INTRODUCTION

Urolithiasis is increasing globally, especially as regards kidney stones, and affects different subgroups of sex, race and age; it is also prevalent among children. A US study found an increased incidence of 4% per calendar year from 1984 to 2008, and an Icelandic study found an increase from 3.7/100 000 in 1985-1989 to 8.7/100 000 in 2010-2013, with most incident cases occurring in girls 13-17 years of age, thus resulting in a slight female predominance. The higher risk in girls in relation to boys was first shown in an Icelandic study and was confirmed in other studies, including a review and with the highest risk found in adolescent girls. The global increase in kidney stones, in particular, could be explained by a number of factors, such as ageing of...
populations, changes in diet and global warming with associated insufficient fluid intake.11

There are regional differences in incidence and prevalence of urolithiasis between different regions and countries of the world, and also within countries, and also traditionally higher rates in the Western world.12 In migrant populations, some studies of urolithiasis conducted among immigrant groups in the Western world have been published. For example, in the UK, immigrants from some countries with a known high incidence of urolithiasis seem to retain their risk, such as immigrants from some East European countries, Turkey and South Asia.13

In Sweden, the number of first-generation immigrants has increased largely over recent decades, and in 2015 a total of 17% of the Swedish population was comprised of first-generation immigrants, and 25% including second-generation immigrants.14 A slightly higher risk of urolithiasis in Sweden was found in first-generation immigrant men and women aged 45 years of age and older, but this was not found in second-generation immigrants.15 However, for specific groups, higher risks were noted in first-generation immigrants from Central and Eastern Europe, Russia, Latin America, Africa and Asia, and also among second-generation immigrants with parents from both some Western and Central European countries.15 To some extent, the findings among second-generation immigrants were unexpected, hence why further exploration among second-generation immigrant children is desirable.

The aim of this study was to compare the risk of urolithiasis among second-generation immigrant children in Sweden with that of individuals with Swedish-born parents.

2 | METHODS

All procedures performed in studies involving human participants were done in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was not applicable as the study was based on anonymised data from registers. The study was approved on February 6, 2013 by the regional ethics boards at Lund University (ref no. 2012/795).

2.1 | Design

Patients were identified by searching the computerised Swedish National Patient Register (NPR) for International Classification of Diseases (ICD) codes suggestive of kidney stone disease or urolithiasis in the years 1998 to 2015. The NPR was established in 1987 and has had nationwide coverage of hospitalisations, including diagnoses from hospital ambulatory care since 2001, including emergency visits, but not from primary care. The Swedish Population Register is maintained by the Swedish Tax Agency and served as a source of demographic information containing individual level data on age, sex, education and country origin of individuals including country of origin of parents. Even if data are public, some data are protected by secrecy. Subjects aged 0-17 years of age were included in the study. The follow-up period ran from January 1, 1998 until hospitalisation/outpatient treatment for urolithiasis, death, emigration or the end of the study period on December 31, 2015, whichever came first. Outpatient diagnoses were included nationwide from 2001 and onwards from specialist care, not primary health care.

2.2 | Outcome variable

The major outcome variable was the first urolithiasis diagnosis. Secondary outcome variables were upper and lower urinary tract stones and stones associated with other diseases (for specific ICD-10 codes, see Supporting information).

2.3 | Co-morbidities

We also identified co-morbidities according to ICD-10 for the following diagnoses (for specific ICD-10 codes, see Supporting information): ESKD; other kidney diseases including obstructive or reflux uropathy, cystic kidney disease and congenital obstructive defects; metabolic disturbances including cystinuria, hyperoxaluria, hypomagnesaemia and hypercalciuria; malabsorption; and preterm birth.

2.4 | Demographic and socioeconomic variables

2.4.1 | The study population was stratified by sex

Educational attainment for parents was categorised as ≤9 years (partial or complete compulsory schooling), 10-12 years (partial or complete secondary schooling) and >12 years (attendance at college and/or university).

Geographic region of residence was included in order to adjust for possible regional differences in hospital admissions and was categorised as (a) large cities, (b) southern Sweden and (c) northern
|                              | Boys |                   |                      | Girls |                   |                      |
|------------------------------|------|-------------------|---------------------|-------|-------------------|---------------------|
|                              | Population | Events | Events | Population | Events | Events |
| Total population             | 944 439  | 658    | 895 749 | 995         |
| Swedish-born parents         | 766 425  | 508    | 726 240 | 802 80.6    |
| Parents born other countries | 178 014  | 150    | 169 509 | 193 19.4    |
| Total events                 |        |        |         |             |
| Upper urolithiasis           |        |        |         |             |
| Lower urolithiasis           |        |        |         |             |
| Other disease with urolithias|        |        |         |             |
| Age (years)                  |        |        |         |             |
| 0-4                          | 199 804 | 253    | 190 219 | 371 37.3    |
| 5-9                          | 301 551 | 267    | 286 016 | 365 36.7    |
| 10-14                        | 255 227 | 127    | 241 541 | 241 24.2    |
| 15-17                        | 187 857 | 11     | 177 973 | 18 1.8      |
| Educational level of parents|        |        |         |             |
| ≤9                           | 183 206 | 139    | 174 240 | 232 23.3    |
| 10-12                        | 369 353 | 259    | 351 235 | 394 39.6    |
| >12                          | 391 880 | 260    | 370 274 | 369 37.1    |
| Region of residence          |        |        |         |             |
| Large cities                 | 445 251 | 346    | 422 551 | 507 51.0    |
| Southern Sweden              | 321 421 | 230    | 304 886 | 340 34.2    |
| Northern Sweden              | 177 767 | 82     | 168 312 | 148 14.9    |
| Marital status of parents    |        |        |         |             |
| Married                      | 592 448 | 369    | 561 364 | 590 59.3    |
| Not married                  | 351 991 | 289    | 334 385 | 405 40.7    |
| Neighbourhood deprivation    |        |        |         |             |
| Low                          | 148 376 | 95     | 141 277 | 148 14.9    |
| Middle                       | 460 472 | 298    | 436 454 | 469 47.1    |
| High                         | 127 772 | 100    | 121 282 | 139 14.0    |
| Unknown                      | 207 819 | 165    | 196 736 | 239 24.0    |
| Hospital diagnosis of ESRD  | 469    | 3      | 328     | 4 0.4       |
| Hospital diagnosis of other kidney diseases | 1979 | 77 11.7 | 2703 | 68 6.8 |
| Hospital diagnosis of metabolic disturbances | 192 | 15 2.3 | 252 8 0.8 |
| Hospital diagnosis of malabsorption | 6084 | 8 1.2 | 11 224 20 2.0 |
| Preterm birth                | 57 391  | 45     | 48 952  | 64 6.4      |

**Table 1** The population of children and number of cases of urolithiasis events categorised by sex.
Sweden. Large cities were defined as municipalities with a population of >200 000 and comprised the three largest cities in Sweden: Stockholm, Gothenburg and Malmö.

2.5 | Neighbourhood deprivation

Neighbourhoods were derived from Small Area Market Statistics (SAMS). The neighbourhood deprivation index used four variables: low educational status, low income, unemployment and social welfare recipients. A summary measure was categorised into three groups: more than one standard deviation (SD) below the mean (high SES or low-deprivation level), more than one SD above the mean (low SES or high-deprivation level) and within one SD of the mean (middle SES or middle-deprivation level), with neighbourhood status classified as high, middle or low SES (corresponding to the categories low-, middle- and high-deprivation in the index).16

2.6 | Statistical analysis

Cox regression analysis was used to calculate the relative risk of urolithiasis in second-generation immigrant children compared to children with Swedish-born parents. Model 1 was adjusted for age and region of residence in Sweden. Model 2 was adjusted for age, region of residence in Sweden, neighbourhood deprivation, and educational level and marital status in parents. In model 3, we added co-morbidities to the variables in model 2. Age was used as a continuous variable in the analysis.

Age-standardised incidence rates were analysed categorised by sex and according to immigrant status, that is with foreign- or Swedish-born parents. We also analysed the trends of incidence rates over time for boys and girls between 1998 and 2015. Besides, we analysed the incidence rates in different age groups between 1998 and 2015.

A two-sided P-value of <.05 was considered statistically significant for variables in the Cox regression. All analyses were performed in SAS 9.4.

3 | RESULTS

In total, 1653 incident cases were registered, 658 among boys and 995 among girls. Upper urolithiasis dominated with 94%-97% of the events. The most common co-morbidities were other kidney diseases, especially among boys, and were also largely over-represented among cases with urolithiasis (Table 1). Metabolic disturbances were seldom reported, although were more common in children with urolithiasis. Second-generation immigrant boys showed a slightly higher risk of end-stage kidney disease (ESKD) vs boys with Swedish-born parents (1.3% vs 0.2%), while no diagnoses of malabsorption were present among immigrant boys (0% vs 1.2%). For immigrant girls, the corresponding rates were 0.5% vs 0.4% for ESKD and 1.6% vs 2.1% for malabsorption, respectively. In general, the urolithiasis risk showed higher rates for kidney diseases excluding ESKD, and for metabolic disturbances in all studied groups (Tables S1-S4).

The mean annual incidence per 100 000 person-years for all urolithiasis events for children with Swedish-born parents was 4.0 (95% CI 3.7-4.3) for boys and 6.7 (95% CI 6.2-7.2) for girls, respectively (Tables S5-S6). For children with foreign-born parents, the corresponding incidence rates were 5.3 (95% CI 5.1-5.4) for boys and 7.2 (95% CI 6.9-7.4) for girls, respectively (Tables S5-S6). For the different groups of second-generation immigrants (Table S6), the number of cases was highest among children with parents from Asia (boys 51 and girls 63) and among those with parents from the Nordic countries (boys 38 and girls 49). Some groups showed a very low number of cases (< 10 cases), that is boys and girls with parents from Southern Europe, the Baltic countries, North America and Russia, and boys with parents from Latin America.

The risk for all urolithiasis was not statistically significant, in general, for the second-generation immigrants, that is neither for boys nor for girls (Tables 2 and 3). However, the risk among boys showed a trend value (HR 1.20) and was significant in the model not adjusting for co-morbidities. The risk was significantly higher among boys with parents from Western Europe and Asia. Among girls, no statistically significant differences compared to girls with Swedish-born parents were found. The total numbers of cases 1998-2015 by age groups showed an increasing incidence over time, with incidence rates per 100,000 person-years in the years 1998-2002, 2003-2007, 2008-2012 and 2013-2015 for boys 4.6, 7.1, 8.1 and 10.3, respectively, and for girls 6.1, 9.0, 11.6 and 11.9, respectively (Figure S1). Regarding the incidence rates for different age groups, the rates per 100,000 person-years in the age groups 0-4, 5-9, 10-14 and 15-17 years were for boys 1.67, 3.14, 6.05 and 15.10, respectively, and for girls 0.88, 2.37, 6.12 and 31.43, respectively (Figure S2).

Regarding upper and lower urolithiasis for boys, the fully adjusted HRs were similar, that is the HRs were 1.20 (95% CI 0.99-1.48) and 1.19 (95% CI 0.55-2.57), respectively. For girls, the corresponding fully adjusted HRs were 0.94 (95% CI 0.79-1.11) and 1.18 (95% CI 0.51-2.75), respectively.

In a supplementary analysis (Table S6), we noted metabolic disturbances in the NPR 1998-2015, with disorders of calcium metabolism being most common, that is 6637 cases.

4 | DISCUSSION

In this national Swedish study of urolithiasis among second-generation immigrant children, we found an increased risk among boys from Western European and Asian countries. In accordance with this, there was a trend towards an increased risk of urolithiasis, in general, in second-generation immigrant boys, driven by the two mentioned high-risk groups. Otherwise, the urolithiasis risk was not significantly different from that of children with Swedish-born parents.
In general, our reported mean annual incidence per 100 000 person-years of between 4 and 7 is lower than the reported incidence from Iceland 2010-2013 of 8.7, 4.3 among boys and 14.2 among girls, and the reported incidence from an American study of 18.5. This discrepancy could be explained by our approach, that is only register an individual once during the time interval, or that using the Swedish NPR, could be suboptimal. We found a higher risk in girls compared to boys, especially in teenage girls, in accordance with earlier results.4,17 An American study found different sex patterns among white and black individuals, with a higher risk among white men compared to white women, but no difference between black men and women.18 We also found an increasing risk over time in both boys and girls, in accordance with earlier studies.6

Most studies on immigrants with urolithiasis were performed on adults and on first-generation immigrants. A British study indicated that migrants from countries with a higher incidence of urolithiasis tend to retain this increased risk in the new country.13 Besides, in that study, a higher risk in individuals from Asian countries, that is similar to our findings, was also found in first-generation immigrants from South Asia in London,13 and for immigrants from the Middle East in New Zealand.19 In an earlier Swedish study in individuals aged 45 years of age and older, a slightly higher risk among first-generation immigrant men and women was found, but not among second-generation immigrants.15 As regards specific groups of first-generation immigrants, higher risks were noted among men and women from Central and Eastern Europe, Russia, Latin America, Africa and Asia.15 Thus, the patterns among adults and children seem to be different, even if there were some overlapping findings.

The risk of urolithiasis could be affected by hereditary factors as well as by environmental factors. As shown in earlier studies, genetic factors could substantially influence the risk of nephrolithiasis both on Iceland and China.21 The hereditary risk has been estimated to 50%-60% of the risk of nephrolithiasis, and genetic factors have been identified that increase, but also decrease, the risk. The shift to more Western dietary habits in populations in many non-Western countries seems to contribute to the changes, and parallels the increase in obesity and diabetes prevalence. A high intake of meat is associated with a higher risk of urolithiasis as compared to individuals with a lower meat intake, or to individuals with a high intake of fish or vegetables.25 In Sweden, meat consumption has increased over the last decades, from 53.8 kg per capita in 1973-71.5 kg per capita in 1998 up to 87.7 kg per capita in 2015.26 Why this only has affected some groups and not others in the same way is unclear but could be explained by different levels of meat intake in different immigrant groups or by genetic factors.

|              | Model 1       |          |          | Model 2       |          |          | Model 3       |          |          |
|--------------|---------------|----------|----------|---------------|----------|----------|---------------|----------|----------|
|              | HR 95% CI     |          |          | HR 95% CI     |          |          | HR 95% CI     |          |          |
| Sweden       | 1             |          |          | 1             |          |          | 1             |          |          |
| All          | 1.18 0.98 1.42| 1.20 1.03 1.07 | 1.20 0.99 1.46 |
| immigrant    |               |          |          |               |          |          |               |          |          |
| groups       |               |          |          |               |          |          |               |          |          |
| Nordic       | 1.02 0.73 1.42| 1.03 0.74 1.44 | 1.04 0.74 1.45 |
| countries    |               |          |          |               |          |          |               |          |          |
| Southern     | 0.96 0.40 2.33| 0.99 0.41 2.39 | 0.99 0.41 2.40 |
| Europe       |               |          |          |               |          |          |               |          |          |
| Western      | 1.76 1.02 3.06| 1.92 1.10 3.33 | 1.92 1.10 3.33 |
| Europe       |               |          |          |               |          |          |               |          |          |
| Eastern      | 0.84 0.47 1.49| 0.89 0.50 1.58 | 0.89 0.50 1.59 |
| Europe       |               |          |          |               |          |          |               |          |          |
| Baltic       | 3.84 0.54 27.33| 4.70 0.66 33.45 | 4.73 0.66 33.76 |
| countries    |               |          |          |               |          |          |               |          |          |
| Central      | 1.70 0.93 3.09| 1.69 0.93 3.09 | 1.70 0.93 3.09 |
| Europe       |               |          |          |               |          |          |               |          |          |
| Africa       | 1.38 0.79 2.40| 1.40 0.81 2.45 | 1.41 0.81 2.48 |
| North        | -             |          |          | -             |          |          | -             |          |          |
| America      |               |          |          |               |          |          |               |          |          |
| Latin        | 0.29 0.07 1.16| 0.30 0.08 1.21 | 0.30 0.08 1.21 |
| America      |               |          |          |               |          |          |               |          |          |
| Asia         | 1.48 1.10 1.99| 1.45 1.07 1.97 | 1.46 1.07 1.99 |
| Russia       | 3.18 0.79 12.74| 3.34 0.83 13.39 | 3.37 0.84 13.52 |

Note: Bold values are statistically significant.
Model 1: adjusted for age and region of residence in Sweden; model 2: adjusted for age, region of residence in Sweden, educational level and marital status, and neighbourhood deprivation; model 3: model 2+ co-morbidities.
As regards region in Sweden, the risk was found to be lower in northern Sweden. For educational level among parents in general, the risk was lower among parents with higher educational level, but not for boys with foreign-born parents with middle educational level. We have no plausible explanation for these findings. Factors such as latitude, sun exposure, diet or fluid intake could have an influence but should be expected to contribute only marginally to these findings.

There are some limitations to our study. The use of statistical significance level could be questioned as we have studied many different subgroups, but we consider all second-generation immigrants at the main outcome and that the results from the different subgroups should be interpreted with some caution. Only two subgroups showed significant but distinct results. Furthermore, we analysed all urolithiasis events together, which may be questioned as the pathogenesis differ, but the upper stones totally dominated the results. Furthermore, even if the quality of Swedish registers in general is known to be high, the validity of the diagnosis of urolithiasis has not been analysed. Diagnoses of urolithiasis could be expected to show a high coverage, as the NPR contains data from hospitals, including outpatient clinics. As most patients with a stone pain would go to the hospital emergency department, we judge that the sensitivity could be regarded as high, even if this has not been proven. However, our coverage could have been suboptimal. We included all types of urolithiasis, although with a clear dominance of nephrolithiasis, in order not to miss important findings.

In conclusion, we found a higher risk of urolithiasis only in two subgroups of second-generation immigrant boys with parents from Western Europe and Asia. No significantly higher risk compared to girls with Swedish-born parents was seen in girls with foreign-born parents. Thus, it seems that once they are settled in Sweden, there are bigger differences in adult immigrants compared to Swedish-born individuals than in their children.

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CONFLICT OF INTEREST
The authors have no conflict of interest to report.

ORCID
Per Wändell https://orcid.org/0000-0001-5169-2965
Xinjun Li https://orcid.org/0000-0002-5559-4657

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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