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Urolithiasis in immigrant groups: a nationwide cohort study in Sweden

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ABSTRACT
Objective: To study the association between country of birth and incident urolithiasis in immigrant groups in Sweden, using individuals born in Sweden (or with Swedish-born parents in the second-generation study) as referents.
Methods: This nationwide follow-up study included first- and second-generation immigrants residing in Sweden between 1 January 1998 and 31 December 2012. Urolithiasis was defined as having at least one registered diagnosis of urolithiasis in the National Patient Register. Cox regression analysis was used to estimate the risk (hazard ratios (HR) with 95% confidence intervals (CI)) of incident urolithiasis. The models were stratified by sex and adjusted for age, sociodemographic status and co-morbidity.
Results: Compared to referents, slightly higher incidence rates and HRs of urolithiasis (HR; 95% CI) were observed among first-generation men (1.06; 1.04–1.09) and women (1.12; 1.08–1.16) but not among second-generation immigrants (persons born in Sweden with foreign-born parents). Among first-generation immigrants, higher HRs were noted among men and women from Central and Eastern Europe, Russia, Latin America, Africa and Asia. Lower HRs were seen among men and women from the Nordic countries, most Western European countries and North America. Among second-generation immigrants, higher HRs were noted among men and women from Denmark, Germany and Hungary, in men from Austria, and in women from the Netherlands and Poland. Lower HRs were seen in second generation immigrants from Latin America, Africa and Asia (men and women).
Conclusions: We observed substantial differences in incidence of urolithiasis between certain immigrant groups and the Swedish-born population, of importance in the clinical situation.

Introduction
Urolithiasis or urinary tract stone disease in most cases originates with stones formed in the kidney and leaves the body in the urine stream through the ureter, urine bladder and urethra [1, 2]. While small stones can pass without any symptoms, stones of larger size, i.e. above 5 mm, may lead to severe stone colic cause through blockage in the ureter. Besides, urine bladder stones may also cause obstruction, but then of the urethra, also leading to problems with emptying the bladder.

Urolithiasis is a global problem. Historically, bladder stones have been known and treated since long ago, even if renal stones are more common nowadays [3]. However, the incidence and prevalence of kidney stones in particular are increasing globally [4], including in subgroups of sex, race, and age [5]. The figures of prevalence and incidence of urolithiasis in different regions and countries of the world do differ, with traditionally higher rates in the Western world [6], but there are large differences in the estimated levels even within countries, at least partly depending on methodological issues. Urolithiasis is more common among men than women [6, 7], and background dietary risk factors for urolithiasis also differ by age and sex [6]. The global rise in especially kidney stones may be due to different factors [7], such as aging populations, changes in diet, and global warming [8], but also with higher registering of events owing to the use of more accurate diagnostic tools. In many non-Western countries, a shift to more Western diet habits seem to contribute to the changes [7], thus paralleling the increase in e.g. diabetes prevalence.

There are some studies of urolithiasis among immigrant groups in the Western world. A British study found immigrants from some countries with a known high incidence of urolithiasis retain their risk, such as immigrants from some...
East European countries, Turkey, and South Asia [9]. A study from New Zealand reported urolithiasis to be most frequent among individuals of Middle East origin, while immigrants from other Asian countries showed an incidence similar to that of individuals of European descent [10]. Some ethnic differences in risk for urolithiasis have also been described, especially in the US, with a higher risk among Caucasian populations and lower risk among African-Americans [6], but high also among Native Americans.

In Sweden, the number of immigrants has increased largely over the last decades, now reaching 17% for first-generation immigrants and, including second-generation immigrants, up to 25% [11].

The aim of this study was to explore the risk of being diagnosed with urolithiasis among first- and second-generation immigrants in Sweden and whether that risk differed from the Swedish-born reference population, after taking potential confounders into account.

Methods

Design

In the present study we used data from the National Patient Register, which includes diagnoses from in-hospital care, and from 2001 and onwards also from out-patient clinics, but not from primary health care. We also used data from the Total Population Register. We included subjects aged 45 years and older. The follow-up period ran from 1 January 1998 until hospitalisation/out-patient treatment of urolithiasis at an age of diagnosis of 45 years or more, death, emigration or the end of the study period on 31 December 2012, whichever came first.

Outcome variable

Upper urolithiasis: N20 (including N20.0 (calculus of kidney), N20.1 (calculus of ureter), N20.2 (calculus of kidney with calculus of ureter), N20.9 (urinary calculus, unspecified)).
N13.2 (hydronephrosis with renal and ureteral stone).

Lower urolithiasis: N21 (including N21.0 (calculus in bladder); N21.1 (calculus in urethra), N21.8 (other lower urinary tract calculus), N21.9 (calculus of lower urinary tract, unspecified)).

Urolithiasis in other diseases: N22.0 (urinary calculus in schistosomiasis).
N22.8 (calculus of urinary tract in other diseases classified elsewhere), E72.0 (cystinuria).
E74.8 (primary hyperoxaluria), and E79.8 (xanthine and 2,8-dihydroxyadenine stones).

Time was calculated from 1 January 1998 until hospitalisation/out-patient treatment of urolithiasis, and until 31 December 2012.

Co-morbidities

The following co-morbidities according to ICD-10 codes were identified: obesity (E65 and E66); diabetes mellitus (E10–E14); hyperlipidemia (E78.0, E78.1, E78.2, E78.3, E78.4, and E78.5); hypertension (I10–I15); coronary heart disease (I20–I25); gout (M10); ESRD (N18.5 (i.e. CKD stage 5), T82.4, Y84.1, Z49, Z94.0, and Z99.2 (ICD-10 codes for ESRD, dialysis or transplantation), and V9211, V9212, V9200, V9531, V9532, V9507, KAS00, KAS10, KAS20, KAS40, KAS50, KAS60, KAS96, KAS97, JAK10, TJAA33, TJAA35, and TKA20 (surgical codes for transplantation or dialysis)).

Demographic and socioeconomic variables

We stratified the study population by sex, as there sex differences in the urolithiasis risk [6].

Age was used as a continuous variable in the analysis.

Educational level was categorized 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 used to be able to adjust for possible regional differences in hospital admissions. The region of residence was categorized as (1) large cities, defined as municipalities with a population of >200,000 and included Stockholm, Gothenburg and Malmö, i.e. the three largest cities in Sweden; (2) southern Sweden; and (3) northern Sweden.

Neighborhood deprivation

Data on neighborhood socio-economic status (NSES) was derived from Small Area Market Statistics (SAMS). The NSES index was categorized into three groups: more than one standard deviation (SD) below the mean (high NSES or low-deprivation level), more than one SD above the mean (low NSES or high-deprivation level), and within one SD of the mean (middle NSES or middle-deprivation level), with neighborhood status classified as high, middle or low NSES (corresponding to the categories low, middle and high-deprivation in the index).

Statistical analysis

The number of urolithiasis cases was presented for first-generation and second-generation immigrants and across baseline subject characteristics. We also categorized urolithiasis into upper urolithiasis, lower urolithiasis and urolithiasis due to other diseases. However, we decided to analyse using all incident urolithiasis cases as outcomes, as most stones belonged to the upper urolithiasis group. Cox regression analysis was used to estimate the risk (hazard ratios (HR) with 95% confidence intervals (CI)) of incident urolithiasis in different immigrant groups compared to the Swedish-born population during the follow-up time. All analyses were stratified by sex. Three models were used in our analyses:

Model 1 was adjusted for age and region of residence in Sweden.
Model 2 was adjusted for age, region of residence in Sweden, educational level, marital status and neighborhood deprivation.
SES, to examine to what extent SES explained the association between country of birth and urolithiasis incidence. Model 3 was constructed as Model 2 with the inclusion of relevant co-morbidities to examine if other diagnoses explained the association between country of birth and urolithiasis incidence.

The study was approved by the regional ethics boards at Karolinska Institutet and Lund University.

Table 1. Baseline characteristics and incident cases of urolithiasis in the study population.

| First generation individuals | Second generation individuals |
|-----------------------------|------------------------------|
| No. Events | No. Events | No. Events | No. Events |
| Total population | 6452996 | 101302 | 8399203 | 84216 |
| Upper urolithiasis | 87695 | 86.6 | 87003 | 85.9 |
| Lower urolithiasis | 13456 | 13.3 | 14299 | 14.1 |
| Other disease with urolithiasis | 151 | 0.1 | 1477060 | 17.6 |
| Gender | 3053499 | 47.3 | 30129 | 29.7 |
| Males | 339957 | 52.7 | 14299 | 14.1 |
| Females | 7173 | 70.3 | 1477060 | 17.6 |
| Immigrant status* | 5309659 | 82.3 | 87003 | 85.9 |
| Swedish | 1143337 | 17.7 |
| Foreign born | 0.0 |
| Educational level | 30129 | 29.7 | 27098 | 32.2 |
| <9 | 2018070 | 31.3 | 36302 | 35.8 |
| 10–12 | 1629336 | 25.2 | 29081 | 28.7 |
| >12 | 2805590 | 43.5 | 35919 | 35.5 |
| Region of residence | 30129 | 29.7 | 27098 | 32.2 |
| Large cities | 2069959 | 32.1 | 34204 | 33.8 |
| Southern Sweden | 2697908 | 41.8 | 45809 | 45.2 |
| Northern Sweden | 1685129 | 26.1 | 21289 | 21.0 |
| Marital status | 30129 | 29.7 | 27098 | 32.2 |
| Married | 4760887 | 73.8 | 6243961 | 74.3 |
| Not married | 1692109 | 26.2 | 5883 | 25.7 |
| Neighborhood deprivation | 30129 | 29.7 | 27098 | 32.2 |
| Low | 891508 | 13.8 | 15554 | 15.4 |
| Middle | 3045109 | 47.2 | 51762 | 51.1 |
| High | 1793845 | 27.8 | 22511 | 22.2 |
| Unknown | 30129 | 29.7 | 27098 | 32.2 |
| Hospital diagnosis of COPD | 6163920 | 95.5 | 94448 | 93.2 |
| No | 289076 | 4.5 | 6854 | 6.8 |
| Yes | 30129 | 29.7 | 27098 | 32.2 |
| Hospital diagnosis of obesity | 6367591 | 98.7 | 939394 | 11.2 |
| No | 85405 | 1.3 | 116204 | 1.4 |
| Hospital diagnosis of CHD | 5918432 | 91.7 | 84261 | 83.2 |
| No | 534564 | 8.3 | 17041 | 16.8 |
| Yes | 30129 | 29.7 | 27098 | 32.2 |
| Hospital diagnosis of diabetes | 6102823 | 94.6 | 83980 | 88.2 |
| No | 350173 | 0.8 | 11922 | 13.1 |
| Hospital diagnosis of alcohol-related diseases | 6316607 | 97.9 | 99512 | 98.2 |
| No | 136389 | 2.1 | 1790 | 0.8 |
| Hospital diagnosis of stroke | 6080958 | 94.2 | 91143 | 90.0 |
| No | 37032 | 5.8 | 17041 | 16.8 |
| Hospital diagnosis of hypertension | 5692192 | 88.2 | 75121 | 74.2 |
| No | 760804 | 11.8 | 26181 | 25.8 |
| Hospital diagnosis of heart failure | 6128396 | 95.0 | 94192 | 93.0 |
| No | 324600 | 5.0 | 7110 | 7.0 |
| Hospital diagnosis of atrial fibrillation | 6085599 | 94.3 | 91034 | 89.9 |
| No | 367397 | 5.7 | 10268 | 10.1 |
| Hospital diagnosis of gout | 6419641 | 99.5 | 100102 | 98.8 |
| No | 3355 | 0.5 | 1200 | 1.2 |
| Hospital diagnosis of hyperlipidemia | 6335796 | 98.2 | 96923 | 95.7 |
| No | 117200 | 1.8 | 4379 | 4.3 |
| Hospital diagnosis of ESRD | 6432973 | 99.7 | 100659 | 99.4 |
| No | 120023 | 0.3 | 643 | 0.6 |
| All | 6452996 | 100.0 | 101302 | 100.0 |

*Immigrant status in the second-generation individuals based on the country of birth of parents.
Results

Baseline characteristics of the first- and second-generation samples are shown in Table 1. The study of the first-generation sample comprised of 6,452,996 individuals aged 45 years and older, out of whom 1,143,337 (17.7%) were immigrants. The study of second-generation sample comprised of 8,399,203 individuals, out of whom 1,690,384 (20.1%) were second-generation immigrants. The proportion of incident cases of urolithiasis was larger in first- (1.6%) compared to second-generation immigrants (0.9%). Males were overrepresented among both samples, and immigrants were underrepresented in both samples. The distribution of subgroups of stones were different in the two samples, with highest frequency, however, for upper stones (86.6% in the first- and 80.0% in the second-generation sample), but with a much larger frequency of urolithiasis in other diseases in the second-generation sample (13.3% vs 0.1% in the first-generation sample).

The HRs for being diagnosed with urolithiasis among first-generation immigrant men and women are shown in Tables 2a and 2b, respectively. Compared to Swedish-born individuals, the risk for urolithiasis was lower among men and women from the Nordic countries, most Western European countries and North America; but higher in men and women from Central and Eastern Europe, Russia, Latin America, Africa and Asia.

The HRs for being diagnosed with urolithiasis among second-generation immigrant men and women are shown in Tables 3a and 3b, respectively. Compared to individuals with Swedish-born parents, the risk for urolithiasis was lower in men and women with parents from Latin America, Africa and Asia; but higher in men and women with parents from Denmark, Sweden, Northern America, Latin America, Chile, South America, Asia, and Russia.

Table 2a. HR of Urolithiasis in first-generation male immigrants.

| Region                | HR 95% CI  | Model 1 | HR 95% CI  | Model 2 | HR 95% CI  | Model 3 |
|-----------------------|------------|----------|------------|----------|------------|----------|
| Sweden                | 1.00       | 1.00     | 1.00       | 1.05     | 1.10       | 1.06     |
| All male immigrants   | 1.02       | 1.00     | 1.04       | 1.07     | 1.05       | 1.10     |
| Nordic countries      | 0.54       | 0.52     | 0.57       | 0.55     | 0.53       | 0.57     |
| Denmark               | 0.80       | 0.74     | 0.87       | 0.80     | 0.74       | 0.87     |
| Finland               | 0.48       | 0.46     | 0.51       | 0.49     | 0.47       | 0.52     |
| Iceland               | 0.28       | 0.19     | 0.41       | 0.28     | 0.19       | 0.42     |
| Norway                | 0.58       | 0.53     | 0.65       | 0.60     | 0.54       | 0.66     |
| Southern Europe       | 1.01       | 0.94     | 1.08       | 1.03     | 0.96       | 1.11     |
| France                | 1.00       | 0.81     | 1.24       | 1.04     | 0.84       | 1.29     |
| Greece                | 0.98       | 0.87     | 1.10       | 1.00     | 0.89       | 1.12     |
| Italy                 | 0.90       | 0.78     | 1.04       | 0.94     | 0.81       | 1.09     |
| Spain                 | 1.20       | 1.00     | 1.42       | 1.23     | 1.03       | 1.47     |
| Other Southern European countries | 1.23 | 1.00 | 1.52 | 1.22 | 0.99 | 1.50 |
| Western Europe        | 0.87       | 0.82     | 0.93       | 0.88     | 0.83       | 0.94     |
| The Netherlands       | 0.87       | 0.69     | 1.08       | 0.89     | 0.71       | 1.11     |
| UK and Ireland        | 0.65       | 0.56     | 0.75       | 0.66     | 0.57       | 0.76     |
| Germany               | 0.97       | 0.89     | 1.06       | 0.99     | 0.90       | 1.07     |
| Austria               | 1.08       | 0.91     | 1.28       | 1.11     | 0.93       | 1.32     |
| Other Western European countries | 0.72 | 0.53 | 0.97 | 0.75 | 0.56 | 1.01 |
| Eastern Europe        | 1.97       | 1.90     | 2.05       | 1.90     | 1.83       | 1.97     |
| Bosnia                | 2.23       | 2.09     | 2.39       | 2.19     | 2.05       | 2.34     |
| Former Yugoslavia     | 1.76       | 1.68     | 1.85       | 1.71     | 1.63       | 1.80     |
| Croatia               | 1.54       | 1.26     | 1.88       | 1.45     | 1.19       | 1.77     |
| Romania               | 2.10       | 1.85     | 2.39       | 2.06     | 1.81       | 2.35     |
| Bulgaria              | 1.92       | 1.52     | 2.34       | 1.90     | 1.51       | 2.41     |
| Other Eastern European countries | 3.86 | 3.41 | 4.37 | 3.57 | 3.15 | 4.04 |
| Baltic countries      | 0.89       | 0.75     | 1.04       | 0.91     | 0.77       | 1.07     |
| Estonia               | 0.75       | 0.62     | 0.92       | 0.78     | 0.64       | 0.95     |
| Latvia                | 1.38       | 1.03     | 1.84       | 1.41     | 1.06       | 1.88     |
| Central Europe        | 1.47       | 1.38     | 1.57       | 1.46     | 1.37       | 1.55     |
| Poland                | 1.69       | 1.56     | 1.84       | 1.67     | 1.54       | 1.82     |
| Other Central European countries | 1.08 | 0.89 | 1.30 | 1.10 | 0.91 | 1.33 |
| Hungary               | 1.30       | 1.16     | 1.47       | 1.30     | 1.15       | 1.47     |
| Africa                | 1.39       | 1.30     | 1.49       | 1.40     | 1.30       | 1.50     |
| Northern America      | 0.67       | 0.57     | 0.78       | 0.69     | 0.59       | 0.80     |
| Latin America         | 1.65       | 1.54     | 1.76       | 1.67     | 1.56       | 1.79     |
| Chile                 | 1.99       | 1.84     | 2.16       | 2.02     | 1.86       | 2.19     |
| South America         | 1.16       | 1.02     | 1.31       | 1.19     | 1.05       | 1.35     |
| Asia                  | 2.58       | 2.52     | 2.65       | 2.54     | 2.47       | 2.61     |
| Turkey                | 2.29       | 2.15     | 2.44       | 2.23     | 2.09       | 2.38     |
| Lebanon               | 2.92       | 2.71     | 3.15       | 2.86     | 2.65       | 3.09     |
| Iran                  | 2.46       | 2.32     | 2.59       | 2.48     | 2.34       | 2.62     |
| Iraq                  | 4.14       | 3.97     | 4.32       | 4.12     | 3.94       | 4.30     |
| Other Asian countries | 1.51       | 1.52     | 1.70       | 1.60     | 1.51       | 1.70     |
| Russia                | 1.47       | 1.26     | 1.73       | 1.50     | 1.28       | 1.77     |

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 neighborhood deprivation; Model 3: model 2 + comorbidities.

Bold values are statistically significant.
Germany and Hungary, in men with parents from Austria, and in women with parents from the Netherlands and Poland.

The differences in risk for urolithiasis between first- and second-generation immigrants while focusing on specific population groups were also reported. For example, looking at Asia, risk was higher in first-generation immigrants compared to Swedish-born, while it was the other way around for second-generation immigrants.

As regards types of urolithiasis, upper stones were most frequent, but with other diseases as causes more frequent in the second-generation study (10.6–15.8%) compared to the first-generation (0.1–0.2%) (Supplementary Tables S1a ‘Population in first-generation and number of cases of urolithiasis events categorized by sex’, 1b ‘Population in second-generation and number of cases of urolithiasis events categorized by sex’, 2a ‘Population in first-generation and number of cases of urolithiasis events in men’, 2b ‘Population in first-generation and number of cases of urolithiasis events in women’, 2c ‘Population in second-generation and number of cases of urolithiasis events categorized in men’ and 2d ‘Population in second-generation and number of cases of urolithiasis events categorized in women’). In the first-generation study, lower stones were more common in Swedish-born men compared to foreign-born, i.e. 18.2% vs 9.6% (Supplementary Table S2a ‘Population in first-generation and number of cases of urolithiasis events in men’).

Regarding co-morbidities, rates among individuals with urolithiasis were higher for most diseases, especially for cardiovascular diseases, with highest rates for hypertension and CHD, but also for diabetes. There were no seemingly different patterns of co-morbidities between Swedish-born or foreign-born men and women.

Table 2b. HR of Urolithiasis in first-generation female immigrants.

| Region                        | Model 1 | Model 2 | Model 3 |
|-------------------------------|---------|---------|---------|
| HR, 95% CI                    | HR, 95% CI | HR, 95% CI | HR, 95% CI |
| Sweden                        | 1       | 1       | 1       |
| All female immigrants         | 1.07    | 1.03    | 1.10    |
| Nordic countries              | 0.63    | 0.60    | 0.66    |
| Denmark                       | 0.84    | 0.74    | 0.95    |
| Finland                       | 0.60    | 0.56    | 0.63    |
| Iceland                       | 0.38    | 0.24    | 0.61    |
| Norway                        | 0.65    | 0.59    | 0.74    |
| Southern Europe               | 0.93    | 0.81    | 1.07    |
| France                        | 0.73    | 0.48    | 1.11    |
| Greece                        | 0.95    | 0.77    | 1.18    |
| Italy                         | 0.83    | 0.58    | 1.17    |
| Spain                         | 1.28    | 0.93    | 1.75    |
| Other Southern European      | 0.84    | 0.55    | 1.29    |
| Western Europe                | 0.95    | 0.86    | 1.05    |
| The Netherlands               | 0.82    | 0.55    | 1.23    |
| UK and Ireland                | 0.56    | 0.42    | 0.75    |
| Germany                       | 1.10    | 0.98    | 1.24    |
| Austria                       | 1.24    | 0.92    | 1.68    |
| Other Western European countries | 0.42 | 0.22 | 0.81 |
| Eastern Europe                | 2.29    | 2.18    | 2.40    |
| Bosnia                        | 2.29    | 2.10    | 2.49    |
| Former Yugoslavia            | 2.27    | 2.12    | 2.42    |
| Croatia                       | 1.41    | 1.04    | 1.91    |
| Romania                       | 2.13    | 1.80    | 2.52    |
| Bulgaria                      | 2.47    | 1.87    | 3.26    |
| Other Eastern European countries | 3.73  | 3.16 | 4.40 |
| Baltic countries              | 0.76    | 0.59    | 0.97    |
| Estonia                       | 0.63    | 0.46    | 0.87    |
| Latvia                        | 1.08    | 0.74    | 1.59    |
| Central Europe                | 1.51    | 1.39    | 1.64    |
| Poland                        | 1.63    | 1.49    | 1.79    |
| Other Central European        | 1.96    | 0.80    | 1.41    |
| Hungary                       | 1.34    | 1.10    | 1.63    |
| Africa                        | 1.43    | 1.29    | 1.59    |
| Northern America              | 0.63    | 0.49    | 0.81    |
| Latin America                 | 2.00    | 1.84    | 2.17    |
| Chile                         | 2.41    | 2.18    | 2.67    |
| South America                 | 1.47    | 1.27    | 1.71    |
| Asia                          | 2.07    | 1.99    | 2.15    |
| Turkey                        | 2.41    | 2.20    | 2.64    |
| Lebanon                       | 2.43    | 2.16    | 2.73    |
| Iran                          | 2.24    | 2.06    | 2.44    |
| Iraq                          | 3.28    | 3.07    | 3.51    |
| Other Asian countries         | 1.28    | 1.19    | 1.37    |
| Russia                        | 1.25    | 1.04    | 1.49    |

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; Model 3: model 2 + neighborhood deprivation.

Bold values are statistically significant.
Discussion

In this national study with more than 6 million individuals in the first-generation study, we found urolithiasis to be more common in many immigrant groups in Sweden, including immigrants from Central and Eastern Europe, Latin America, Africa and Asia. However, the risk was lower among first-generation immigrants from the Nordic countries, some Western European countries and North America. Second-generation immigrants from Asia and Latin America showed lower risk, in contrast to the higher risk among first-generation immigrants from these regions of the world.

There are few studies on urolithiasis among immigrants in the Western world. In the mentioned British study, some groups, i.e. immigrants from Bulgaria, Romania, Turkey, Pakistan and India, i.e. from countries with a high incidence, showed an increased risk, a study from New Zealand found individuals of Middle Eastern descent to show the highest incidence, while individuals from other Asian countries and individuals of European descent showed a similar risk [10]. We found patterns similar to this, with a high incidence in the mentioned groups, but also with a higher incidence in many other groups, in other Central and Eastern European countries, and in immigrants from Africa and Latin America. Among the second-generation immigrants excess risk could also, to some extent, be found in immigrants with parents from Central and Eastern Europe but also from some Western European countries, but, however, lower risks among second-generation immigrants from Asia, Africa and Latin America.

Urolithiasis is associated with different diseases, especially cardio-metabolic diseases such as obesity, diabetes, gout, hypertension, chronic kidney disease (CKD) with end-stage renal disease (ESRD), and also other cardiovascular

| Model | HR | 95% CI |
|-------|----|--------|
| Sweden | 1 | 1 |
| Nordic countries | 0.93 | 0.89 | 0.96 |
| Denmark | 1.24 | 1.15 | 1.35 |
| Finland | 0.77 | 0.73 | 0.82 |
| Iceland | 0.14 | 0.04 | 0.55 |
| Norway | 1.07 | 0.99 | 1.15 |
| Southern Europe | 1.02 | 0.88 | 1.19 |
| France | 1.11 | 0.78 | 1.58 |
| Greece | 0.84 | 0.62 | 1.14 |
| Italy | 1.19 | 0.94 | 1.50 |
| Spain | 1.00 | 0.66 | 1.52 |
| Other Southern European countries | 0.65 | 0.29 | 1.44 |
| Western Europe | 1.07 | 0.99 | 1.16 |
| The Netherlands | 0.97 | 0.69 | 1.38 |
| UK and Ireland | 0.57 | 0.41 | 0.79 |
| Germany | 1.13 | 1.03 | 1.24 |
| Austria | 1.33 | 1.07 | 1.64 |
| Other Western European countries | 0.85 | 0.54 | 1.34 |
| Eastern Europe | 0.86 | 0.73 | 1.00 |
| Bosnia | 0.58 | 0.35 | 0.97 |
| Former Yugoslavia | 0.86 | 0.72 | 1.04 |
| Croatia | 1.04 | 0.47 | 2.31 |
| Romania | 1.01 | 0.64 | 1.61 |
| Bulgaria | 1.14 | 0.48 | 2.75 |
| Other Eastern European countries | 1.04 | 0.34 | 3.23 |
| Baltic countries | 0.89 | 0.78 | 1.02 |
| Estonia | 0.83 | 0.72 | 0.96 |
| Latvia | 1.25 | 0.94 | 1.67 |
| Central Europe | 1.39 | 1.24 | 1.56 |
| Poland | 1.48 | 1.26 | 1.74 |
| Other Central European countries | 1.18 | 0.90 | 1.54 |
| Hungary | 1.40 | 1.14 | 1.71 |
| Africa | 0.40 | 0.24 | 0.65 |
| Northern America | 0.90 | 0.78 | 1.03 |
| Latin America | 0.65 | 0.46 | 0.91 |
| Chile | 0.71 | 0.46 | 1.09 |
| South America | 0.56 | 0.32 | 0.96 |
| Asia | 0.54 | 0.44 | 0.65 |
| Turkey | 0.80 | 0.60 | 1.05 |
| Lebanon | 0.30 | 0.12 | 0.71 |
| Iran | 0.27 | 0.13 | 0.54 |
| Iraq | 0.24 | 0.11 | 0.53 |
| Other Asia countries | 0.57 | 0.42 | 0.77 |
| Russia | 0.89 | 0.71 | 1.11 |

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 neighborhood deprivation; Model 3: model 2 + comorbidities.

Bold values are statistically significant.
diseases and risk factors, including smoking and dyslipidaemia [6]. Besides, patterns of co-morbidities did not differ obviously between Swedish-born and foreign-born individuals.

The conflicting results for the first- and second-generation immigrant groups could indicate that environmental factors rather than genetic factors are most important for stone formation. Different factors may be involved, such as environmental factors with urbanisation in first-generation immigrants moving from a lower to a higher industrialised country [12], and also dietary changes with adaptation to Western dietary habits [7], which then would rather affect the second-generation immigrants. A high intake of meat is associated with a lower risk of urolithiasis, compared to those with lower meat intake, or a high intake of fish or vegetables [13]. However, possible association with different dietary habits are difficult to understand considering the increased risk in many different groups, with seemingly no common dietary patterns. Thus, we have no good explanation for the seemingly contradictory results between the first- and second-generation immigrants to what could be expected.

There are also genetic factors with familial clustering of urolithiasis [14]. Nephrolithiasis has been more common in developed countries, but the prevalence of urolithiasis in at least some developing countries, especially in tropical regions, has been found to be similar to rates of Western countries, with an association with the warmest part of the year [6].

We found cardiovascular diseases, diabetes and hyperlipidaemia to be more associated with urolithiasis (Table 1), in accordance with a review, reporting that urolithiasis is related to diseases such as the metabolic syndrome, cardiovascular disease, and chronic kidney disease [15].

### Table 3b. HR of Urolithiasis in second-generation female immigrants.

| Region                        | Model 1 | Model 2 | Model 3 |
|-------------------------------|---------|---------|---------|
|                               | HR      | 95% CI  | HR      | 95% CI  | HR      | 95% CI  |
| Sweden                        | 1       | 1       | 1       |
| All female immigrants         | 0.98    | 0.93    | 1.03    | 1.01    | 0.96    | 1.06    |
| Nordic countries              | 1.02    | 0.96    | 1.08    |
| Denmark                       | 1.28    | 1.13    | 1.44    |
| Finland                       | 0.92    | 0.85    | 0.99    |
| Iceland                       | 0.15    | 0.02    | 1.03    |
| Norway                        | 1.99    | 0.97    | 1.22    |
| Southern Europe               | 0.87    | 0.68    | 1.11    |
| France                        | 0.82    | 0.44    | 1.52    |
| Greece                        | 0.70    | 0.43    | 1.15    |
| Italy                         | 1.06    | 0.72    | 1.56    |
| Spain                         | 0.83    | 0.41    | 1.66    |
| Other Southern European countries | 0.85  | 0.32    | 2.26    |
| Western Europe                | 1.15    | 1.03    | 1.29    |
| The Netherlands               | 1.56    | 1.03    | 2.37    |
| UK and Ireland                | 0.78    | 0.51    | 1.18    |
| Germany                       | 1.22    | 1.07    | 1.39    |
| Austria                       | 0.88    | 0.59    | 1.30    |
| Other Western European countries | 1.24  | 0.70    | 2.19    |
| Eastern Europe                | 0.90    | 0.72    | 1.13    |
| Bosnië                        | 0.51    | 0.23    | 1.14    |
| Former Yugoslavia             | 0.96    | 0.74    | 1.24    |
| Croatia                       | 1.72    | 0.72    | 4.13    |
| Romania                       | 0.89    | 0.42    | 1.86    |
| Bulgaria                      | 0.89    | 0.22    | 3.57    |
| Baltic countries              | 0.66    | 0.52    | 0.83    |
| Estonia                       | 0.69    | 0.54    | 0.88    |
| Latvia                        | 0.49    | 0.24    | 0.97    |
| Central Europe                | 1.31    | 1.10    | 1.56    |
| Poland                        | 1.09    | 0.83    | 1.44    |
| Other Central European countries | 1.05  | 0.69    | 1.62    |
| Hungary                       | 1.81    | 1.39    | 2.37    |
| Africa                        | 0.30    | 0.14    | 0.67    |
| Northern America              | 0.79    | 0.64    | 0.99    |
| Lartin America                | 0.40    | 0.22    | 0.75    |
| Chile                         | 0.55    | 0.28    | 1.10    |
| South America                 | 0.19    | 0.05    | 0.76    |
| Asia                          | 0.39    | 0.28    | 0.54    |
| Turkey                        | 0.72    | 0.47    | 1.10    |
| Lebanon                       | 0.12    | 0.02    | 0.84    |
| Iran                          | 0.22    | 0.07    | 0.67    |
| Iraq                          | 0.08    | 0.01    | 0.56    |
| Other Asian countries         | 0.35    | 0.20    | 0.62    |
| Russia                        | 1.13    | 0.83    | 1.53    |

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; Model 3: model 2 + neighborhood deprivation.

Bold values are statistically significant.
Nephrolithiasis has been found to be related to incident hypertension, while the reverse causation does not seem to be true [15].

We chose to include all types of urolithiasis, although upper stones, nephrolithiasis, dominated especially among first-generation immigrants. In the second-generation study, i.e. of second-generation immigrants and Swedish-born individuals with Swedish-born parents, a higher rate of urolithiasis owing to other diseases was found, most probably an effect of the lower age in these groups.

There are some limitations in this study. We used data from the National Patient register, where data from primary care are not included, meaning that the rates of diabetes and hypertension are underestimated [16]. Besides, the rate of obesity is low, as this diagnosis is rarely set in the patient records.

There are also several strengths with the study. We used national Swedish data, with the high quality of Swedish registers [17,18]. All types of urolithiasis were included, although nephrolithiasis dominated, in order not to miss important findings. Many diseases are noted in the National Patient register with data from hospitals, including diagnosis from out-patient clinics. Thus diagnoses of urolithiasis could be expected to show a high coverage, as well as data for ESRD. We also included co-morbidities of known importance.

For clinical practice it is of importance to know that the risk for urolithiasis is increased in many first-generation immigrant groups. Furthermore, it is of importance to perform further studies to be able to understand the mechanisms behind the results found.

In conclusion, we found presence of urolithiasis to be more common among many groups of first-generation men and women in Sweden compared to Swedish-born, while most second-generation men showed a lower rate compared to Swedish-born men with Swedish-born parents. This has to be further studied, and in clinical practice attention should also be paid to this.

Disclosure statement

No potential conflict of interest was reported by the authors.

Ethical approval

All procedures performed in studies involving human participants were 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 by the regional ethics boards at Karolinska Institutet and Lund University.

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