Complex tibial fractures are associated with lower social classes and predict early exit from employment and worse patient-reported QOL

a prospective observational study of 46 complex tibial fractures treated with a ring fixator

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Cultural background, non-therapeutic circumcision and the risk of meatal stenosis and other urethral stricture disease: Two nationwide register-based cohort studies in Denmark 1977–2013

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ABSTRACT

Background: Meatal stenosis is markedly more common in circumcised than genitally intact males, affecting 5–20 per cent of circumcised boys. However, no population-based study has estimated the relative risk of meatal stenosis and other urethral stricture diseases (USDs) or the population attributable fraction (AF_p) associated with non-therapeutic circumcision.

Methods: In two nationwide cohort studies (comprising 4.0 million males of all ages and 810 719 non-Muslim males aged 0–36 years, respectively), we compared hospital contact rates for USD during 1977–2013 between circumcised and intact Danish males. Hazard ratios (HRs) were obtained using Cox proportional hazards regression, and the AF_p estimated the proportion of USD cases in <10 year-old boys that is due to non-therapeutic circumcision.

Results: Muslim males had higher rates of meatal stenosis than ethnic Danish males, particularly in <10 year-old boys (HR 3.44, 95 per cent confidence interval 2.42–4.88). HRs linking circumcision to meatal stenosis (10.3, 4.53–23.4) or other USDs (5.14, 3.48–7.60) were high, and attempts to reduce potential misclassification and confounding further strengthened the association, particularly in <10 year-old boys (meatal stenosis: 26.3, 9.37–73.9; other USDs: 14.0, 6.86–28.6). Conservative calculations revealed that at least 18, 41, 78, and 81 per cent of USD cases in <10 year-old boys from countries with circumcision prevalences as in Denmark, the United Kingdom, the United States and Israel, respectively, may be attributable to non-therapeutic circumcision.

Conclusion: Our study provides population-based epidemiological evidence that circumcision removes the natural protection against meatal stenosis and, possibly, other USDs as well.

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Introduction

With approximately one third of the world's males being circumcised for cultural, religious or other non-medical reasons, non-therapeutic childhood circumcision is arguably the world's most common surgery.[1] As with any surgical procedure, circumcision carries risks of procedural and postoperative complications as well as long-term adverse outcomes. However, the nature and extent of such unintended outcomes are not well-understood; estimates for various complications range widely depending upon the data source, the clinical definitions used, the follow-up window applied, and other study-specific factors.[2] In a systematic 2010 review of complications after neonatal, infant and childhood circumcision, researchers identified 52 studies from 21 countries, of which only one small study of 43 circumcised boys provided information about complications beyond the first year after the circumcision.[3] To the best of our knowledge, a thorough evaluation of long-term complications of non-therapeutic circumcision in childhood has never been undertaken.

Nevertheless, it is widely agreed that one of the more common late complications of circumcision is meatal stenosis, a pathological narrowing of the urethral opening. Indeed, as early as 1881, surgeon William M. Mastin reported that meatotomy to treat meatal stenosis was so common in Jewish males that "*the operation had been designated by many of them as their "second circumcision"*" and that, among Jewish males, a "*marked narrowing is believed to exist in, at least, 95 per cent. of all cases*".[4] Subsequent accounts confirmed the impression of a problem largely restricted to circumcised males.[5,6] In 1921, pediatrician Joseph Brennemann wrote that his "*attention was drawn with increasing frequency to a peculiar lesion of the meatus urinarius occurring only in circumcised male children*". What he described was meatal ulceration and its likely sequel, meatal stenosis,[6] whose symptoms may include painful urination, spraying or deflection of the urinary stream, urgency and frequency of the need to urinate, hematuria and enuresis.[7]

Contemporary research also supports the view that meatal stenosis is a frequent, if not the single most common, late-occurring (i.e., occurring months to years after the operation) complication of childhood circumcision.[8–12] In 1984, the American Academy of Pediatrics wrote in a pamphlet with guidelines for parents with genitally intact boys: "*The foreskin shields the glans; with circumcision this protection is lost. In such cases, the glans and especially the urinary opening (meatus) may become irritated or infected, causing ulcers, meatitis (inflammation of the meatus), and meatal stenosis (a narrowing of the urinary opening). Such problems virtually never occur in uncircumcized penises. The foreskin protects the glans throughout life*".[13]

Considering the frequency and potentially severe consequences of meatal stenosis and other urethral stricture diseases (USDs), the long suspected etiological link to circumcision has received remarkably limited attention in recent years. Presumably, this has to do with the rather polarized and sensitive atmosphere that has dominated medical debates over circumcision,[14–16] ever since its introduction into Anglo-American medicine in the Victorian era to prevent masturbation and to cure a range of childhood ills including: enuresis, clubfoot, spondylitis, paraplegia, nervousness and epilepsy.[17–20] Moreover, in countries such as the United States, where circumcision grew in popularity to become the cultural norm, the average family doctor or pediatrician may not have noticed the lower burden of urethral troubles in their increasingly smaller proportion of genitally intact male patients.

In 1966, urologist A. Ranald MacKenzie reported that 28 of 140 (20%) neonatally circumcised boys examined 9–21 days later had meatal ulceration, which he referred to as "*the chief factor in the development of meatal stenosis*". This was contrasted with the implausible claim of zero complications in a total of 15 433 circumcised boys in four contemporaneous reports.[21] Such serious omissions exhibited in the latter reports illustrate well the claim by urologist Meredith F. Campbell in 1943 that "*Stenosis of the external urethral meatus is the neglected stepchild among serious urinary tract obstructions*".[22]

Several studies confirm the more than century-old clinical impression of a marked excess of urethral problems in circumcised boys. While universally acknowledged to be rare in intact boys, recent clinical evidence from studies relying on direct penile examination from as varied geographical areas as the United States, the United Kingdom, Bangladesh and Iran, suggests that meatal stenosis will develop in somewhere between 5% and 20% of boys circumcised during infancy or childhood by the use of conventional surgical techniques.[12,23–28]

Here, to the best of our knowledge, we provide for the first time population-based estimates of the relative risk of meatal stenosis and other USDs associated with non-therapeutic circumcision, comparing hazard rates of such urethral lesions among circumcised and genitally intact Danish males. We also provide estimates of the fraction of pediatric USD cases in various geographical settings that may be attributable to non-therapeutic circumcision.

Methods

The study consists of two parts, each designed as a register-based national cohort study, using data from the continuously updated Danish Civil Registration System.[29] Each cohort member was recorded by his (or her) unique 10-digit personal identification number, a key variable used to record and track health-relevant data in national registers as well as to identify family relations through links to parents. In part I, we compared rates of hospital contact for meatal stenosis and other USDs in Danish males with circumcising (Muslim) *v* non-circumcising cultural backgrounds. In part II, which was restricted to non-Muslims, we used information about non-therapeutic circumcisions carried out by Danish doctors to compare rates of hospital contact for meatal stenosis and other USDs in circumcised *v* genitally intact males. We used asthma as a control outcome in both study parts, because prior investigations suggest that circumcision is not a risk factor for childhood asthma.[30,31]

Part I: Risk of USD according to cultural background

Cohort

The cohort for this part of the study consisted of 4 022 381 males who resided in Denmark (excluding Greenland and the Faroe Islands) for at least one day between January 1, 1977 and

November 30, 2013, the latter date being the end of the month for which data on study outcomes were complete at the time of data extraction.

Exposure categories
Cohort members were divided into the following categories according to their likely cultural background, as follows:

i) As our reference category, we identified 3 143 654 (78.2%) males for whom available birthplace information in the Civil Registration System suggested that neither they nor any of their parents or grandparents were born outside Denmark. Because Muslims were few in Denmark before the late 1960s, and only around 0.05% of the Danish population are believed to have converted to Islam,[32] we refer in the following to these Danish-born individuals with Danish-born ancestors as *ethnic Danish males*.
ii) As *Muslim male immigrants* (generation 1) we identified 97 489 (2.4%) male residents in Denmark whose birthplace information indicated that they were born in one of the following 17 predominantly Muslim countries: Turkey, Iraq, Pakistan, Iran, Somalia, Lebanon, Afghanistan, Morocco, Egypt, Syria, Indonesia, Algeria, Jordan, Bangladesh, Kuwait, Tunisia and Kosovo. No other predominantly Muslim country in the world accounts for more than 0.1% of all non-Danish born citizens.[31]
iii) We also identified 63 306 (1.6%) Danish-born sons of the Muslim male immigrants identified above (i.e., Muslim male descendants, generation 2). Similarly, we identified 4980 (0.1%) Danish-born sons of these second generation Muslim male descendants (i.e., Muslim male descendants, generation 3). Together, these 68 286 (1.7%) second or third generation Muslim male descendants are referred to in the following as *Muslim male descendants*. In some analyses, the combined total 165 775 (4.1%) Muslim male immigrants and descendants are referred to collectively as *Muslim males*.
iv) The remaining group of 712 952 (17.7%) males, who were not included in the above-defined categories of ethnic Danish males or Muslim males, are referred to as *other males*. These comprised (a) 450 042 males (including 13 331 born in Greenland and 12 033 born in the Faroe Islands) born abroad in any country other than the 17 above-specified predominantly Muslim countries, (b) 258 519 Danish-born males with at least one parent or grandparent born abroad in a country other than the above-mentioned 17 Muslim countries, and (c) 4391 Danish-born males whose mother, maternal grandmother, maternal grandfather and/or paternal grandmother (but not father or paternal grandfather) was born in one of the above-mentioned 17 Muslim countries. Thus, the vast majority (>99%) of *other males* did not have a Muslim cultural background as judged from their birthplace or that of their parents or grandparents.

Outcomes
We identified all hospital contacts for meatal stenosis, other USDs and asthma recorded in the Danish National Patient Register for the period between January 1, 1977 and November 30, 2013, including inpatient admissions for the entire period and outpatient ambulatory contacts since 1995.[33] Specifically, diagnoses of meatal stenosis were identified under the International Classification of Diseases, 8th edition (ICD-8) code 59803 (period 1977–1993) or its 10th edition (ICD-10) code N358A (period 1994–2013). Other USDs were identified under ICD-8 code group 598 (excluding 59803) or ICD-10 code groups N35 (excluding N358A) and N991. Asthma diagnoses were identified under ICD-8 code group 493 or ICD-10 code groups J45 and J46.

Covariates
Some sexually transmitted infections (STIs) causing urethral inflammation (e.g., gonorrhea, chlamydia) may be associated with an elevated risk of USD.[34–36] Therefore, in a robustness analysis we used information about hospital contacts for any STIs identified under ICD-8 codes 05402, 07983, 07984, 091xx–099xx or 131xx, or ICD-10 codes A51–A60, A63–A64 or B20–B24 (including gonorrhea, chlamydia, HIV/AIDS, syphilis, genital herpes, ulcus molle, granuloma inguinale, trichomoniasis, condyloma acuminatum and other and unspecified STIs) to address possible confounding by STI history. While most of the STIs included do not specifically cause urethral inflammation, we deliberately covered a broad range of STIs to better capture those cohort members whose behaviors rendered them at elevated risk of (also) contracting STIs associated with urethral inflammation and, thus, an elevated risk of USD.

Analysis
We followed cohort members from their date of birth or January 1, 1977, whichever came later, until the date of first recorded meatal stenosis, other USD or asthma diagnosis, emigration, death or end of follow-up on November 30, 2013, whichever came first. All statistical analyses of the association with cultural background were carried out as Cox proportional hazards regression analyses with age as the underlying time scale, stratifying the baseline hazard rates for birth year.[37] Specifically, hazard ratios (HRs) with 95% confidence intervals (CIs) compared the hazard rates of each outcome among Muslim males, other males, and the reference population of ethnic Danish males. To determine if the proportional hazards assumption was acceptable in our main model for the association of cultural background with risk of meatal stenosis, for each age interval 0–9, 10–19, 20–39, 40–59 and 60 + years we plotted the martingale-based residuals as a function of the underlying time,[38] an exercise which revealed visually satisfactory model fit.

Robustness analyses. In one robustness analysis, we aimed to reduce the risk of possible confounding from different STI histories in the compared groups. To do so, we first evaluated the association of cultural background with STI risk in a separate Cox proportional hazards regression analysis. Next, we recalculated the HRs linking cultural background to risk of USD, using STI history as a time-dependent stratification variable whose value changed from unexposed to exposed on the date of first recorded STI diagnosis.

Secondly, to evaluate the possible impact of socioeconomic factors we ranked Denmark's 98 municipalities by their average disposable household income in 2013 (Statistics Denmark, www.statistikbanken.dk). We used this ranking plus information about the population size in each municipality to generate five municipality categories of approximately equal size reflecting quintiles of average disposable household income (273 760–305 458, 305 742–322 403, 323 556–339 384, 340 184–358 568 and 359 050–599 126 Danish Kroner). In a Cox proportional hazards model, we used this municipality-based socioeconomic variable as a time-dependent stratification variable, whose value depended on each cohort member's actual day-to-day place of residence during follow-up.

Thirdly, we repeated the main analysis of the association of cultural background with the risk of meatal stenosis, this time among Danish girls and women. We did this to explore whether associations observed among males could plausibly be explained by gender independent risk factors present in Muslim families. To ensure comparability of results for the two sexes, we used definitions of cultural background for females identical to those described above for males, which resulted in the following categories: i) *ethnic Danish females*, ii) *Muslim female immigrants*, iii) *Muslim female descendants* and iv) *other females*.

Fourth, due to the widespread practice of male circumcision among Muslims we anticipated a higher male:female ratio of meatal stenosis in this group. To address this expectation we carried out a Cox proportional hazards regression analysis in a combined dataset for males and females to calculate HRs of meatal stenosis associated with being male for each of the three groups (ethnic Danes, Muslims and others), using age as the underlying time scale and sex as the independent variable. The HRs thus obtained served as inherently age-adjusted male:female ratios of meatal stenosis rates in the three groups, and simple ratios (with Wald-based 95% confidence intervals) of these group-specific HRs served as estimates of the relative impact of being male among the three groups, using ethnic Danes as the reference.

Part II: Risk of USD according to foreskin status in non-Muslim males

Muslim authorities in Denmark claim that almost all boys in this religious group undergo circumcision at some point during infancy, childhood or adolescence.[39] In a recent study, however, we found that only 10.9% of boys in Muslim families were circumcised in a hospital or a publicly subsidized private clinic before their 10th birthday between 1994 and 2003.[31] This suggests that many, and very likely, the majority, of Muslim male circumcisions take place outside of such environments. Unfortunately, the unavailability of supplementary register data about non-therapeutic circumcisions by non-medical circumcisers or foreign doctors precludes an accurate distinction between circumcised and intact males with a Muslim cultural background. Additionally, clinical suspicion of USD in a boy with a Muslim family background might theoretically lead to his circumcision at an earlier age than he would otherwise undergo the ritual. Records of such cases could lead to the false impression of USDs occurring in circumcised individuals when, in fact, the USD was present before the circumcision. Consequently, to avoid bias toward the null by major non-differential misclassification of the exposure variable in Muslim males and, conversely, to avoid inflated HRs resulting from miscounted cases of USD in these males, we restricted this part of the study to the majority population of non-Muslim Danish males. We did this, assuming that virtually all circumcisions in this group were performed by Danish doctors.

Cohort

We used the Civil Registration System to identify 855 654 males born in Denmark (excluding Greenland and the Faroe Islands) between January 1, 1977 and December 31, 2003.[29] Next, we excluded 44 935 males with at least one parent or grandparent born in one of the 17 predominantly Muslim countries specified above in part I. The remaining 810 719 males constituted our study cohort, whom we followed for the occurrence of USD or asthma over the age span 0–36 years between January 1, 1977 and November 30, 2013.

Exposure categories

Boys and men in our cohort who underwent non-therapeutic circumcision in a hospital setting were identified in the National Patient Register under surgery codes 55620 (period 1977–1995) or KKGV20 (since 1996).[33] Non-therapeutic circumcisions performed in private clinics by surgeons or gynecologists and subsidized by the national healthcare system were identified under disbursement code 5301 in the National Health Service Register (since 1994).[40] From 2004 onwards, non-therapeutic circumcision was gradually removed from regional lists of publicly subsidized surgical procedures, thus resulting in incomplete records for non-therapeutic circumcisions after 2003.

We also searched the files of these registries for all recorded cases of foreskin surgery other than non-therapeutic circumcision (e.g. phimosis surgery), using National Patient Register surgery codes 56640, 56680, 56700, 56720, or 56760 (period 1977–1995) and KKGH10, KKGV10, KKGV00, KKGH80, or KKGH80A (since 1996), and disbursement codes 3101, 3132, 3201, 3232, 4132, 4154, 4232, or 6422 in the National Health Service Register (since 1994). As explained below, we used this information to enable clean comparisons of rates of USD and asthma in males undergoing non-therapeutic circumcision *v* intact males.

Outcomes

Definitions used to identify cohort members treated in a Danish hospital for meatal stenosis, other USD or asthma between January 1, 1977 and November 30, 2013 were identical to those used in part I.

Analysis

We followed cohort members from their date of birth until the date of first recorded meatal stenosis, other USD or asthma diagnosis, emigration, death or end of follow-up on November 30, 2013, whichever came first. All statistical analyses of the association with foreskin/circumcision status during the period 1977–2013 were carried out as Cox proportional hazards regression analyses with age as the underlying time scale, stratifying the baseline hazard rates for birth year.[37] Specifically, HRs with 95% CIs compared the hazard rates of each outcome between males undergoing non-therapeutic circumcision and intact males. Each cohort member's foreskin/circumcision status was treated as a time-dependent variable being intact from birth and, when relevant, shifting to circumcised on the recorded date of non-therapeutic circumcision. Boys and men undergoing other foreskin surgeries were censored on the date of such surgery.

By restricting the cohort to non-Muslims, using birth year as a stratification variable for the baseline hazard rates, using age as the underlying time scale in all analyses, and censoring on the date of other foreskin surgery, we ensured that all HRs were based on culturally comparable, same-aged strata of circumcised and intact males observed during comparable calendar years. To determine if the proportional hazards assumption was acceptable in our main model for the association of non-therapeutic circumcision with risk of meatal stenosis, for each age interval 0–9, 10–19 and 20–36 years we plotted the martingale-based residuals as a function of the underlying time,[38] an exercise which revealed visually satisfactory model fit.

Robustness analyses. In one robustness analysis, we ended follow-up for meatal stenosis and other USDs on December 31, 2003 to eliminate exposure misclassification due to incomplete data on non-therapeutic circumcisions performed after 2003.

In a second robustness analysis aimed to address the possible impact of both exposure misclassification and socioeconomic confounding, we recalculated HRs for the restricted follow-up period until December 31, 2003, this time stratifying for a variable capturing municipality-based disposable household income level in quintiles, as described in part I.

Thirdly, we re-estimated the HR for meatal stenosis in boys younger than 10 years in the hypothetical situation that one less circumcised boy (i.e., three boys instead of four) developed meatal stenosis in that age-interval. Specifically, in four separate Cox regression analyses we censored follow-up for one of the four circumcised boys who developed meatal stenosis in the main analysis on the day before their recorded date of meatal stenosis. We used the mean of the resulting four HR estimates as a summary HR estimate for meatal stenosis in this age interval, and the associated 95% confidence interval was calculated based on the mean variance in the four analyses plus the variance between the four HR estimates.

Population attributable fraction (AF_p). Finally, we calculated estimates of the AF_p, using different values of the relative risk (RR) for meatal stenosis or other USDs and different values of exposure (circumcision) prevalence (P_e).[41] The AF_p represents the fraction of USD cases in a given population that is attributable to circumcision and, thus, the fraction that is theoretically preventable by not circumcising healthy boys. The AF_p was calculated using the formula

$$AF_p = 100*P_e*(RR - 1)/(P_e*(RR - 1) + 1).$$

As values of the RR we used HRs obtained in our Cox proportional hazards regression analyses, and as values of P_e we used published estimates of male circumcision prevalence in Denmark (5%), the United Kingdom (16%), the United States (80%), and Israel (99%).[42–45]

All Cox proportional hazards regression analyses were carried out using the PHREG procedure in SAS, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Part I: Risk of USD according to cultural background

In the cohort of 4 022 381 males, the total observation period at risk for meatal stenosis was 95.6 million person-years, with 84.0 million person-years (87.9%) in ethnic Danish males, 1.6 million person-years (1.6%) in Muslim male immigrants, 1.0 million person-years (1.0%) in Muslim male descendants, and 9.1 million person-years (9.5%) in other males. During follow-up, altogether 4856 males were diagnosed with meatal stenosis, 32 865 with other USDs, and 159 798 with asthma (Table 1).

Cultural background and risk of USD

Overall risks of meatal stenosis were higher in Muslim male immigrants (HR 1.77, 95% CI 1.36–2.31) and descendants (2.82, 2.08–3.81) than in ethnic Danish males; risk was inconspicuous in other males (1.02, 0.90–1.17) (Table 1). A similar pattern was seen for other USDs, with elevated risk among Muslim male immigrants (1.79, 1.64–1.97) and descendants (1.75, 1.45–2.11), but only marginally so among other males (1.07, 1.02–1.13) (Table 1).

HRs varied considerably by age (Table 2). The overall doubled risk of meatal stenosis in the combined group of Muslim males (2.12, 1.74–2.60) was composed of a particularly high HR in <10 year-old boys (3.44, 2.42–4.88) and HRs between 1.48 and 2.04 in older age groups. The overall risk of other USDs among Muslim males was 79% elevated (1.79, 1.64–1.94), being doubled in <10 year-old boys (2.03, 1.59–2.60) (Table 2).

Cultural background and risk of asthma

Overall, the rate of asthma was 68% elevated among Muslim male immigrants (1.68, 1.62–1.74), but only marginally so among their descendants (1.08, 1.05–1.11) and other males (1.01, 1.00–1.03) (Table 1). Boys age 0–9 years had by far the heaviest asthma burden; in that age interval, boys with a Muslim background had inconspicuous rates of asthma (1.02, 0.99–1.05), while boys in the other males category had slightly lower rates (0.94, 0.92–0.96). Above that age, however, Muslim males had elevated rates of asthma, resulting in an overall 25% higher risk in Muslims (1.25, 1.22–1.28) (Table 2).

Robustness analyses. To evaluate whether STI histories might confound our estimates, we first calculated HRs for any STI in the studied groups. Overall, rates of hospital contact for any STI were modestly elevated in Muslim male immigrants (1.10, 1.04–1.18) and descendants (1.19, 1.07–1.33). However, including STI history as a time-dependent stratification variable produced virtually unchanged HRs for meatal stenosis (2.14, 1.75–2.62) and other USDs (1.79, 1.64–1.94) in the combined group of Muslim males. This indicates that the

Table 1 – Hazard ratios (95% confidence intervals) of hospital contacts for meatal stenosis, other urethral stricture disease and asthma according to cultural background in males (all ages), Denmark 1977–2013.[a]

	Ethnic Danish males			Muslim male immigrants (generation 1)			Muslim male descendants (generation 2 or 3)			Other males		
	Person-years	Cases	Hazard ratio[b]	Person-years	Cases	Hazard ratio[b] (95% CI)	Person-years	Cases	Hazard ratio[b] (95% CI)	Person-years	Cases	Hazard ratio[b] (95% CI)
Meatal stenosis	84 022 481	4496	1 (ref)	1 571 367	56	1.77 (1.36–2.31)	953 706	49	2.82 (2.08–3.81)	9 097 391	255	1.02 (0.90–1.17)
Other urethral stricture disease	83 779 881	30 560	1 (ref)	1 567 148	468	1.79 (1.64–1.97)	953 018	116	1.75 (1.45–2.11)	9 082 416	1721	1.07 (1.02–1.13)
Asthma	82 581 916	130 470	1 (ref)	1 541 318	2989	1.68 (1.62–1.74)	902 770	5079	1.08 (1.05–1.11)	8 874 357	21 260	1.01 (1.00–1.03)

[a] Cohort of 4 022 381 males residing in Denmark for at least one day between January 1977 and November 2013 and followed for meatal stenosis, other urethral stricture disease and asthma.
[b] Hazard ratios stratified for birth year with age as the underlying time scale.

increased risk of urethral problems in Muslim males was not due to their slightly higher burden of STIs.

Having a Muslim cultural background became more strongly associated with risk of meatal stenosis after stratification for municipality-based disposable household income (2.41, 1.93–3.01), and the particularly high HR in <10 year-old boys from Muslim families was corroborated (3.85, 2.56–5.80). Income stratification did not materially affect HRs for other USDs in Muslim males (overall: 1.81, 1.65–1.99; <10 year-old boys: 1.97, 1.46–2.65).

Thirdly, the overall risk of meatal stenosis in the combined group of Muslim female immigrants and descendants was statistically inconspicuous (1.13, 0.50–2.54), based on altogether 6 cases of meatal stenosis in Muslim females *v* 1103 cases in ethnic Danish females.

A clear male predominance of meatal stenosis was present in all groups. However, as anticipated, HRs associated with being male were markedly higher in Muslim immigrants and descendants (14.1, 6.17–32.0) than ethnic Danes (4.89, 4.58–5.23) or other persons (7.44, 5.46–10.1). Accordingly, the impact of being male on the risk of meatal stenosis was almost three times higher in Muslims than in ethnic Danes (ratio of HRs 2.87, 1.26–6.56). For <10 year-old children with a Muslim background, the male:female ratio of meatal stenosis rates was extreme, yet inestimable (40 male cases during 592 797 boy-years *v* 0 female cases during 565 554 girl-years). Corresponding male:female ratios among <10 year-old children were 2.44 for ethnic Danes (based on 198 male cases during 9 472 813 boy-years *v* 77 female cases during 8 996 553 girl-years) and 4.75 for other children (based on 38 male cases during 1 984 968 boy-years *v* 8 female cases during 1 984 066 girl-years), respectively.

Part II: Risk of USD according to foreskin status in non-Muslim males

In the cohort of 810 719 non-Muslim males, the total observation period at risk for meatal stenosis between January 1, 1977 and November 30, 2013 was 17.7 million person-years in genitally intact males and 73 432 person-years in circumcised males. During follow-up, 3375 males (0.42%) underwent non-therapeutic circumcision in a hospital department or a doctor's clinic. For cohort members born 1994 to 2003, when circumcision data were available from both hospital departments and private clinics, the median age at circumcision was 5.9 months (range 0 days–10 years). Overall, 182 cohort members were diagnosed with meatal stenosis, 1091 with other USDs, and 56 983 with asthma.

Non-therapeutic circumcision and risk of USD

Risks of meatal stenosis and other USDs were markedly elevated in circumcised males. Six circumcised and 176 intact males developed meatal stenosis during follow-up (HR 10.3, 95% CI 4.53–23.4), and 26 circumcised and 1065 intact males developed other USDs (5.14, 3.48–7.60) (Table 3). HRs were particularly high in <10 year-old boys (meatal stenosis: 16.5, 6.03–45.3; other USDs: 10.7, 5.31–21.7).

Non-therapeutic circumcision and risk of asthma

Rates of asthma were statistically inconspicuous among circumcised <10 year-old boys (1.20, 0.97–1.48) and males

Table 2 – Hazard ratios (95% confidence intervals) of hospital contacts for meatal stenosis, other urethral stricture disease and asthma according to cultural background in males (all ages), Denmark 1977–2013.[a]

	Age, years	Ethnic Danish males			Muslim male immigrants and descendants (generation 1, 2 or 3)			Other males		
		Person-years	Cases	Hazard ratio[b]	Person-years	Cases	Hazard ratio[b] (95% CI)	Person-years	Cases	Hazard ratio[b] (95% CI)
Meatal stenosis	0–9	9 472 813	198	1 (ref)	592 797	40	3.44 (2.42–4.88)	1 984 968	38	0.95 (0.67–1.35)
	10–19	10 683 027	189	1 (ref)	478 170	14	1.75 (1.00–3.05)	1 707 903	24	0.80 (0.52–1.23)
	20–39	23 994 673	388	1 (ref)	891 309	23	2.04 (1.33–3.12)	3 126 040	45	1.06 (0.78–1.45)
	40–59	23 100 114	861	1 (ref)	473 046	20	1.56 (1.00–2.45)	1 675 544	59	1.20 (0.92–1.57)
	60+	16 771 854	2860	1 (ref)	89 751	8	1.48 (0.74–2.97)	602 936	89	1.01 (0.82–1.25)
	total	84 022 481	4496	1 (ref)	2 525 073	105	2.12 (1.74–2.60)	9 097 391	255	1.02 (0.90–1.17)
Other urethral stricture disease	0–9	9 471 560	496	1 (ref)	592 618	76	2.03 (1.59–2.60)	1 984 698	93	0.79 (0.64–0.99)
	10–19	10 679 687	606	1 (ref)	477 733	47	1.59 (1.18–2.15)	1 707 117	139	1.36 (1.13–1.64)
	20–39	23 971 269	2799	1 (ref)	890 253	162	1.52 (1.30–1.78)	3 122 596	403	1.11 (0.99–1.23)
	40–59	23 047 622	5519	1 (ref)	471 129	173	1.93 (1.65–2.25)	1 671 319	360	1.05 (0.95–1.17)
	60+	16 609 743	21 140	1 (ref)	88 433	126	1.95 (1.64–2.33)	596 686	726	1.06 (0.99–1.14)
	total	83 779 881	30 560	1 (ref)	2 520 166	584	1.79 (1.64–1.94)	9 082 416	1721	1.07 (1.02–1.13)
Asthma	0–9	9 176 510	52 317	1 (ref)	567 651	4575	1.02 (0.99–1.05)	1 915 834	12 945	0.94 (0.92–0.96)
	10–19	10 347 255	11 746	1 (ref)	455 745	865	1.20 (1.12–1.29)	1 637 011	2560	1.11 (1.07–1.16)
	20–39	23 666 732	15 772	1 (ref)	873 781	1456	1.95 (1.85–2.06)	3 076 785	2714	1.12 (1.07–1.17)
	40–59	22 866 089	21 194	1 (ref)	460 679	948	2.02 (1.89–2.16)	1 651 596	1999	1.21 (1.15–1.27)
	60+	16 525 330	29 441	1 (ref)	86 232	224	1.72 (1.50–1.96)	593 131	1042	1.03 (0.97–1.10)
	total	82 581 916	130 470	1 (ref)	2 444 088	8068	1.25 (1.22–1.28)	8 874 357	21 260	1.01 (1.00–1.03)

[a] Cohort of 4 022 381 males residing in Denmark for at least one day between January 1977 and November 2013 and followed for meatal stenosis, other urethral stricture disease and asthma.
[b] Hazard ratios stratified for birth year with age as the underlying time scale.

Table 3 – Hazard ratios (95% confidence intervals) of hospital contacts for meatal stenosis, other urethral stricture disease and asthma according to foreskin status in 0–36 year-old non-Muslim males, Denmark 1977–2013.[a]

		Meatal stenosis		Other urethral stricture disease		Asthma	
		Intact	Circumcised	Intact	Circumcised	Intact	Circumcised
Age interval							
0–9 years	Cases	98	4	351	8	43 419	87
	Person-years	7 858 687	17 674	7 857 579	17 648	7 588 202	17 120
	Hazard ratio[b] (95% CI)	1 (ref)	16.5 (6.03–45.3)	1 (ref)	10.7 (5.31–21.7)	1 (ref)	1.20 (0.97–1.48)
	Hazard ratio[c] (95% CI)	1 (ref)	26.3 (9.37–73.9)	1 (ref)	14.0 (6.86–28.6)	1 (ref)	1.24 (0.99–1.55)
10–19 years	Cases	50	1	330	10	10 041	61
	Person-years	6 158 551	28 294	6 155 665	28 194	5 817 992	26 860
	Hazard ratio[b] (95% CI)	1 (ref)	7.16 (0.98–52.4)	1 (ref)	6.57 (3.49–12.4)	1 (ref)	1.43 (1.11–1.84)
	Hazard ratio[c] (95% CI)	1 (ref)	14.0 (1.76–111.2)	1 (ref)	7.99 (4.07–15.7)	1 (ref)	1.55 (1.18–2.03)
20–36 years	Cases	28	1	384	8	3348	27
	Person-years	3 675 005	27 464	3 670 922	27 343	3 520 909	26 023
	Hazard ratio[b] (95% CI)	1 (ref)	4.84 (0.66–35.6)	1 (ref)	2.85 (1.41–5.74)	1 (ref)	1.08 (0.74–1.57)
	Hazard ratio[c] (95% CI)	1 (ref)	NA	1 (ref)	3.57 (0.87–14.6)	1 (ref)	0.98 (0.44–2.20)
Total	Cases	176	6	1065	26	56 808	175
	Person-years	17 692 243	73 432	17 684 166	73 185	16 927 103	70 003
	Hazard ratio[b] (95% CI)	1 (ref)	10.3 (4.53–23.4)	1 (ref)	5.14 (3.48–7.60)	1 (ref)	1.25 (1.08–1.45)
	Hazard ratio[c] (95% CI)	1 (ref)	22.2 (8.77–56.1)	1 (ref)	8.47 (5.33–13.5)	1 (ref)	1.32 (1.12–1.57)

[a] Cohort of 810 719 non-Muslim Danish born males born January 1977 through December 2003 and followed for meatal stenosis, other urethral stricture disease and asthma in age interval 0–36 years between January 1977 and November 2013.
[b] Hazard ratios in main analysis stratified for birth year with age as the underlying time scale.
[c] Hazard ratios in robustness analysis stratified for birth year and municipality-based household income with age as the underlying time scale, ending follow-up on December 31, 2003, based on altogether 5 circumcised *v* 65 intact cases of meatal stenosis, 19 circumcised *v* 477 intact cases of other urethral stricture disease, and 135 circumcised *v* 41 985 intact cases of asthma.

aged 20–36 years (1.08, 0.74–1.57) (Table 3). However, the rate was notably elevated in 10–19 year-old circumcised boys (1.43, 1.11–1.84), thus yielding a 25% increased overall rate of asthma in circumcised males (1.25, 1.08–1.45).

Robustness analyses. Ending follow-up on December 31, 2003 to reduce exposure misclassification yielded an overall HR for meatal stenosis that was even higher than in the main analysis (20.4, 8.12–51.1, based on 5 cases of meatal stenosis in circumcised males v 65 cases in intact males). The HR was particularly high among <10 year-old boys (22.9, 8.20–63.9). Likewise, the overall HR for other USDs was higher than in the main analysis (8.31, 5.23–13.2, based on 19 cases in circumcised males v 477 cases in intact males), most notably so in <10 year-old boys (13.1, 6.47–26.7).

Addressing the combined influence of exposure misclassification and socioeconomic confounding – by ending follow-up on December 31, 2003 and stratifying for municipality-based disposable household income – yielded very high HRs (meatal stenosis: 22.2, 8.77–56.1; other USDs: 8.47, 5.33–13.5), particularly in <10 year-old boys (meatal stenosis: 26.3, 9.37–73.9; other USDs: 14.0, 6.86–28.6) (Table 3).

We also examined the robustness of our HR estimate for meatal stenosis in <10 year-old boys (HR = 16.3, 6.03–45.3), assuming that three, not four, circumcised boys developed meatal stenosis in that age interval. HRs with 95% CIs in the four analyses ranged from a low of 12.4 (3.89–39.3) to a high of 12.6 (3.96–40.0), with a summary HR estimate of 12.5 (3.92–39.6).

Population attributable fraction (AF_p). Considering the international consensus among clinicians that meatal stenosis is markedly more common in circumcised than intact males,[8–12] we assumed that our findings might apply outside the study cohort of non-Muslim Danish males. Specifically, we used our HR point estimates for <10 year-old boys (16.5 for meatal stenosis; 10.7 for other USDs) to estimate the AF_p in populations with reported overall circumcision prevalences of 5%, 16%, 80%, and 99%, corresponding to the situation in Denmark, the United Kingdom, the United States and Israel, respectively. Such calculations revealed that 44%, 71%, 93%, and 94% of cases of meatal stenosis, and 33%, 61%, 89%, and 91% of other USDs, in <10 year-old Danish, U.K., U.S. and Israeli boys, respectively, may be attributable to non-therapeutic circumcision. When applying much more conservative HR values, corresponding to the lower 95% confidence limits for our HRs (6.03 for meatal stenosis; 5.31 for other USDs), AF_p calculations revealed that 20%, 45%, 80% and 83% of cases of meatal stenosis and 18%, 41%, 78% and 81% of other USDs in <10 year-old Danish, U.K., U.S., and Israeli boys, respectively, may be attributable to non-therapeutic circumcision.

Discussion

Our two-armed study provides epidemiological confirmation of the widely accepted, longstanding clinical impression of a markedly increased relative risk of meatal stenosis in circumcised males.[4–6,22,46,47] Recent clinical studies relying on direct penile examination have estimated that between 5% and 20% of boys undergoing non-therapeutic circumcision will eventually develop meatal stenosis.[12,23,24,26–28] Lately, the protective properties of the foreskin have also been observed in boys with medical conditions necessitating foreskin surgery. In Britain, the proportion of boys treated with foreskin-preserving preputioplasty for lichen sclerosus, who subsequently needed surgery for meatal stenosis, was notably lower (6%) than in similarly affected boys undergoing circumcision (19%–20%),[48,49] a finding, however, which might be influenced by differences in disease severity between the treatment groups. While the underlying physiological mechanism behind this protection remains a matter of debate, two plausible mechanisms are discussed in the following.

Meatal irritation

In as early a year as 1915, pediatrician John Zahorsky stated that "*the prepuce protects the meatus*", and he suggested that mechanical and chemical irritation from an ammoniacal diaper produced blister formation and subsequent ulceration of the urethral opening, an underappreciated problem in circumcised boys.[47] Ever since, the predominant etiological theory has been that repeated cycles of ulceration, inflammation, scab formation and fibrosis of the meatal mucosa will eventually give rise to meatal stenosis in a non-trivial proportion of circumcised boys.[7,10,11,13,21,26,46,50]

In one series of 152 children (126 boys, 26 girls) with meatal stenosis, the youngest patient was diagnosed at age 7 weeks, but 75% of cases only came to the pediatrician's attention after the age of 2 years.[22] In another, 70% of 160 children (150 boys, 10 girls) with meatal stenosis came to the urologist's attention only after the age of 4 years.[51] It is not clear if these age patterns imply that prolonged mucosal irritation is required for meatal stenosis to develop in most cases; serious diagnostic delay in those with no or initially mild clinical symptoms offers a plausible alternative explanation.

Meatal ischemia

Several circumcision techniques cause damage to the frenular branches of the dorsal penile artery, and it has been proposed that the resulting ischemia of the meatus and, possibly, the distal part of the urethra may be responsible for meatal stenosis development in circumcised males.[26] Two recent investigations assessing the impact of frenular artery sparing circumcision techniques lend support for this theory. In one,[28] traditional infant circumcision preceded by ligation of the frenular artery was followed by meatal stenosis development in 15% of 105 boys during a mean follow-up period of 9 years; the corresponding proportion among 101 boys undergoing the same circumcision procedure but without initial ligation of the frenular artery was only 2%. In another,[52] a frenulum-preserving circumcision technique provided successful treatment of phimosis and other penile conditions in 42 males age 4–64 years, reportedly without any subsequent cases of meatal stenosis or other major complications during 1–4 years of follow-up.

Regardless of etiology, however, if not treated early, even asymptomatic meatal stenosis may lead to potentially serious conditions, such as vesicoureteral reflux, hydronephrosis, or kidney damage in a noticeable fraction of cases.[23,51,53–55] In one Israeli study, two of 14 (14%) boys with isolated meatal stenosis who had been circumcised in the neonatal period had radiographically confirmed vesicoureteral reflux.[53] Likewise, from data presented in the abovementioned study of 150 boys and 10 girls with meatal stenosis, it can be derived that the proportion of circumcised boys with urography-determined hydronephrosis was between 12% and 20% at the time of first clinical presentation.[51] It should be borne in mind, however, that some cases of vesicoureteral reflux and hydronephrosis in these boys might have had other causes than circumcision-induced urethral obstruction.

Relative v *absolute risk*

Many cases of meatal stenosis with no or only mild symptoms may remain undiagnosed for extended periods after the circumcision.[22,23,51,53,56] In studies assessing the frequency of meatal stenosis from hospital data, asymptomatic or mild cases will either be missed entirely, or they may occur with considerable diagnostic delay. Still other cases may escape detection due to inaccurate diagnostic coding. Moreover, the overwhelming majority of health care visits for USD in males are managed in office settings.[57] Importantly, therefore, the implausibly low *absolute* rates of USD reported in studies based on hospital data must not be used inappropriately to underestimate the magnitude of the problem.[58–61]

To illustrate this caveat, using the best available data in an oft-cited 2014 report by El Bcheraoui et al., who relied on reimbursement claims from U.S. hospitals, the authors identified a mere 26 cases of USD in 241 751 neonatally circumcised boys followed for a maximum of 180 days after the surgery.[58] This finding actually represented a doubled *relative* risk of USD in circumcised male infants (RR 2.14, 95% CI 1.08–4.25), an unnoticed result pointing in the same direction as our findings. However, federal U.S. health authorities ignored the notorious incompleteness of the underlying data and referred instead to the study as trustworthy evidence of very low *absolute* risks of USDs and other complications after neonatal circumcision.[62,63]

While incomplete register data may produce seriously misleading estimates of the *absolute* risk,[58–61] estimates of the *relative* risk based on the same data may well be valid, provided the ascertainment of USD takes place independently of the foreskin/circumcision status in members of the studied populations. In the present study, we consider it unlikely that any parents' decision to contact their son's doctor, or any doctor's ability to diagnose USD in boys with symptoms suggestive of urethral obstruction, would depend systematically on the boys' foreskin/circumcision statuses. Still, however, should such a spurious mechanism truly exist that would lead to better ascertainment of USDs in circumcised boys, it cannot plausibly explain the observed 10–26 fold elevated rates of meatal stenosis or the 5–14 fold elevated rates of other USDs among circumcised boys in our study. Against a backdrop of century-old clinical evidence supporting the plausibility of our findings, we believe there is good reason to consider our markedly elevated *relative* risk estimates as being reliable, regardless of our inability to provide accurate measures of *absolute* risk.

Male predominance in meatal stenosis

In part I of our study, we found that the male:female ratio of meatal stenosis was high in all groups studied, which confirms the long-established male predominance of this problem.[4,6,22,51] However, the almost threefold *higher* male:female ratio in Muslims (HR 14.1) than ethnic Danes (HR 4.9) supports the idea that circumcision – the only obvious penile difference among the groups – could be responsible for the observed particular male excess of USDs in Muslims. This impression is further supported by our findings in <10 year-old children with a Muslim cultural background, among whom not even one case of meatal stenosis was diagnosed in girls *v* 40 cases in boys during comparable periods of follow-up in the two sexes.

We used asthma as a control outcome, because this disease has previously been found not to be associated with foreskin/circumcision status in boys.[30,31] The absence in our study of any unusual risk of asthma in <10 year-old Muslim males (Table 2) or <10 year-old circumcised non-Muslims (Table 3) confirms our expectation that circumcision is not a risk factor for childhood asthma. The higher HRs of asthma in Muslim male immigrants is most likely due to a higher prevalence of socioeconomic and lifestyle-related risk factors for asthma, such as smoking, in this group.[64,65]

Strengths

Both study parts relied on national register data that have been widely used for epidemiological research purposes.[66] We constructed our cohorts using high-quality administrative data on country of birth (part I) or hospital contacts or publicly paid subsidies to private practitioners (part II) to identify cohort members presumed (part I) or known (part II) to have undergone non-therapeutic circumcision. In both parts, we identified study outcomes in the National Patient Register.[33] Methodologically, in part II, we used information about other foreskin operations to enable a clean comparison of USD risks in circumcised and genitally intact males. Also, we performed a parallel analysis of the risk of meatal stenosis in females with Muslim and non-Muslim cultural backgrounds, an exercise whose unremarkable results corroborated the specificity of our findings for males.

Limitations

A number of limitations need consideration. First of all, because our study was carried out in a country where non-therapeutic circumcision is uncommon, numbers of cases of USD in circumcised males in part II of our study were limited (6 cases of meatal stenosis, 26 cases of other USDs), whereas among intact males numbers were considerably higher (176 cases of meatal stenosis, 1065 cases of other USD). Despite this limitation, our study had sufficient power to show with 95% confidence that the true circumcision-associated HR for meatal stenosis is at least 6-fold elevated, and our findings remained statistically significant in a robustness analysis with one case less of meatal stenosis in circumcised boys younger than 10 years. For comparison, USD case numbers were markedly lower (26 cases in circumcised boys and only 12 cases in intact boys) in a U.S. study of complications after infant circumcision,[58] whose findings were highlighted as particularly informative by U.S. health authorities.[62,63] In part I of our study, there were 40 cases of meatal stenosis and 76 cases of other USDs in <10 year-old boys with a Muslim background alone (*v* 198 and 496 such cases, respectively, among <10 year-old ethnic Danish boys). Consequently, our findings, notably for <10 year-old boys, remain robust notwithstanding small numbers in some analyses.

Unfortunately, we did not have access to individual-level socioeconomic variables for our cohort members. To partially overcome this limitation, we stratified the background rates by municipality-based disposable household income levels in one of the robustness analyses for both parts of the study. In both situations, HRs for USD were unchanged or even higher than in the main analyses, suggesting that any residual socioeconomic confounding, unaccounted for by the municipality-level stratification used, may render our HRs too conservative.

For each inpatient visit with a diagnosis of USD, data from the United States suggest that around 300 such visits will occur in office settings.[57] As outcomes in our study, we only had information about USD cases treated in Danish hospitals. Therefore, our findings, like those of prior reports based on hospital data,[58–61] may not necessarily apply to milder cases managed in clinic settings. Theoretically, if some spurious referral mechanism rendered USD patients among Muslim males (part I) or circumcised non-Muslim males (part II) more likely to receive treatment for mild USD symptoms in a hospital setting, such selection bias could have inflated our HRs. However, considering the free and equal access to public health care for all residents in Denmark and the absence of any plausible mechanism for such religious or circumcision-associated referral bias, this concern appears to be of mostly theoretical relevance.

Potential impact on public health

By using comprehensive epidemiological data from the *Urologic Diseases in America Project*, researchers estimated that male USD in the United States is the cause of more than 5000 inpatient visits and approximately 1.5 million office visits per year at an annual cost of approximately US$ 200 million.[57] To the best of our knowledge, our study is the first to report on the potential impact of circumcision on the burden of USD beyond the first few days or months of life.[58–61] With AF_p estimates of at least 18%, but more likely around 33%–44%, for <10 year-old boys in Denmark, our study suggests that the impact of non-therapeutic circumcision is considerable. Even more strikingly, however, assuming that our HRs apply in other countries, a major proportion of USD cases in <10 year-old U.K. boys (at least 41%, but more likely around 61%–71%), U.S. boys (at least 78%, but more likely around 89%–93%), and Israeli boys (at least 81%, but more likely around 91%–94%), may be attributable to circumcision. From both a patient and a public health perspective, therefore, our findings should prompt researchers in other countries with access to high-quality data on relevant study variables to reexamine our findings.

In conclusion, our two-part epidemiological investigation corroborates longstanding clinical knowledge that non-therapeutic circumcision puts boys at markedly elevated relative risk of USD. These findings, combined with clinical evidence that somewhere between 5% and 20% of circumcised boys will eventually develop meatal stenosis, call for a thorough assessment of the burden of urethral troubles and other adverse outcomes after non-therapeutic circumcision of boys.

Ethical approval

This register-based study was approved by the Danish Data Inspection Board (approval numbers 2008-54-0472 and 2009-41-4154).

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Contributors

MF conceived the study idea, planned the study, obtained the necessary permissions, coordinated the statistical analyses, drafted the manuscript, and is the guarantor of the study. JS planned the study, performed all statistical analyses, revised the manuscript, and approved the final version before submission.

Competing interests

The authors declare that they have no conflicts of interest. MF has been an author of articles on health-related and sexual consequences of male circumcision and has taken part in national and international debates on the ethics of male and female circumcision. From a medical ethics perspective, MF is generally sceptical about the advisability of performing non-therapeutic genital surgeries on minor children.

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