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Meta-analysis of the Risk Factors for Urinary Tract Infection in Children

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Context: The incidence of urinary tract infection (UTI) varies with age, but there is limited evidence on the role of other risk factors.

Objective: The aim of this meta-analysis was to investigate the risk factors for UTIs in children.

Data sources: PubMed from 1966 to May 2019.

Study selection: All studies assessing at least 1 possible risk factor for occurrence or recurrence of UTI with a clear definition of symptomatic UTI in children were eligible. We excluded studies with UTIs related to hospital treatment or severe congenital renal abnormalities.

Data extraction: After the quality assessment we extracted data on the given risk factor in children with and without UTI. The data were extracted separately for the occurrence and recurrence of UTIs.

Results: We included 24 studies in the meta-analysis. Circumcision decreased the occurrence of UTIs with an odds ratio (OR) of 0.1 [95% confidence interval (CI): 0.06–0.17) and breast-feeding with an OR of 0.4 (CI: 0.19–0.86), both with low heterogeneity. Being overweight or obese increased the risk of UTI (OR: 2.23; CI: 1.37–3.63). Both poor fluid intake (OR: 6.39; CI: 3.07–13.39) and infrequent voiding (OR: 3.54; CI: 1.68–7.46) were associated with recurrent UTIs.

Limitations: The design, populations and definitions varied between the studies.

Conclusions: Being overweight or obese and having poor fluid intake are modifiable risk factors that increase the risk for UTIs in children. Breast-feeding and circumcision are associated with a decreased occurrence of UTIs.

Key Words: systematic review, obesity, fluid intake, infrequent voiding, breast-feeding, circumcision

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Urinary tract infections (UTIs) are one of the most common bacterial infections in children.[1] UTIs occur throughout childhood, from the neonatal period to late adolescence, but the incidence is highest in the youngest age groups.[2] The cumulative incidence of UTI has been estimated to be 2.2% in boys and 2.1% in girls at the age of 2 years.[3] At the age of 6 years, the cumulative incidence has been reported to reach 6.6% in girls.[4] About 12%–15% of children with UTI experience at least one recurrence.[5]

The incidence of UTI has been shown to vary with age and different ethnic groups in children.[6] There is limited evidence, however, on the role of other risk factors for UTI. In boys, circumcision status has been found to decrease the occurrence of UTIs.[6,7] In a meta-analysis of 12 studies circumcision reduced the incidence of UTI with an OR of 0.13.[8] Besides circumcision, most earlier studies have focused on vesicoureteral reflux (VUR) as a risk factor for UTI.[9] Little is known about the environmental, hygiene or everyday life factors affecting the occurrence of UTI.[10] In narrative reviews, bladder and bowel dysfunction have been mentioned as possible risk factors for UTI.[11]

The aim of the present study was to investigate the risk factors of UTIs in children. We performed a systematic literature search and meta-analysis on the risk factors for the occurrence and recurrence of UTIs in children.

METHODS

Oversight

This study was a systematic literature review and meta-analysis of risk factors for UTI and recurrent UTI in children. We followed the checklist according to the Meta-analysis of Observational Studies in Epidemiology group.[12] This study was registered in PROSPERO (CRD 42020178552).

Literature Review

We performed a PubMed search of the medical literature from 1966 to May 7, 2019 with MeSH terms "urinary tract infection" AND all fields "risk". We included only published articles and did not contact the authors. We excluded reports not published in English and animal studies. Bibliographies of relevant retrieved studies and recent reviews were hand-searched for additional publications. The primary search revealed 5854 articles (Fig. 1). In addition, the manual search of the reference lists of the articles revealed 10 relevant articles. We reviewed the title and the abstract of 5864 articles to identify the articles selected for a full critical appraisal (Fig. 1).

Inclusion and Exclusion Criteria

Studies were included for full review if they fulfilled the following criteria: (1) study design was an original clinical or epidemiological study assessing at least one possible risk factor for occurrence or recurrence of UTI in children younger than 18 years, (2) study used a clear definition of symptomatic UTI with relevant urine culture results according to sample type, (3) study presented the results from adequate control groups and

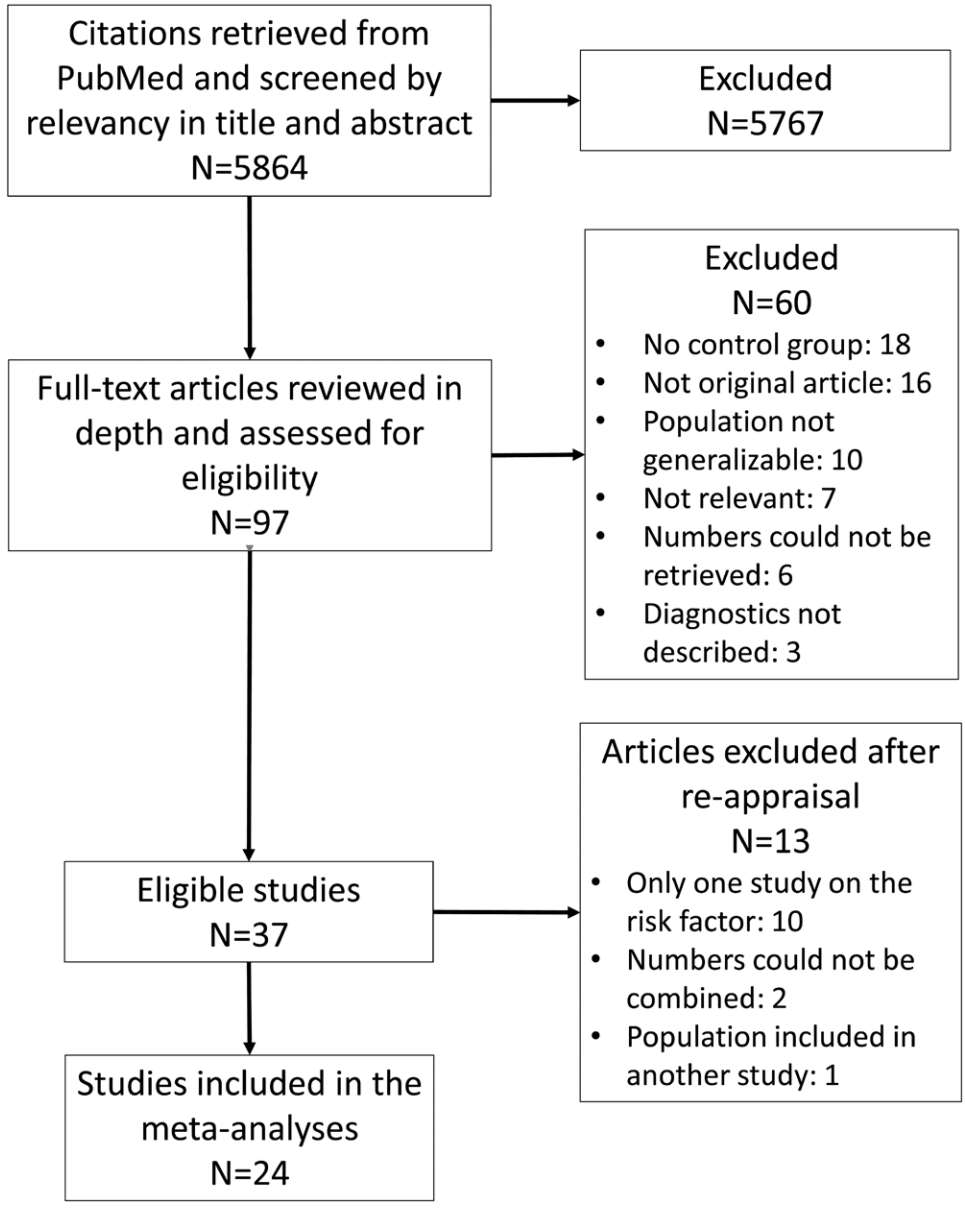

FIGURE 1. Flow chart of the study selection process.

reported the actual numbers of patients, and (4) study was of sufficient quality, according to the Newcastle-Ottawa scale.[13] We excluded studies for asymptomatic bacteriuria and studies for UTIs related to hospital treatment or severe congenital renal abnormalities.

Outcomes

Symptomatic UTI and recurrent symptomatic UTI were the outcomes of interest, as defined in each study.

Data Extraction and Quality Assessment

Four authors (M.U., T.T., M.R. and J.S.) independently reviewed the selected articles and extracted the data. The actual numbers of patients with and without the risk factor of interest and with or without the outcome [UTI (yes/no) or recurrence of UTI (yes/no)] were collected using a standardized data sheet. Quality assessment of the included articles was undertaken using the Newcastle-Ottawa scale.[13] Disagreements between authors were resolved by regular group discussions.

Data Analysis and Presentation

When factors of interest were reported by 2 or more studies, effect estimates were combined with the random effects model in Comprehensive Meta-analysis (version 3.3.070), which yielded pooled odds ratios (OR) with 95% confidence intervals (CIs). We chose to use the random-effects model because we suspected a priori that studies would come from different study populations and have different study designs (eg, case-control, cohort or cross-sectional studies). Heterogeneity between studies was assessed by comparison of study settings, populations and design, supplemented with the I^2 statistic and Cochrane Q. We performed all analyses with Comprehensive Meta-Analysis software version 3.3.070 and drew

the graphics with OriginPro Version 2020b, OriginLab Corporation, Northampton, Maria, USA.

RESULTS

We found a total of 5864 articles (Fig. 1). Altogether 97 articles were reviewed in depth and assessed for eligibility. During full critical appraisal, we further excluded 60 articles (Fig. 1). In total, 37 studies fulfilled our inclusion criteria (Fig. 1). Twelve studies presented a risk factor not presented in any other studies or the numbers could not be combined. One study was excluded because the population was already included in another study. Finally, we included 24 studies in the meta-analyses, 19 reporting the occurrence of UTI and 5 reporting the recurrence of UTI (Table, Supplemental Digital Content 1, http://links.lww.com/INF/E766). The most common study designs were case-control (9 studies), followed by cross-sectional (8 studies) and cohort studies (7 studies). We performed meta-analyses for 10 risk factors——five for the risk of occurrence of UTI (Fig. 2) and five for recurrence (Fig. 3).

Occurrence of UTI

Circumcision

Circumcision was reported in 10 studies included in the meta-analysis.[14–23] The study design of these studies was cross-sectional (n = 5), cohort (n = 3) or case-control study (n = 2). In all cohort studies, circumcision was verified from the medical registries and in other studies data on circumcision were collected either from medical records, parental interviews or by clinical examination. In all studies, the occurrence of UTI was significantly lower in circumcised than in noncircumcised boys. In a meta-analysis, the combined OR was 0.1 (CI: 0.06–0.17) with low heterogeneity (I^2: 7.5%) (Fig. 2). To exclude the possibility of diagnostic bias due to better sampling among the circumcised patients we performed a meta-analysis separately according to the urine sampling method. With the 3 studies using high-quality UTI diagnostics, through either suprapubic aspiration or catheterization, OR was 0.03 (CI: 0.01–0.12).[14–16] In the other 7 studies, allowing urine bag diagnostics OR was 0.14 (0.08–0.26) (Fig. 4).[17–23]

Breast-feeding

The effect of breast-feeding on the occurrence of UTI was reported in 3 case-control studies[24–26] and breast-feeding at the time of hospitalization decreased the occurrence of UTI in 2 of them.[24,25] In a meta-analysis of the 3 studies, breast-feeding significantly decreased the occurrence of UTI (OR: 0.4; CI: 0.19–0.86) with low heterogeneity (Fig. 2). In the study by Mårild et al,[25] a longer duration of breast-feeding was associated with a lower risk of UTI even after weaning. The protective role of breast-feeding seemed to be strongest right after birth and disappeared after the age of 7 months.[25]

Overweight and Obesity

Obesity was analyzed as a risk factor of UTI in 4 studies (Fig. 5).[27–30] Obesity increased the occurrence of UTI in all of them. The combined OR from the 4 studies was 2.23 (CI: 1.37–3.63). In a large register-based study, obesity increased the occurrence of UTI in obese females but not in males.[28] The occurrence of UTI was higher in both overweight and obese children.[27] The overweight and obesity were associated with UTI also in children younger than 2 years.[29]

Enuresis

Day or night enuresis and occurrence of UTI were analyzed in two studies.[31,32] Enuresis during day or night was not associated with the occurrence UTI significantly (Fig. 2).

Recurrent UTI

Obstipation

Obstipation was analyzed as a risk factor of recurrent UTI in 3 studies included in the meta-analysis.[33–35] In all these studies, the data on obstipation were collected from the parents either by phone or a written questionnaire. Obstipation was most commonly defined as less than 2–3 bowel movements per week

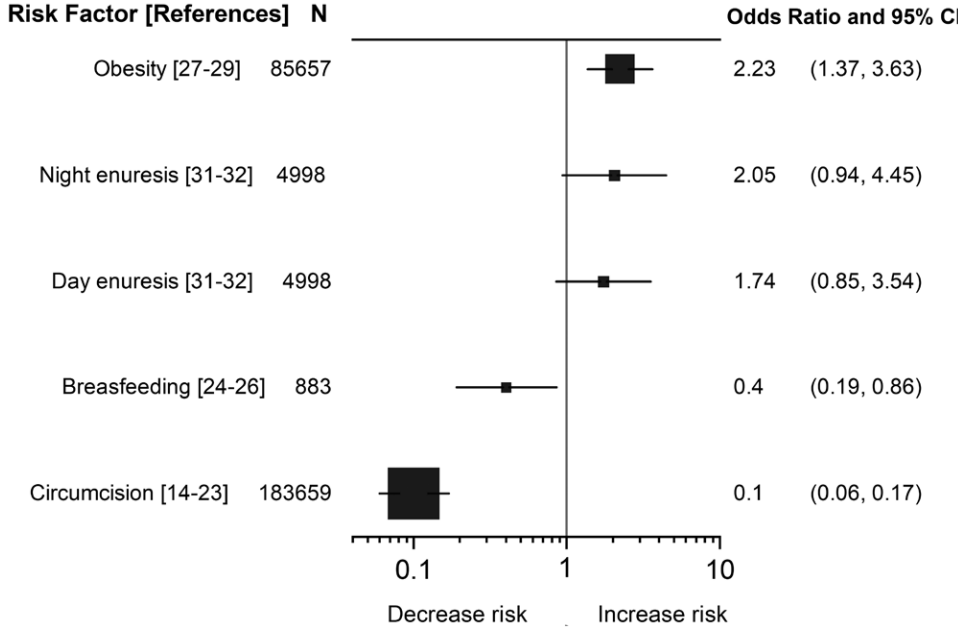

FIGURE 2. Pooled odds ratios with 95% confidence intervals (CIs) of risk factors for occurrence of urinary tract infection in children.

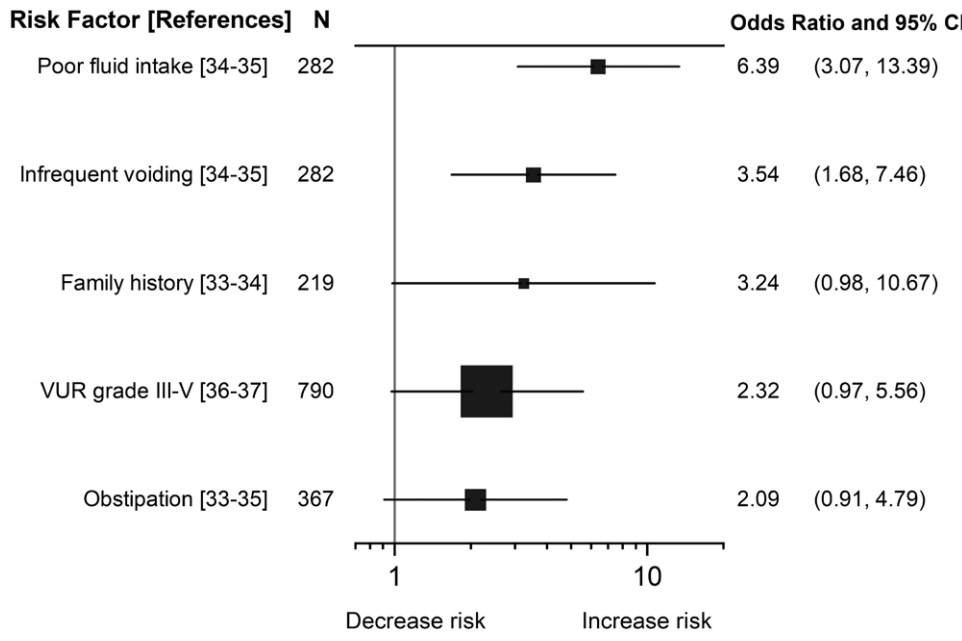

FIGURE 3. Pooled odds ratios with 95% confidence intervals (CIs) from studies reporting risk factors for recurrence of urinary tract infection in children.

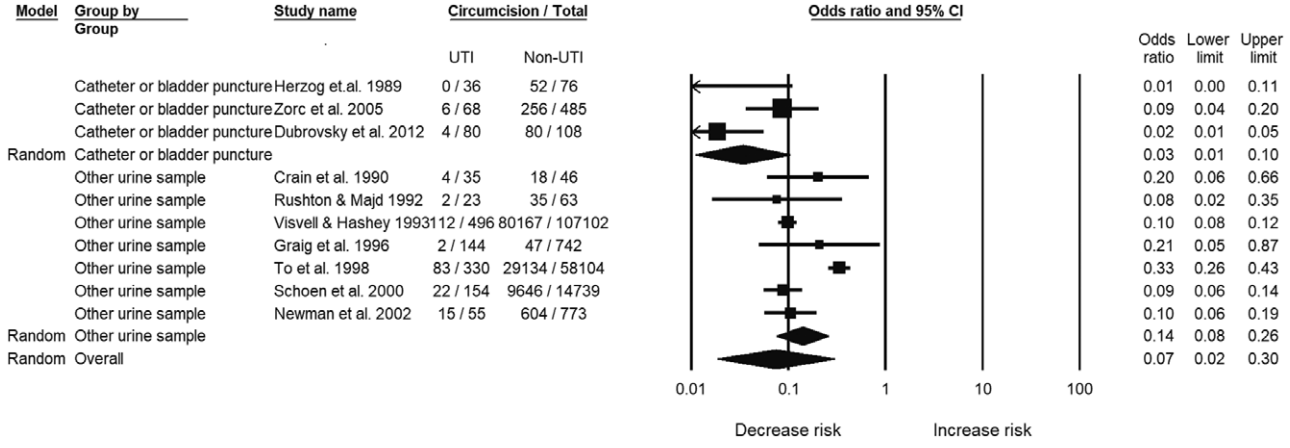

FIGURE 4. Forest plot of studies reporting the association of circumcision and urinary tract infection in children stratified by urine sampling method.

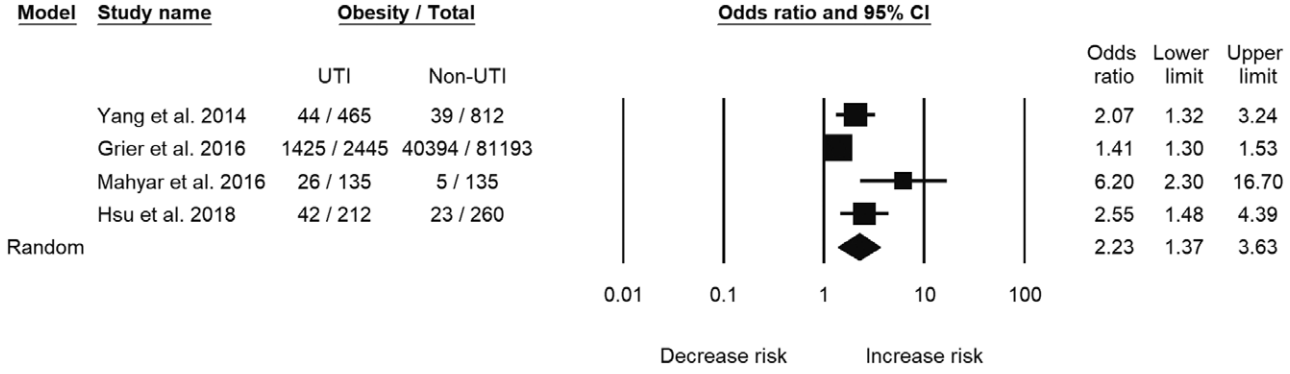

FIGURE 5. Forest plot of studies reporting obesity as a risk factor for urinary tract infection in children.

in the studies. In 1 case-control study performed on girls, obstipation increased the risk of recurrent UTI.[34] In 1 case-control study including only girls[35] and 1 follow-up of a cohort study with young children, with the first UTI at the age of <6 months,[33] a significant association was not found. When we combined the data from these 3 studies in a meta-analysis, obstipation was not associated with the risk of recurrent UTI statistically significantly (OR: 2.09; CI: 0.91–4.79) (Fig. 3).

Poor Fluid Intake and Infrequent Voiding

Poor fluid intake and infrequent voiding were studied as risk factors for recurrent UTI in 2 studies.[34,35] These studies were case-control studies performed in preschool and school-age girls and the data were collected with voiding-drinking diaries. Both poor fluid intake (OR: 6.39; CI: 3.07–13.39) and infrequent voiding (OR: 3.54; CI: 1.68–7.46) were associated with recurrent UTI.

Family History

Family history of recurrent UTI was studied in 1 follow-up study of a cohort of young children, with the first UTI at the age of <6 months[33] and in 1 case-control study of preschool and school age girls.[34] Family history of UTI was 3 times more probable in the children with recurrent UTI episodes than in the controls, but the result did not reach statistical significance in the meta-analysis (Fig. 3).

VUR

VUR as a risk factor for the recurrence of UTI was studied in 2 cohorts of young children.[36,37] In both studies, VUR grade 3–5 was associated with the recurrence of UTI. When combined in a meta-analysis VUR grade 3–5 increased the risk of recurrence of UTI with OR: 2.32 (CI: 0.97–5.56).

DISCUSSION

In this meta-analysis, we found that obesity appeared to be a significant risk factor for UTI in children. Furthermore, poor fluid intake increased the risk of recurrent UTI 6-fold and infrequent voiding 3-fold. Circumcision and breast-feeding were protective factors for UTI.

Currently, we have limited possibilities to protect children from the first UTI in clinical practice. Prophylactic antibiotics have been used to prevent reoccurrences of UTI, but along with a recent Cochrane report their effect size is small.[38] Use of cranberry products has been suggested to be as effective as prophylactic antibiotics in otherwise healthy children.[39] UTIs are equally common in boys and girls during the first year of life and then become more common in girls.[11] In addition to age and sex, immunological and genetic features have been shown to increase the risk of UTI in children.[11] In earlier narrative reviews, family history, bladder and bowel dysfunction and VUR have been suggested as possible risk factors for UTI.[11] In the present meta-analysis they were more common in cases than in controls and were not statistically significantly associated with recurrent UTI. Instead, we identified several risk factors for UTI which may be useful in preventing UTIs in clinical practice.

Our result on the protective effect of circumcision is in line with the previous meta-analysis of Singh-Grewal.[8] Variations in UTI diagnostics procedures and sample contamination may create a bias when analyzing the risk factors for UTI. For instance, the protective effect of circumcision on the occurrence of UTI might be related to the better quality of urine samples in circumcised boys. In this meta-analysis, however, the protective effect of circumcision was even stronger in the studies with high-quality sampling with suprapubic aspiration or catheterization. Thus, the protective effect of circumcision appeared not to be explained by the confounding due to urine sampling quality.

In clinical practice, patients with a tendency to recurrent UTI have usually been advised for sufficient fluid intake. The evidence behind this advice, however, has been weak. In this meta-analysis, poor fluid intake and infrequent voiding increased the risk of recurrent UTI. Earlier, mild dehydration has been suggested to increase the risk of UTI in adults.[40] Recently a systematic review and meta-analysis of 7 randomized trials in adults concluded that increased fluid intake might decrease the overall rate of recurrent UTIs with a rate ratio of 0.46 (95% CI from 0.40 to 0.56).[41] This meta-analysis included several studies where the sort of the fluid might have affected the outcome: for example cranberry juice or D-mannose, but similar effect was achieved also with plain water.[42] The effect of increased fluid intake in the occurrence of UTI has not been studied with randomized design in children.

The strength of this study is a systematic review of large amount of articles studying risk factors for first and recurrent UTI in children. We carefully evaluated the quality of the studies. We did not choose only 1 risk factor but systematically evaluated all previously reported risk factors. The limitations include the difficulty to combine results from different study populations and study designs. For this reason, we chose the random effect model in our meta-analyses.

CONCLUSION

In this meta-analysis, poor fluid intake, infrequent voiding and obesity significantly increased the occurrence of UTI and breast-feeding and circumcision decreased it. Reducing the risk of UTI in childhood may be one additional benefit of breast-feeding and normal weight.

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