, renal transplant). Studies involving invasive bladder function tests (e.g., urodynamic testing, any tests involving contrast medium or carbon dioxide, or tests involving sedation or anesthesia) were also excluded. Studies reporting outcomes for boys and girls were included if there was a subgroup analysis available for girls meeting the above criteria. All studies meeting the aforementioned inclusion criteria were included in the qualitative analysis, but only studies that reported outcomes using measures of central tendency and statistical dispersion were included in the quantitative analysis.

Study Selection

Studies were assessed for eligibility independently by at least two reviewers, first based on title and then based on abstract review. Studies found to be potentially relevant were retrieved for full-text review. Reasons for exclusion were recorded. Any disagreements on eligibility for inclusion were resolved by a third reviewer.

Data Extraction

Data were extracted from each article by two independent reviewers using a REDCap (Research Electronic Data Capture)[17] data extraction form developed specifically and piloted for this review and hosted in the Washington University School of Medicine Institute for Informatics, Informatics Core Services. Extracted data included: study-level variables (study design, authors, year of publication, journal, country where the study was performed); study eligibility criteria (age eligibility and definition of "healthy" or "asymptomatic" used for inclusion); and participant age. We also extracted details on outcomes, including method of measurement: voiding frequency (daytime), voided and postvoid residual volumes and uroflowmetry parameters (mean and maximum flow rate, time to maximum flow, flow time, and voided volume). Discrepancies in extracted information between reviewers were identified in REDCap and resolved through discussion with another reviewer.

Assessment of Methodological Quality

In order to assess methodological quality of included estimates, we created an instrument similar to the one used by Sorel et al [10]. We felt this was necessary as we were unable to identify any instruments designed specifically to evaluate the methodological quality of normative reference values. Our instrument included four questions: two evaluating the characteristics of the study sample and two evaluating the quality of data collection. Items evaluating study sample characteristics included: 1) whether studies explicitly excluded girls with LUTS or other urological disorders, and 2) whether the age of the sample was precisely defined using a measure of central tendency and statistical dispersion. This was felt to be important for determining methodological quality because bladder function may vary with age and age is a known risk factor for LUTS. Questions evaluating the quality of data collection included: 1) whether a standardized method was used to assess self-reported bladder function outcomes (e.g. bladder diary), and 2) whether a standardized method was used to measure non-invasive tests of bladder function (e.g. uroflowmetry, bladder ultrasonography). Studies were assessed for methodological quality by two independent reviewers using a rating scale of "yes," "no," "unclear," and "not applicable." Discordant responses were resolved through discussion between reviewers. This instrument was used to assess methodological quality of estimates included in a recent systematic review and meta-analysis on normative refence values for non-invasive bladder function tests in adult women [11] and worked well for this purpose.

Data Synthesis and Analysis

Random-effects models were used to calculate means and 95% confidence intervals (CIs) of bladder function parameters (voided and postvoid residual volumes, and uroflowmetry parameters). We performed meta-analysis for parameters reported by 2 or more studies[18, 19]. For each bladder function parameter, forest plots were constructed. Heterogeneity was assessed using the I^2 statistic, and was categorized as low, moderate, or high using common cut-off points [low (I^2 =25%), moderate (I^2 =50%), high (=75% or higher)][16]. For studies that reported bladder function parameters for multiple groups, each group was treated as an independent study in the analysis as we generally expected high heterogeneity between groups. One study [20] reported a likely typographical error for voided volume in girls age 9. Attempts were made to contact the corresponding author, but were unsuccessful. The correct value for this age group was estimated based on the values reported in Table 1 of the original manuscript.

The overall estimate and 95% confidence interval for each bladder function parameter were calculated using the DerSimonian-Laird random effects method[21]. 95% normative reference values for individual participants were also estimated using the fixed-effects model under the log-normal distribution assumption[11]. Whereas 95% confidence intervals explain how precisely the overall mean has been estimated across studies, normative reference values explain how widely bladder function parameters vary across individual participants. For example, assuming model assumptions are valid, 95% of participants would have bladder function parameter values that fall within the interval[22–24]. Normative reference values for postvoid residual volumes and uroflowmetry parameters were rounded to integer numbers for utility in clinical practice. Normative reference values for voided volume on diary and voided volume measured on uroflowmetry are not presented, as bladder capacity is known to increase with age and we felt there was little meaning in presenting a normative reference value for the entire population. R software version 3.4.3 was used for the meta-analysis.

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RESULTS

We identified 13,675 articles from our database search through 10/2019 (10,739 through 2/2017, an additional 1053 through 12/2018, and 1,883 through 10/2019; Figure 1). An additional two articles were identified through hand-searching for a total of 13,677 articles. After removing duplicates, we screened 7,473 titles and abstracts, and excluded 7,034 articles that did not meet our eligibility criteria. Full texts of the remaining 439 articles were reviewed, and a further 422 were excluded, leaving 17 studies in the combined qualitative and quantitative synthesis [20, 25–40], and 10 in the quantitative synthesis [20, 25–33]. While one study did report data using mean and standard deviation, the data were further subdivided by voided volume [38], which precluded inclusion in the meta-analysis.

Studies included in the qualitative analysis

Study characteristics for the seven studies included in the qualitative analysis are presented in Table 1 [34–40]. These studies varied in terms of sample size, geography, age, and definition of “healthy”. Sample size ranged from 39–513, but most (57%) studies included fewer than 100 participants[34, 36, 37, 39], and one study did not report sample size[40]. Studies were performed in Sweden[34], Germany and the United States [35], Denmark[36, 37], Spain[38], Germany[39], and the Netherlands [40]. Study participants ranged in age from 3–16 years. Three studies did not define “healthy”[38–40], two studies included measures of height and weight in the inclusion criteria and required participants to have no current or prior urologic disease or symptoms [34, 37], and one study determined “health” by the absence of urologic symptoms on a questionnaire[36]. Two studies included an assessment of urine for inclusion (dipstick analysis [37], urine creatinine [41]). Study outcomes are presented in Supplemental Table 1. Most reported outcomes related to voided volumes[35, 37, 39, 40] or uroflowmetry parameters[34, 36, 38]. One study reported outcomes related to voiding frequency (mean=5 voids/day)[37].

Studies included in the quantitative analysis

Ten studies were included in the quantitative synthesis (Table 1). Similar to those included in the qualitative synthesis, these studies varied widely in terms of sample size, geography, age, and definition of “healthy.” Most (70.0%) studies included ≥100 participants, with only three including <100 participants (range: 93–538 participants). One study was performed in North America (Canada[33]), four in Europe (Poland[26], Turkey[27], Germany[31], and Hungary[32]), one in the Middle East (Iran[29]), two in South Asia (India[28, 30]), and two in East Asia (Taiwan[25] and South Korea[20]). Study populations ranged in age from 3 to 18 years, with mean ages of 7.6 to 10.1 years. All studies included children 7–11 years of age. With respect to their definition of “healthy”, all studies required participants to be free of any or select urological abnormalities, disorders, or symptoms, both in the past and currently. Some studies additionally required participants to be free of renal abnormalities/disorders (5 studies), neurological disorders (6 studies), psychological/psychiatric disorders (3 studies), and gastrointestinal symptoms, including constipation (1 study). One study additionally required participants to void 4–7 times/day and one required them to have bell-shaped flow curves. No studies investigated voiding frequency, one examined voided volume [20], and the remaining nine investigated uroflow and postvoid residual volume [25–33].

Methodological quality

Table 2 contains a summary of the methodologic quality of estimates included in the qualitative and quantitative syntheses. Only one study (6%) met all applicable quality criteria[20]. Six studies (35%) clearly documented that participants were without urologic symptoms or disorders[20, 26, 28, 34, 36, 37]. However the majority of studies (53%) simply described the children as healthy without documenting the presence or absence of urinary tract symptoms [25, 27, 29–33, 35, 40]. Eight studies (47%) described age precisely using a measure of central tendency and statistical dispersion[20, 25, 27, 29, 33, 35, 37, 39]. Outcome measures were collected almost uniformly with standardized non-invasive techniques. One trial (6%) incorporated a self-reported measure (voided volume [20]). Fourteen studies (82%) used noninvasive laboratory tests of bladder function (e.g., uroflowmetry or post void residuals) and described their methods adequately[12, 25, 26, 28–36, 39, 40].

Maximum voided and postvoid residual volume

Only one study presented estimates on voided volume[20], specifically maximum voided volume (Table 3). This small study of 94 participants observed a mean maximum voided volume (MVV) of 233.4 ml (95% confidence interval (CI): 204.3–262.6 ml) in Korean girls ages 5 to 13 years, using a 48-hour frequency volume chart. A sub-analysis was performed after dividing this sample into age ranges of 5 to 7 years, 8 to 10 years, and 11 to 13 years with resulting MVV estimates of 216 ml (95% CI 189–243 ml), 224 ml (95% CI 196–252 ml), and 274 ml (95% CI 229–319 ml) respectively (Supplemental Table 2). Although not part of the quantitative analysis, one study included in the qualitative analysis reported similar MVV values: mean daytime MVV=286±118 ml and mean nighttime MVV=240±79ml (Supplemental Table 1)[37].

Two studies presented quantitative data on postvoid residual volume in girls ages 6 to 13 years [25, 26]. The pooled mean estimate from these two studies was 8.6 ml (95% CI: 4.8–12.4 ml), with a 95% normative reference value of 0–31 ml (Supplemental Table 3). Both studies were of moderate methodologic quality; it was unclear whether symptomatic children were excluded from the first study[25] and the age range of participants was unclear in the second study [26]. Heterogeneity was high among studies presenting PVR estimates (I^2=89%).

Uroflowmetry parameters

A greater number of studies examined uroflowmetry parameters than voided or postvoid residual volumes in children (Table 3). Study settings included clinic [25, 26, 28, 30–33] and school [27, 29], and the number of included uroflows per child ranged from one [26, 27, 29, 30, 33] to three [31, 32] voids. Seven studies presented data on maximum flow rate [25, 27–31], seven on mean flow rate[27–32], four on time to maximum flow [28, 30, 31], four on flow time [28, 30, 31], and nine on voided volume obtained on uroflowmetry [25–33] (Supplemental Table 4). Pooled mean estimates for these parameters were 21.5

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ml/sec (95% CI: 20.5–22.5 ml/sec) for maximum flow rate, 12.5 ml/sec (95% CI: 11.2–13.8 ml/sec) for mean flow rate, 6.8 sec (95% CI: 4.4–9.3 sec) for time to maximum flow, 15.7 (95% CI: 13.0–18.5 sec) for flow time, and 198.7 ml (95% CI: 154.2–234.2 ml) for uroflowmetry voided volume. 95% normative reference values were 6–38 ml/sec for maximum flow rate, 2–23 ml/sec for mean flow rate, 0–15 sec for time to maximum flow, 1–31 sec for flow time, and 0–418 ml for uroflowmetry voided volume. Although not part of the meta-analysis, studies included in the qualitative analysis reported similar estimates (Supplemental Table 1). Heterogeneity was high for all parameters estimated, ranging from an I^2 of 90.2% to 99.6%. Included studies were of moderate quality, primarily because of difficulties determining whether symptomatic children had been excluded and the age range of participants (Table 2).

DISCUSSION

This study provides a systematic review and meta-analysis of non-invasive normative data for seven voiding variables in in healthy, asymptomatic school age and adolescent girls: maximum voided volume, uroflow voided volumes, postvoid residual urine, uroflow time, uroflow mean and maximum flow rates, and time to maximum flow rate.

Maximum voided volume

Our review revealed one small study evaluating the range of maximum voided volume, including first morning voids, in Korean girls ages 5–13 years, using a 48-hour frequency volume chart. Consistent with equations estimating bladder capacity in children, MVV increased with age and revealed a wide 95% normative reference value of 29–432 mL for the pooled age range of 5–13-year-old girls. Subdividing into age ranges of 5 to 7 years, 8 to 10 years, and 11 to 13 years provided more meaningful mean MVV of 216 mL, 224 mL, and 274 mL for these age ranges, respectively.

MVV is a practical parameter to screen bladder function and is considered a reasonable proxy for bladder capacity in children. Formulas for estimating bladder capacity in children are commonly based on age, irrespective of gender. However, estimates of bladder capacity can vary based on the method of data collection [7]. The long held Koff formula for estimating bladder capacity ((30 x [age in years +2] mL)) in children was based on a small number of healthy children who underwent cystometry under anesthesia for procedures unrelated to the lower urinary tract [42]. Later challenged as an overestimate of bladder capacity [43], the Koff formula was refined to the currently accepted ICCS formula (30 x [age in years +1] mL) [12] based on MVV data, excluding first morning voids, in healthy children [37].

A wide range of voided volumes throughout the day is typical between children of the same age and between voids in the same child [44, 45]. In > 70% of children, the first morning void is the largest void of the day [37, 44, 45]. Utilization of MVV as a reference value requires knowing whether a first morning void was included. First morning voids were included in the single study of MVV in this analysis [20], which revealed MVV of 225 mL and 240 mL in 5 and 6 year old girls, respectively (Supplemental Table 2). These values are notably larger than estimates of bladder capacity in children this age derived from the ICCS

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formula which did not include first morning voids. The exclusion of children with nocturnal enuresis from the Kim study [20], a condition not uncommon in young children and which may be indicative of a smaller bladder capacity, may also contribute to this difference.

Postvoid residual volume

Postvoid residual urine is a risk factor for urinary tract infection and its recurrence.[46] The ICCS standard for elevated PVR in children 7–12 years old is > 20 mL for a single measurement or > 10 mL on repetitive PVR assessment. The two studies presenting quantitative data on postvoid residual urine volumes in healthy girls ages 6 to 13 years produced a pooled mean estimate of 8.6 mL (95% CI: 4.8–12.4 mL) PVR [25, 26], consistent with a non-elevated PVR by the ICCS definition [12].

Uroflowmetry parameters

In this meta-analysis, the maximal and mean urine flow rates for girls ages 5–13 years were 21.5 and 12.5 ml/sec, respectively, with time to maximum flow of 6.8 sec with an average voided volume of 199 mL. Based on our normative reference value calculations, maximal and mean urine flow rates range from 3–38 mL/sec and 2–23 mL/sec. Urine flow rate parameters (Qmean, Qmax, time to Qmax, flow time) can be difficult to interpret as a single value because maximum and average urine flow rates are proportional to the voided volume. Voided volumes increase with age, and as volume increases, uroflow rates also increase. These studies were conducted under various conditions, and some children were given instruction to come ready to urinate, while others were asked to void when they felt a desire to void. In the setting of an expectation to void, anticipation can change perception of a need to void and impact the voided volume. In a study of uroflow volumes collected at home [33], voided volumes at home were greater than those collected in a clinic setting. Under these various conditions one would expect a wide range of uroflow voided volumes and uroflow parameters.

There are several limitations to this study starting with the limited number of eligible studies. Excluding MVV and uroflow voided volume data for boys limited the pool of data. Others have demonstrated no significant difference in MVV or bladder capacity between genders. However, we chose to exclude these data as our focus is on understanding normative function in girls. In addition, only one study reported voiding frequency, which was insufficient to estimate reference ranges, so we are unable to draw conclusions about normative ranges for voiding frequency in children and adolescents. With regard to uroflowmetry parameters, a range of uroflow volumes were included starting at 25 mL [32]. The value for the minimum voided volume necessary for interpretation is not well established in children; however, uroflow recordings with a voided volume of less than 50% of the functional capacity are considered unreliable [12].

As a further limitation, we found marked heterogeneity of results. This is likely due to several factors including the variability in populations studied, which included samples from nine different countries, each with a slightly different definition of “healthy” for inclusion, and representing a wide age range from childhood to adolescents. Data on race and ethnicity of the individual study participants were not available, thus we are unable to comment on

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generalizability of these findings to various race or ethnic groups. Bladder function matures with age, yet most studies presented outcomes across the range of included ages rather than in specific age groups. Because of the small number of studies, we were also forced to pool some estimates across age ranges that may not be clinically relevant. Conditions varied under which the various non-invasive measures, including uroflowmetry, were performed, and the decision whether to include nocturnal urine production and first morning voids likely further contributed to the heterogeneity observed among the included studies. Finally, the presentation of outcomes in some studies prevented inclusion of these studies in the meta-analysis. While this did not affect the heterogeneity of results presented in the meta-analysis, this did limit the overall sample size available for meta-analysis.

Despite these limitations, this study has several strengths. This is the first analysis of pooled data on non-instrumented voided volumes and uroflow parameters in healthy girls. This study builds on data presented in a prior systematic review and meta-analysis on maximum voided volume in children[7] with the addition of new studies and report on additional variables of clinical interest. The utilization of strict eligibility criteria resulted in a population of healthy, asymptomatic girls, and enabled meta-analyses on voided volume, post-void residual volume, and uroflowmetry parameters.

CONCLUSION

Data on normative bladder function parameters collected by noninvasive means in healthy, asymptomatic girls are limited. Although we were able to calculate pooled mean estimates for several parameters, the small number of included studies and the wide age ranges of participants preclude generalization of reference values to all healthy girls. Knowledge of the range of normative parameters in this population would be valuable when designing research and interventions to prevent future LUTS development. Future studies should include well-characterized populations; clearly describe methods used to measure outcomes; measure and report data on voiding frequency; and analyze participants in discrete, clinically-meaningful age ranges.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

The Prevention of Lower Urinary Symptoms (PLUS) Research Consortium is supported by the National Institutes of Health (NIH) through cooperative agreements (grants U01DK106786, U01DK106853, U01DK106858, U01DK106898, U01DK106893, U01DK106827, U01DK106908, U01DK106892). Additional support is provided by the National Institute on Aging, NIH Office of Research on Women's Health, and NIH Office of Behavioral and Social Sciences Research.

The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

We thank Melissa Milbrandt for her work with data extraction and the PLUS Research Consortium personnel at each center.

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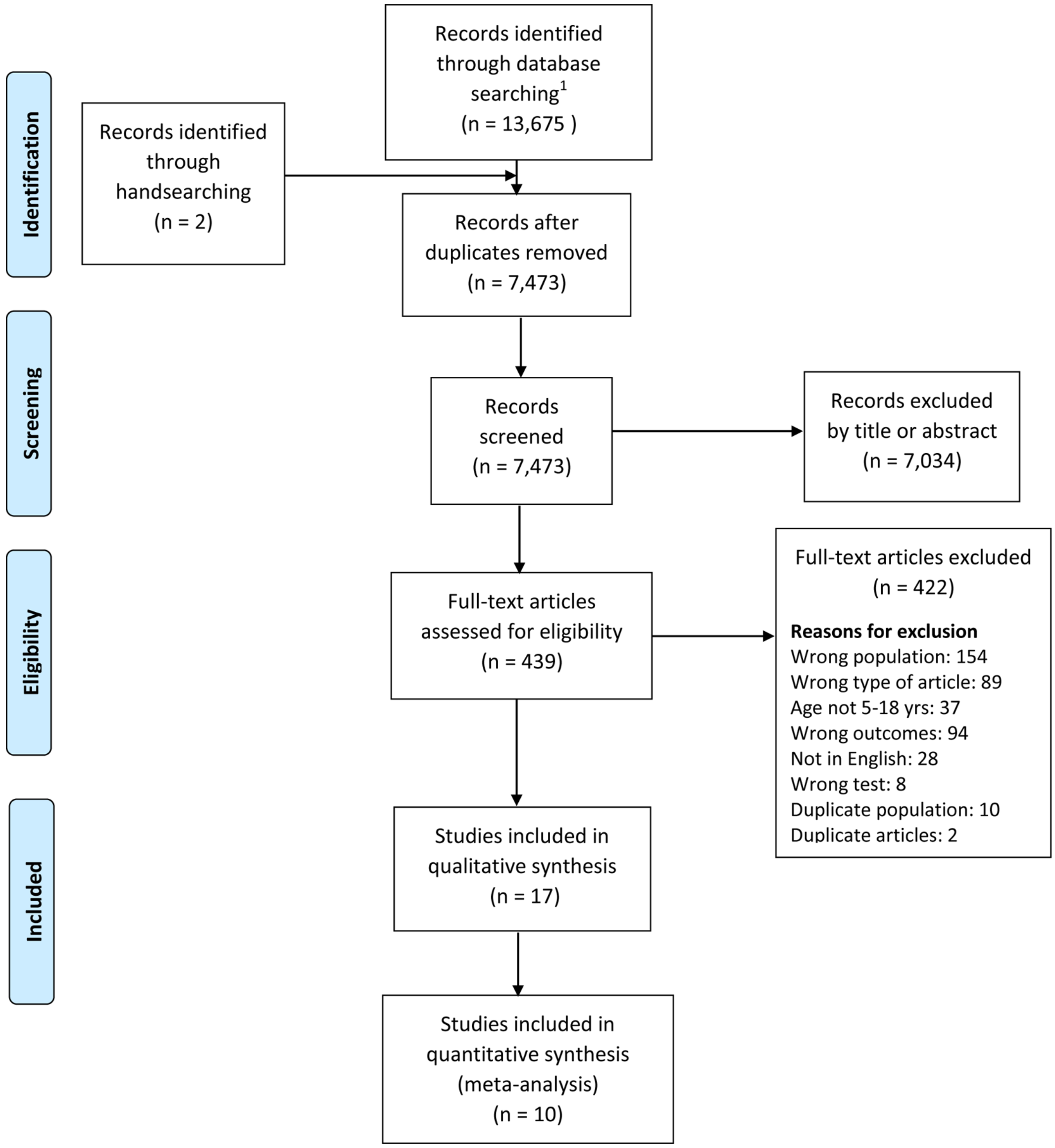

Figure 1. Study selection flow diagram.

[1]Initial search performed in 2/2017 (10,739 records retrieved), updated in 12/2018 (1,053 additional records retrieved) and again in 10/2019 (1,883 additional records retrieved).

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Table 1.

Study Characteristics

First Author	Sample Size Meeting Inclusion Criteria	Country	Age Inclusion Criteria	Age of Participants	Definition of Healthy Population	Outcomes			
						Voiding Frequency[a]	Voided Volume[a]	Postvoid Residual Volume[a]	Uroflow[a]
Studies Included in Qualitative and Quantitative Analysis									
Chang	528	Taiwan	Not specified	Mean (SD): 7.6 (2.2)	Children without congenital genitourinary tract anomaly, neurological anomaly, or history of UTI			*PVR (US)*	*Qmax, VV-U*
Chrzan	139	Poland	6–14 yrs	Not specified	Children voiding 4–7 times per day without any signs or symptoms of dysfunction of the LUT, UTIs or any congenital or acquired urinary tract diseases			*PVR (US)*	*VV-U*
Dogan	101	Turkey	5–11 yrs	Mean: 8.5	Children who were considered to have normal function by their parents and had not seen a doctor for any urinary tract problem				*Qmax, Qave, VV-U*
Gupta	259	India	5–15 yrs	Not specified	Normal, healthy children free of renal, urological, psychological and neurological disorders, and without present or past urinary symptoms				*Qmax, Qave, TQmax, Tvv, VV-U*
Kajbafzadeh	192	Iran	7–14 yrs	Mean (SD): 9.7 (2.2)	Children without history of renal, urological, psychological or neurological disorder, and with bell shape flow curves				*Qmax, Qave, VV-U*
Kim	94	South Korea	5–13 yrs	Range: 5–13	Healthy children without a history of UTI, previous or current urological symptoms, nephrourological pathology, including VUR, urinary incontinence, and non-monosymptomatic/ monosymptomatic nocturnal enuresis, or gastrointestinal symptoms,		*VVmax24-D,* VVmax-C		

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First Author	Sample Size Meeting Inclusion Criteria	Country	Age Inclusion Criteria	Age of Participants	Definition of Healthy Population	Outcomes			
						Voiding Frequency[a]	Voided Volume[a]	Postvoid Residual Volume[a]	Uroflow[a]
					including constipation				
Kumar	93	India	5–15 yrs	Mean: 10.1 Range: 7–14	Healthy children who were not patients with urological complaints and did not have a history of neurological disorders				*Qmax, Qave, TQmax, Tvv, VV-U*
Pompino	103	Germany	3–14 yrs	Mean (SD): 7.9 (2.9)	Children with no signs of acute or urological illness, no complaints in the form of dysuria, stranguria, pollakisuria or vulvovaginitis, and no chronically relapsing or recurring urinary tract infection				*Qmax, Qave, TQmax, Tvv, VV-U*
Szabo	96	Hungary	3–18 yrs	Not specified	Children without renal, urological, psychological, or neurological disorders				*Qave, VV-U*
Toguri	538	Canada	Not specified	Mean (SD): 8.1 (3.3) Range: 3–16	Children without known renal, urological, neurologic, or psychiatric problems				*VV-U*
Studies Included in Qualitative Analysis Only									
Jensen	50	Sweden	7–16 yrs	Range: 7–12	Children were healthy, or normal weight and height, used no medication and had no previous or actual urological disease or symptoms.				Qmax, TQmax, VV-U, Tvv
Manz	355	Germany, US	4–11 yrs	Mean (SD): 6.9 (2.3)	Participants in the DONALD[1] study if age- and sex-related ratio between protein input and nitrogen output was above the 5th percentile and the ratio between energy intake and basic metabolic rate was above 1.06, and accepted urine samples showed a urine creatinine excretion value related to body weight above the 5th percentile of		V24-C		

First Author	Sample Size Meeting Inclusion Criteria	Country	Age Inclusion Criteria	Age of Participants	Definition of Healthy Population	Outcomes			
						Voiding Frequency[a]	Voided Volume[a]	Postvoid Residual Volume[a]	Uroflow[a]
					the corresponding age and sex groups				
Mattsson	39	Denmark	7–13 yrs	Not specified	Reported no urological symptoms on questionnaire.				Qmax, TQmax, Tvv
Rittig	62	Denmark	3–15 yrs	Mean (SD): 9.5 (2.9)	Children with height and weight within 2 standard deviations of normal, no history of day or night urinary or fecal incontinence after age 4, no known current illness or use of any medications, drugs, alcohol, or tobacco and normal urine dipstick analysis at study entry	FD	VN-D, VVN-D, VN-C, VVN-C		
Segura	513	Spain	5–14 yrs	Range: 5–14	Healthy children				Qmax, Qave, TQmax, Tvv
Shi	60	Germany	4–10 yrs	Mean (SD): 7.7 (2.0)	Healthy children		V24-C		
Weykamp		The Netherlands	13–16 yrs	Not specified	Healthy children, no medications		V24-C		

[a]Italicized outcomes indicate inclusion in meta-analysis. LUT, lower urinary tract; LUTS, lower urinary tract symptoms; UTI, urinary tract infection; VN-D, volume-nighttime via diary; VVN-D, nighttime mean voided volume via diary; VN-C, volume-nighttime via collection; VVN-C – nighttime mean voided volume via collection; FD, frequency-daytime; V24-C, volume-24h via collection; Uroflowmetry outcomes: Qmax, maximum flow rate; Qave, mean flow rate; TQmax, time to max flow; Tvv, flow time; VV-U, voided volume

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Table 2.

Summary of Methodological Quality of Studies Included in the Meta-analysis

First Author	Sample		Standardized Outcome Measurement	
	Excluded symptomatic women	Characterized Age in Precise Manner[1]	Self-report Instrument	Noninvasive Laboratory Test
Chang	U	Y	NA	Y
Chrzan	Y	N	NA	Y
Dogan	U	Y	NA	U
Gupta	Y	N	NA	Y
Jensen	Y	N	NA	Y
Kajbafzade	U	Y	NA	Y
Kim	Y	Y	Y	NA
Kumar	U	N	NA	Y
Manz	U	Y	NA	Y
Mattsson	Y	N	NA	Y
Pompino	U	N	NA	Y
Rittig	Y	Y	NA	Y
Segura	N	N	NA	U
Shi	N	Y	NA	Y
Szabo	U	N	NA	Y
Toguri	U	Y	NA	Y
Weykamp	U	N	NA	Y

Ratings: Y = yes; N = no; U = unclear; NA = not applicable

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Table 3.

Summary of Pooled Bladder Function Measurements with 95% Normative Reference Values

	Studies	Groups	Total Sample	Mean Range of Individual Studies	Age range (years)	Overall Estimate (95% CI)	I^2 %	95% Normative Reference Value[1]
Voided and Postvoid Residual Volumes[2]								
Maximum Voided Volume	1	9	94	181–287	5–13	233.4 (204.3, 262.6)	59%	
Postvoid Residual Volume	2	2	667	6.8–10.7	(6–13)	8.6 (4.8, 12.4)	89%	0–31
Uroflowmetry Parameters[2,3,4]								
Maximum flow rate	6	7	1276	18.7–23.5	3–18	21.5 (20.5, 22.5)	90.2%	6–38
Mean flow rate	6	7	844	8.8–16	3–18	.5 (11.2, 13.8)	97.6%	2–23
Time to maximum flow	3	4	455	4.1–8.5	5–15	6.8 (4.4, 9.3)	96.7%	0–15
Flow time	3	4	455	12.3–18.3	5–15	15.7 (13.0, 18.5)	95.6%	1–31
Voided volume	9	11	2049	91–300.5 mL	3–18	198.7 (154.2, 234.2)	99.6%	

[1]Reference values rounded to whole numbers.

[2]Volumes reported in milliliters.

[3]Flow rates in milliliters per seconds.

[4]Flow times in seconds.