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Ritual circumcision and risk of autism spectrum disorder in 0- to 9-year-old boys: national cohort study in Denmark

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Abstract

Objective: Based on converging observations in animal, clinical and ecological studies, we hypothesised a possible impact of ritual circumcision on the subsequent risk of autism spectrum disorder (ASD) in young boys.
Design: National, register-based cohort study.
Setting: Denmark.
Participants: A total of 342,877 boys born between 1994 and 2003 and followed in the age span 0–9 years between 1994 and 2013.
Main outcome measures: Information about cohort members' ritual circumcisions, confounders and ASD outcomes, as well as two supplementary outcomes, hyperkinetic disorder and asthma, was obtained from national registers. Hazard ratios (HRs) with 95% confidence intervals (CIs) associated with foreskin status were obtained using Cox proportional hazards regression analyses.
Results: With a total of 4986 ASD cases, our study showed that regardless of cultural background circumcised boys were more likely than intact boys to develop ASD before age 10 years (HR = 1.46; 95% CI: 1.11–1.93). Risk was particularly high for infantile autism before age five years (HR = 2.06; 95% CI: 1.36–3.13). Circumcised boys in non-Muslim families were also more likely to develop hyperkinetic disorder (HR = 1.81; 95% CI: 1.11–2.96). Associations with asthma were consistently inconspicuous (HR = 0.96; 95% CI: 0.84–1.10).
Conclusions: We confirmed our hypothesis that boys who undergo ritual circumcision may run a greater risk of developing ASD. This finding, and the unexpected observation of an increased risk of hyperactivity disorder among circumcised boys in non-Muslim families, need attention, particularly because data limitations most likely rendered our HR estimates conservative. Considering the widespread practice of non-therapeutic circumcision in infancy and childhood around the world, confirmatory studies should be given priority.

Keywords

circumcision, cohort study, autism spectrum disorder, hyperkinetic disorder, asthma, Denmark

Introduction

Negative long-term psychological consequences of pain- and stressful surgery in early childhood were described almost 70 years ago. Among children operated for a variety of conditions, Levy noted a strong association between the age at operation and the frequency and severity of emotional sequelae. Psychological problems were encountered in 42% of children aged <3 years at the time of operation, as compared with 10% among older children.[1]

Until recently, it was believed that newborns are incapable of interpreting noxious stimuli in a manner comparable to that of older children and adults. This idea has now been abandoned with almost universal consensus that newborns and infants perceive pain and stress very much like older children and adults.[2] In a study of 5-, 12- and 15-month-old infants, Kouider et al.[3] showed that even the youngest infants had full capacity for conscious perception, although their ability to express such perceptions had not yet developed. Also, animal studies and clinical investigations strongly suggest that neonatal pain has an impact on subsequent responses to stress and anxiety later in life.[4–6]

As lately as in the 1990s, practitioner use of pain relief for circumcision of newborn boys was limited.[7,8] Nowadays, it is considered unacceptable practice to circumcise boys without proper pain relief,[9] although some hospitals apparently continue to circumcise neonates without anaesthesia.[10]

A commonly used topical anaesthetic for infant circumcisions, eutectic mixture of local anaesthetics cream, provides only inferior pain relief as compared with the two most common injection methods, the dorsal penile nerve block and the subcutaneous ring block.[8,11,12] Of note, even the most effective of these methods, the subcutaneous ring block, has failure rates of 6–8%.[9,13,14]

Regardless of surgical method, circumcision causes some level of pain and discomfort at the operation table and for several days after until wound healing has completed.[10] In a recent study, parents reported pain during the six postcircumcision weeks in 71% of newborn boys, with levels ranging from 'minimal pain' (14%) over 'acceptable pain' (53%) to 'more than acceptable pain' (2%) and 'much more pain' (2%).[15] The procedural pain associated with neonatal circumcision is plausibly more severe and the postoperative pain of longer duration than in older children and adults, because the foreskin of most neonates must be forcefully separated from the glans to which it is fused before it can be cut off.[16] This leaves the circumcised infant not only with a painful incision of the foreskin but also with a raw, wounded surface of the glans that is exposed to friction and chemical irritation from urine and feces until healing. Older children whose foreskins have already spontaneously separated from the glans will only experience the pain associated with the foreskin incision. None of the most common interventions used to reduce circumcision pain completely eliminates it,[17] and a non-trivial proportion of boys will suffer from pain due to anaesthetic failure.[9,13,14] Thus, while most boys presumably experience mild to moderate levels of pain and discomfort during and after the operation, some boys will endure strongly painful circumcisions.

Levy's early observation that pain and stress from surgery in infancy and early childhood may have serious long-term psychological consequences was revived in the 1980s.[18,19] Observational studies of boys undergoing circumcision showed short- and long-term changes in physiological stress indicators, disturbed adaptation to the postnatal environment, interference with normal mother–child bonding and disruption of breastfeeding patterns,[2,20–23] although a recent, small study failed to confirm an impact on breastfeeding.[24] Neonatally circumcised boys in Canada exhibited significantly more signs of discomfort during routine vaccinations 4–6 months later than boys who were left intact, showing that early life trauma may alter a child's future handling of pain.[4] Long-term psychological, emotional or behavioral effects of circumcision-associated pain beyond the first six months of life have been little studied,[17] but other types of neonatal injury have been shown in animal and clinical studies to produce permanent deficits in responses to stress and an increased rate of psychological problems.[6,25]

To our knowledge, no study has examined the possible association of circumcision-related pain and stress with boys' subsequent risk of developing autism spectrum disorder (ASD). This is surprising, because painful experiences in neonates have been shown in animal[26] and human studies[4,27,28] to be associated with long-term alterations in pain perception, a characteristic often encountered among children with ASD.[29] ASD is a complex group of neurodevelopmental disorders characterised by deficits in skills of reciprocal social interaction or communication with or without the presence of stereotyped behavior, interests and activities,[30] and autistic children often have unusual reactions to sensory stimulation with either lowered or heightened sensitivity to noxious stimuli.

The present investigation was prompted by the combination of recent animal findings linking a single painful injury to lifelong deficits in stress response[25] and an ecological study showing a strong, positive correlation ($r = 0.98$) between a country's neonatal male circumcision rate and its prevalence of ASD in boys. Specifically, using data from nine countries, Bauer and Kriebel[31] observed that with each 10% increase in a population's neonatal circumcision rate, the estimated prevalence of ASD increased significantly by 2.01 per 1000 boys. The present study was carried out to address the hypothesis that ASD might be a rare adverse outcome in boys undergoing ritual circumcision during a vulnerable period of life.

Methods

Cohort

We used data from the continuously updated Danish Civil Registration System to establish a cohort of all children born in Denmark (excluding Greenland and Faroe Islands) between January 1994 and December 2003. Each child is recorded by his or her unique 10-digit ID number, a key variable used to record and track all health-relevant and sociodemographic data in national registers.[32]

Ritual male circumcision

In Denmark, ritual circumcision is an uncommon procedure, except among Muslim and Jewish families. Information about ritual circumcisions carried out by doctors in medical settings was obtained from a combination of two data sources. Ritual circumcisions performed in hospitals between 1994 and 2003 were identified in the Danish National Patient Register under national surgery codes 55620 (period 1994–1995) and KKGV20 (period 1996–2003).[33] Ritual circumcisions performed in private clinics by surgeons and gynaecologists and subsidised by the national healthcare system were identified under disbursement code 5301 in the National Health Service Register (period 1996–2003).[34] In subsequent years, ritual circumcision was no longer a publicly subsidised surgical procedure, thus resulting in incomplete records for circumcisions performed after 2003. Because circumcisions by non-medical, religious circumcisers in private settings were not recorded, information about such procedures was not available. This means that our study missed the few traditional Jewish circumcisions in Denmark.[35] According to Muslim authorities, circumcisions in this group are often done by doctors,[35] but we had no means to identify those Muslim circumcisions that were not carried out by Danish doctors.

We also searched the files of the National Patient Register[33] (period 1994–2003) and the National Health Service Register[34] (period 1996–2003) for all recorded information about foreskin surgery other than ritual circumcision (e.g. operations for phimosis). We used this information to enable a clean comparison of risks of ASD and other outcomes in ritually circumcised boys versus the reference group of intact boys (see below).

Outcomes

Autism spectrum disorder. Since January 1995, in- and outpatient hospital contacts for psychiatric diseases have been recorded in the National Patient Register.[33] Consequently, we searched for all recorded cases of ASD in cohort members before their 10th birthday in the period between January 1995 and April 2013, using International Classification of Diseases, 10th revision (ICD-10) codes F84.0 (infantile autism), F84.1 (atypical autism), F84.5 (Asperger syndrome), F84.8 (other pervasive developmental disorder) or F84.9 (unspecified pervasive developmental disorder).

Supplementary outcomes. For comparison, we also identified all recorded cases of two supplementary outcomes in the cohort of boys, namely hyperkinetic disorder (ICD-10 code group F90, period January 1995 through April 2013) and asthma (ICD-10 code groups J45-J46, period January 1994 through April 2013). No prior study suggests a link between ritual circumcision and either of these outcomes.

Covariates

Cultural background. With estimated current totals of 240,000 Muslims and 8000 Jews in Denmark,[36,37] the vast majority of ritual circumcisions are performed in families with a Muslim cultural background. If not properly addressed, any association between ritual circumcision and ASD risk could theoretically be due to other factors that might differ between boys in Muslim and non-Muslim families. To address any such influences, we created for all cohort members a cultural background variable based on information about the country of birth for their parents and grandparents. Using the criterion of having at least one parent or grandparent 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 accounted for more than 0.1% of all non-Danish born citizens), this variable categorised 7.8% of both boys and girls in the cohort as belonging to a family with a likely Muslim cultural background. To evaluate the precision of our cultural background variable, we applied it to the entire Danish population of 1 January 2013 (5.57 million persons), reaching an estimate of 243,175 Muslims (4.4%) in Denmark, which is close to the abovementioned estimate of 240,000.[36]

Birth and perinatal characteristics. We examined associations with ASD risk for several birth and perinatal characteristics that have previously been implicated in the aetiology of ASD. Specifically, using individual-level data from national registers,[32,38] we examined univariate associations with ASD risk for each of the following characteristics; birth weight in grams (<2000, 2000–2999, 3000–3499, 3500–3999, ≥4000, missing), gestational age in weeks (≤30, 31–36, 37, 38, 39, 40, 41, ≥42, missing), Apgar score 5 min after birth (≤8, 9–10, missing), mode of delivery (vaginal, Caesarean), twin status (singleton, twin or multiplet), birth order (first, second, third or later), congenital malformations or chromosome abnormalities (none, any), maternal age at child's birth (≤19, 20–24, 25–29, 30–34, 35–39, ≥40 years), maternal smoker status during pregnancy (non-smoker, smoker, missing) and mother's marital status at the child's birth (married, not married).

Statistical methods

Birth and perinatal characteristics and ASD risk. To assess individual associations with ASD risk in both boys and girls, we first examined the birth and perinatal characteristics as explanatory variables in a series of univariate Cox proportional hazards regression analyses with stratification on birth year and age as the underlying time scale.[39] Hazard ratios (HRs) with 95% confidence intervals (CIs) served as our effect measure. Next, we used a two-step procedure to select which of the examined birth and perinatal characteristics to include as potential confounders in the main analysis of the association of foreskin status with ASD risk. First, a P value < 0.05 in the associated overall Wald test in univariate analysis qualified birth and perinatal ASD risk factors for further consideration. In the second step, only those birth and perinatal characteristics that were significantly associated with ASD risk in a multivariable model ($P < 0.05$) were subsequently included as potential confounders in the main analysis.

Ritual circumcision and ASD risk. We compared proportions of ASD subtypes in intact and ritually circumcised boys using the Chi-squared test. All statistical analyses of the association of foreskin status with ASD risk and, in separate analyses, with risk of the two supplementary outcomes, hyperkinetic disorder and asthma, were carried out as Cox proportional hazards regression analyses stratified on birth year and cultural background with age as the underlying time scale and with adjustment for birth and perinatal characteristics that were independently associated with ASD risk, as described above.[39] HRs with 95% CIs compared the hazard among ritually circumcised boys with that among the reference group of intact boys. Each boy's foreskin status was treated as a time-dependent variable being intact from birth and, when relevant, shifting to circumcised on the recorded date of ritual circumcision. Boys undergoing foreskin surgery other than ritual circumcision were censored on the date of such surgery. By including the cultural background variable and birth year as stratification variables and using age as the underlying time scale in all analyses, we ensured that all HRs of ASD, hyperkinetic disorder and asthma were based on culturally comparable, same-aged strata of circumcised and intact boys observed during comparable calendar years. To determine if the proportional hazards assumption was acceptable in our main model for the association of ritual circumcision with ASD risk, we plotted the martingale-based residuals as a function of the underlying time, an exercise which revealed visually satisfactory model fit.[40]

Robustness analyses. In a set of supplementary analyses, we evaluated the robustness and specificity of the observed association of ritual circumcision with ASD risk. We had no information about ritual circumcisions in Denmark after 31 December 2003, because ritual circumcisions were no longer performed in Danish hospitals after that date, and surgeons in private clinics no longer reported such operations to the National Health Service Register, because public subsidies were no longer offered. Consequently, our main analysis in which all cohort members were followed from birth to their 10th birthday was limited by incomplete circumcision data, notably among boys born late in the cohort defining period 1994–2003. In one robustness analysis, we ended follow-up for ASD on 31 December 2003, to avoid any influence of misclassification of exposure status in subsequent calendar years. However, the more reliable HR estimate obtained in this robustness analysis came at the cost of reduced statistical power.

In a second robustness analysis, we evaluated in a parsimonious model the possible impact of not including any of the individually significant birth and perinatal ASD risk factors as confounders. The idea was that while the included birth and perinatal characteristics were clearly associated with ASD risk, they might not necessarily be confounders in the association of foreskin status with ASD risk.

Third, we divided the ASD outcome in two subcategories, namely infantile autism and all other ASD diagnoses to learn if infantile autism in the age group 0–4 years was particularly strongly associated with ritual circumcision.

Finally, we studied the risk of ASD between January 1994 and April 2013 among 0- to 9-year-old sisters of circumcised boys and all other girls in Denmark. We did this to explore whether observed associations of ritual circumcision with ASD risk in boys might be explained by family factors that were not adequately accounted for by stratifying on cultural background in the statistical model. Specifically, in a Cox proportional hazards model, we examined relative risk of ASD among all Danish girls in which being a full sibling (i.e. having the same mother and father) of a boy undergoing ritual circumcision was the time-dependent exposure variable shifting from unexposed to exposed on the (first) date of ritual circumcision in a brother (for sisters born before the brother's ritual circumcision) or at birth (for sisters born later). As for the main analysis in boys, this analysis was stratified on birth year and cultural background, and adjusted for all birth and perinatal characteristics that were independent risk factors for ASD in girls (Table 1), again using age as the underlying time scale.[39]

The study was approved by the Danish Data Inspection Board (approval no. 2009-41-4154).

Results

The cohort consisted of 342,877 boys and 325,000 girls born in Denmark between January 1994 and December 2003. During follow-up through April 2013, a total of 5033 boys (1.5%) and 1026 girls (0.3%) were diagnosed with ASD before their 10th

Table 1. Hazard ratios (95% confidence intervals) of autism spectrum disorder according to birth and perinatal characteristics among 0- to 9-year-old boys and girls, Denmark 1994–2013*.

	Boys				Girls			
	No. boys in cohort	No. ASD cases	HR_{univ} (95% CI)†	HR_{adj} (95% CI)‡	No. girls in cohort	No. ASD cases	HR_{univ} (95% CI)†	HR_{adj} (95% CI)‡
Birth weight (grams)								
<2000	6610	100	1.17 (0.95–1.43)	0.81 (0.61–1.06)	6573	37	2.14 (1.52–3.01)	1.90 (1.20–3.02)
2000–2999	42,759	744	1.22 (1.12–1.33)	1.12 (1.01–1.24)	52,119	232	1.59 (1.34–1.88)	1.42 (1.17–1.73)
3000–3499	94,327	1326	0.98 (0.92–1.06)	0.95 (0.88–1.02)	109,039	314	1.03 (0.87–1.20)	0.98 (0.83–1.15)
3500–3999	117,761	1691	1 (ref)	1 (ref)	105,247	298	1 (ref)	1 (ref)
≥4000	78,837	1141	1.00 (0.93–1.08)	1.03 (0.96–1.12)	49,656	135	0.95 (0.78–1.16)	0.96 (0.78–1.18)
Missing	2583	31	0.92 (0.64–1.31)	0.71 (0.48–1.04)	2366	10	1.62 (0.86–1.30)	1.31 (0.66–2.61)
Wald test			$P < 0.001$	$P = 0.001$			$P < 0.001$	$P < 0.001$
Gestational age (weeks)								
≤30	2613	50	1.68 (1.27–2.23)	1.53 (1.05–2.22)	2266	9	1.77 (0.91–3.45)	0.67 (0.30–1.47)
31–36	20,111	319	1.15 (1.02–1.30)	0.99 (0.86–1.15)	16,792	75	1.73 (1.34–2.24)	1.02 (0.75–1.42)
37	17,795	264	1.05 (0.92–1.20)	0.98 (0.85–1.13)	15,682	54	1.31 (0.98–1.77)	1.02 (0.75–1.39)
38	40,698	624	1.10 (1.00–1.21)	1.06 (0.96–1.18)	37,568	149	1.51 (1.23–1.86)	1.32 (1.06–1.63)
39	71,765	1069	1.08 (1.00–1.18)	1.07 (0.99–1.17)	69,013	214	1.21 (1.00–1.45)	1.15 (0.95–1.38)
40	95,331	1298	1 (ref)	1 (ref)	94,358	238	1 (ref)	1 (ref)
41	62,800	956	1.11 (1.02–1.20)	1.09 (1.00–1.18)	61,030	192	1.23 (1.02–1.49)	1.25 (1.03–1.51)
≥42	29,424	421	1.06 (0.95–1.18)	1.00 (0.89–1.11)	26,046	83	1.27 (0.99–1.63)	1.26 (0.98–1.62)
Missing	2340	32	1.13 (0.80–1.61)	1.07 (0.73–1.56)	2245	12	2.40 (1.34–4.29)	2.12 (1.11–4.05)
Wald test			$P = 0.01$	$P = 0.12$			$P < 0.001$	$P = 0.04$

(continued)

Table 1. Continued.

	Boys				Girls			
	No. boys in cohort	No. ASD cases	HR_{univ} (95% CI)†	HR_{adj} (95% CI)‡	No. girls in cohort	No. ASD cases	HR_{univ} (95% CI)†	HR_{adj} (95% CI)‡
Apgar score after 5 min								
≤8	15,192	274	1.32 (1.16–1.49)	1.25 (1.10–1.43)	11,963	43	1.21 (0.89–1.64)	NA
9–10	326,401	4745	1 (ref)	1 (ref)	311,833	982	1 (ref)	
Missing	1284	14	1.04 (0.62–1.76)	1.04 (0.61–1.77)	1204	1	0.37 (0.05–2.63)	
Wald test			$P < 0.001$	$P = 0.003$			$P = 0.30$	
Mode of delivery								
Vaginal delivery	287,362	4069	1 (ref)	1 (ref)	276,277	821	1 (ref)	1 (ref)
Caesarean section	55,515	964	1.19 (1.11–1.28)	1.10 (1.02–1.18)	48,723	205	1.36 (1.17–1.59)	1.12 (0.95–1.32)
Wald test			$P < 0.001$	$P = 0.02$			$P < 0.001$	$P = 0.19$
Twin status								
Singleton	329,711	4865	1 (ref)	NA	312,568	987	1 (ref)	NA
Twin or multiplet	13,166	168	0.86 (0.74–1.00)		12,432	39	0.98 (0.71–1.35)	
Wald test			$P = 0.06$				$P = 0.90$	
Birth order								
First	145,384	2527	1 (ref)	1 (ref)	138,726	488	1 (ref)	1 (ref)
Second	128,958	1726	0.77 (0.72–0.82)	0.76 (0.71–0.81)	121,767	373	0.87 (0.76–0.99)	0.88 (0.77–1.02)
Third or later	68,535	780	0.65 (0.60–0.71)	0.61 (0.56–0.67)	64,507	165	0.73 (0.61–0.87)	0.68 (0.56–0.82)
Wald test			$P < 0.001$	$P < 0.001$			$P = 0.001$	$P < 0.001$
Congenital malformations or chromosome abnormalities								
None	296,512	3949	1 (ref)	1 (ref)	291,466	784	1 (ref)	1 (ref)
Any	46,365	1084	1.76 (1.65–1.88)	1.71 (1.60–1.83)	33,534	242	2.70 (2.34–3.12)	2.58 (2.23–2.99)
Wald test			$P < 0.001$	$P < 0.001$			$P < 0.001$	$P < 0.001$

(continued)

Table 1. Continued.

	Boys				Girls			
	No. boys in cohort	No. ASD cases	HR_{univ} (95% CI)†	HR_{adj} (95% CI)‡	No. girls in cohort	No. ASD cases	HR_{univ} (95% CI)†	HR_{adj} (95% CI)‡
Maternal age at child's birth (years)								
≤19	5961	98	1.22 (0.99–1.49)	1.04 (0.85–1.28)	5631	16	1.02 (0.62–1.69)	0.85 (0.51–1.40)
20–24	48,195	755	1.15 (1.06–1.26)	1.07 (0.98–1.16)	45,701	155	1.23 (1.02–1.48)	1.12 (0.92–1.36)
25–29	126,910	1763	1 (ref)	1 (ref)	120,673	344	1 (ref)	1 (ref)
30–34	113,757	1632	1.01 (0.95–1.08)	1.11 (1.03–1.18)	107,646	328	1.05 (0.90–1.22)	1.12 (0.96–1.31)
35–39	41,983	681	1.12 (1.02–1.22)	1.28 (1.17–1.41)	39,574	151	1.27 (1.05–1.54)	1.40 (1.15–1.71)
≥40	6071	104	1.19 (0.98–1.45)	1.37 (1.12–1.67)	5775	32	1.85 (1.29–2.66)	2.00 (1.38–2.89)
Wald test			$P = 0.002$	$P < 0.001$			$P = 0.003$	$P < 0.001$
Maternal smoker status during pregnancy								
Non-smoker	249,010	3522	1 (ref)	1 (ref)	236,156	687	1 (ref)	1 (ref)
Smoker	78,336	1267	1.18 (1.11–1.26)	1.18 (1.11–1.27)	74,218	293	1.41 (1.23–1.62)	1.34 (1.16–1.54)
Missing	15,531	244	1.19 (1.05–1.36)	1.16 (1.01–1.32)	14,626	46	1.17 (0.87–1.58)	1.00 (0.73–1.37)
Wald test			$P < 0.001$	$P < 0.001$			$P < 0.001$	$P < 0.001$
Mother's marital status at child's birth								
Married	188,143	2610	1 (ref)	1 (ref)	177,951	528	1 (ref)	1 (ref)
Not married	154,734	2423	1.12 (1.06–1.19)	1.01 (0.95–1.07)	147,049	498	1.13 (1.00–1.28)	1.02 (0.90–1.17)
Wald test			$P < 0.001$	$P = 0.86$			$P = 0.04$	$P = 0.74$

ASD: autism spectrum disorder; CI: confidence interval; HR: hazard ratio; NA: not applicable.
*Cohort of 667,877 Danish-born children born January 1994 through December 2003 and followed in age interval 0–9 years between January 1994 and April 2013.
†Hazard ratios obtained in Cox proportional hazards regression analysis stratified for birth year with age as the underlying time scale.
‡Hazard ratios obtained in Cox proportional hazards regression analysis stratified for birth year with age as the underlying time scale and with adjustment for all other birth and perinatal characteristics that were statistically significant ($P < 0.05$) in the univariate analysis for the particular sex.

birthday, yielding a cumulative male:female ASD incidence ratio of 4.6:1. Also, 7050 boys (2.1%) were diagnosed with hyperkinetic disorder and 29,368 boys (8.6%) were diagnosed with asthma during follow-up. Overall, 3347 boys (0.98%) in the cohort were ritually circumcised in a hospital department or a doctor's clinic before their 10th birthday, including 2903 circumcisions among 26,664 boys (10.9%) with a likely Muslim cultural background and 444 circumcisions among 316,213 other Danish boys (0.14%).

Birth and perinatal characteristics and ASD risk

Several examined birth and perinatal characteristics exhibited non-trivial associations with ASD risk, and all, except twin status, had associated Wald test P values < 0.05 in univariate analyses among boys (Table 1). When considered simultaneously, gestational age and mother's marital status were no longer independent ASD risk factors. All subsequent analyses of foreskin status with ASD risk in boys were therefore adjusted for birth weight, Apgar score, mode of delivery, birth order, congenital malformations or chromosome abnormalities, maternal age and maternal smoking during pregnancy.

Ritual circumcision and risk of ASD

With 57 ASD cases in ritually circumcised boys and 4929 ASD cases in intact boys, the overall ASD risk in the age interval 0–9 years was 46% increased in ritually circumcised boys (HR = 1.46; 95% CI: 1.11–1.93). This was due to noticeably increased ASD risk in the first 0–4 years of life (HR = 1.80; 95% CI: 1.25–2.60), but not in the 5–9 years age interval (HR = 1.15; 95% CI: 0.75–1.77). For boys circumcised before their second birthday, overall ASD risk during the first 0–9 years of life was 41% elevated (HR = 1.41; 95% CI: 1.05–1.90). The HR was higher, though not significantly so, for boys circumcised at age 24 months or older (HR = 1.96; 95% CI: 0.93–4.14), an estimate based on only seven cases of ASD in that group (Table 2).

The increased risk of ASD in circumcised boys under the age of 5 years was present among boys in both Muslim and non-Muslim families (Table 2). Risk in this age group was markedly elevated among boys in non-Muslim families (HR = 4.23; 95% CI: 1.90–9.44), a finding based on six ASD cases in circumcised boys versus 1165 cases in intact boys. Among boys in Muslim families, ASD risk was also significantly elevated in those who were circumcised (HR = 1.54; 95% CI: 1.03–2.31), based on 28 ASD cases in circumcised boys versus 160 cases in intact boys.

Ritual circumcision and risk of hyperkinetic disorder

Overall, the risk of hyperkinetic disorder was not elevated among ritually circumcised boys in the first 0–4 years of life (HR = 0.99; 95% CI: 0.43–2.29) or in the 5- to 9-year age group (HR = 1.27; 95% CI: 0.95–1.71) (Table 2).

Among boys in Muslim families, risk of hyperkinetic disorder did not depend on the boys' foreskin status (HR = 1.08; 95% CI: 0.77–1.52). However, risk was significantly increased among circumcised boys in non-Muslim families (HR = 1.81; 95% CI: 1.11–2.96), and risk appeared to be particularly high in the <5 years age window (HR = 3.60; 95% CI: 1.16–11.18), although the latter observation was based on only three cases.

Ritual circumcision and risk of asthma

Associations of ritual circumcision with risk of asthma were consistently negative, both in the 0–4 years (HR = 0.91; 95% CI: 0.78–1.06) and the 5–9 years age interval (HR = 1.16; 95% CI: 0.89–1.51), yielding an inconspicuous overall HR estimate (HR = 0.96; 95% CI: 0.84–1.10) based on a total of 235 cases of asthma in circumcised boys versus 29,002 cases in intact boys. Age at circumcision below or above 24 months also appeared unassociated with risk of asthma, just as the association with foreskin status was negative among boys in both Muslim and non-Muslim families (Table 2).

Robustness analyses for association of ritual circumcision with risk of ASD

In the first robustness analysis, we stopped follow-up on 31 December 2003, thus covering a shorter calendar period during which ritual circumcisions performed by Danish doctors were recorded in the registers. In this analysis, the overall HR for ASD was 62% increased in the 0–9 years age interval (HR = 1.62; 95% CI: 1.05–2.50), based on 24 ASD cases in ritually circumcised boys and 1441 ASD cases in intact boys. When restricting the focus to boys in the 0–4 years age interval, the HR of ASD remained high (HR = 1.83; 95% CI: 1.14–2.92), based on 21 ASD cases in ritually circumcised boys versus 759 ASD cases in intact boys.

Next, we examined the extent to which the included birth and perinatal covariates were actually confounders of the association of foreskin status with ASD risk. To do so, we repeated all analyses using a parsimonious Cox proportional hazards regression model, in which we stratified for birth year and cultural background but included none of the birth and perinatal characteristics in Table 1. All results were

Table 2. Hazard ratios (95% confidence intervals) of autism spectrum disorder, hyperkinetic disorder and asthma according to penile foreskin status among 0- to 9-year-old boys, Denmark 1994–2013*.

	Age 0–4 years			Age 5–9 years			Total		
Penile foreskin status	Cases	HR	95% CI	Cases	HR	95% CI	Cases	HR	95% CI
Autism spectrum disorder									
All boys									
Intact	1325	1	Ref	3604	1	Ref	4929	1	Ref
Circumcised	34	1.80	(1.25–2.60)	23	1.15	(0.75–1.77)	57	1.46	(1.11–1.93)
<24 months of age	32	1.80	(1.24–2.63)	18	1.02	(0.63–1.66)	50	1.41	(1.05–1.90)
≥24 months of age	2	1.74	(0.43–7.04)	5	2.05	(0.84–4.97)	7	1.96	(0.93–4.14)
Boys in Muslim families									
Intact	160	1	Ref	127	1	Ref	287	1	Ref
Circumcised	28	1.54	(1.03–2.31)	22	1.44	(0.92–2.28)	50	1.50	(1.10–2.03)
Boys in non-Muslim families									
Intact	1165	1	Ref	3477	1	Ref	4642	1	Ref
Circumcised	6	4.23	(1.90–9.44)	1	0.22	(0.04–1.57)	7	1.18	(0.56–2.48)
Hyperkinetic disorder									
All boys									
Intact	693	1	Ref	6042	1	Ref	6735	1	Ref
Circumcised	6	0.99	(0.43–2.29)	49	1.27	(0.95–1.71)	55	1.23	(0.93–1.63)
<24 months of age	6	1.07	(0.46–2.47)	41	1.19	(0.86–1.65)	47	1.18	(0.87–1.59)
≥24 months of age	0	–		8	1.93	(0.96–3.89)	8	1.75	(0.87–3.53)
Boys in Muslim families									
Intact	53	1	Ref	259	1	Ref	312	1	Ref
Circumcised	3	0.55	(0.17–1.77)	36	1.18	(0.83–1.67)	39	1.08	(0.77–1.52)
Boys in non-Muslim families									
Intact	640	1	Ref	5783	1	Ref	6423	1	Ref
Circumcised	3	3.60	(1.16–11.18)	13	1.62	(0.94–2.80)	16	1.81	(1.11–2.96)
Asthma									
All boys									
Intact	23,277	1	Ref	5725	1	Ref	29,002	1	Ref
Circumcised	172	0.91	(0.78–1.06)	63	1.16	(0.89–1.51)	235	0.96	(0.84–1.10)
<24 months of age	167	0.90	(0.77–1.05)	55	1.17	(0.89–1.55)	222	0.95	(0.83–1.10)
≥24 months of age	5	1.18	(0.49–2.85)	8	1.09	(0.54–2.19)	13	1.12	(0.65–1.93)

(continued)

Table 2. Continued.

	Age 0–4 years			Age 5–9 years			Total		
Penile foreskin status	Cases	HR	95% CI	Cases	HR	95% CI	Cases	HR	95% CI
Boys in Muslim families									
Intact	1677	1	Ref	395	1	Ref	2072	1	Ref
Circumcised	151	0.90	(0.76–1.06)	55	1.16	(0.87–1.53)	206	0.95	(0.82–1.10)
Boys in non-Muslim families									
Intact	21,600	1	Ref	5330	1	Ref	26,930	1	Ref
Circumcised	21	0.93	(0.60–1.42)	8	1.14	(0.57–2.27)	29	0.98	(0.68–1.40)

CI: confidence interval; HR: hazard ratio.
*Cohort of 342,877 Danish-born boys born January 1994 through December 2003 and followed in age interval 0–9 years between January 1995 (autism spectrum disorder and hyperkinetic disorder) or January 1994 (asthma) and April 2013.
Hazard ratios obtained in Cox proportional hazards regression analysis stratified for birth year and cultural background with age as the underlying time scale and with adjustment for birth and perinatal characteristics that were statistically significant ($P < 0.05$) in multivariable analysis for boys in Table 1.

essentially unchanged. Specifically, overall risk of ASD in this model was 42% increased in the 0–9 years age interval (HR = 1.42; 95% CI: 1.08–1.88), with HR estimates for the 0–4 and 5–9 years age intervals that were close to those shown in Table 2 (HR = 1.75; 95% CI:1.21–2.53 and HR = 1.12; 95% CI: 0.73–1.73, respectively).

Subtypes of ASD differed according to foreskin status, with circumcised boys having proportionally more diagnoses of infantile autism (56%, $n = 32$) than intact boys (35%, $n = 1733$) (Chi-squared test: $\chi^2 = 10.85$, df = 1, $P = 0.001$). For boys in the 0–4 years age interval, risk of infantile autism in circumcised boys was twice that of intact boys (HR = 2.06; 95% CI: 1.36–3.13, based on 27 cases in circumcised boys and 785 cases in intact boys); the risk of all other types of ASD combined was inconspicuous in the same age group (HR = 1.21; 95% CI: 0.55–2.66, based on seven cases in circumcised boys and 540 cases in intact boys).

Finally, we compared ASD risk in 0- to 9-year-old girls who were full siblings of boys undergoing ritual circumcision with that of all other 0- to 9-year-old Danish girls with two known parents. ASD risk in girls was not associated with family factors linked to ritual male circumcision (HR = 1.17; 95% CI: 0.54–2.55), based on seven ASD cases in girls with a ritually circumcised brother and 1012 ASD cases in girls without a ritually circumcised brother.

Discussion

Ritual circumcision among Danish boys is linked to an overall 46–62% increase in ASD risk in the first 10 years of life, with the upper risk estimate obtained after restriction to the period with the most complete data. More strikingly, risk was 80–83% increased in the first 0–4 years of life, an increase that was restricted to infantile autism. Non-therapeutic circumcision is uncommon in Denmark outside Jewish and Muslim communities, but due to our study's national coverage over two decades (1994–2013), findings were based on fairly solid numbers, and a series of robustness analyses confirmed the main findings. To our knowledge, there is no prior evidence to suggest a link between circumcision and hyperactivity disorder, so our finding of an increased risk of this common neurobehavioral disorder among circumcised boys in non-Muslim families was unexpected and needs cautious interpretation. As expected, risk of asthma was independent of the boys' foreskin status, which is in accordance with prior findings for asthma in the first years of life.[24]

Strengths

National register-based cohort studies have a number of advantages over other study designs. Our study relied on unselected national data that have been used extensively for a multitude of research purposes.[41] We constructed a cohort of all children born in Denmark 1994–2003, and we used national data on hospital contacts and public subsidies paid to private practitioners to identify cohort members undergoing ritual circumcision in a doctor's office or in a hospital department. We used national hospital data for ASD, hyperkinetic disorder and asthma, as well as national data on pregnancy complications and birth characteristics to evaluate potential confounding factors. Methodologically, the stratified proportional hazards regression analysis, and our ability to censor boys undergoing foreskin surgery other than ritual circumcision, ensured that our data were analysed in a prospective manner and that HRs of ASD, hyperkinetic disorder and asthma represented appropriate comparisons of risks among ritually circumcised and intact boys of same age, birth year and cultural background.

Weaknesses

Limitations with respect to the exposure variable, ritual circumcision, need careful consideration. Operations by religious circumcisers and non-Danish doctors were not covered due to lacking public surveillance of such procedures. According to Muslim authorities, circumcisions in Danish boys with Muslim parents are often done by doctors,[35] and to the extent such operations took place in public hospitals or in private clinics as part of the public healthcare system in Denmark, they were included in our study. It is unknown to what extent Danish boys in families with a Muslim cultural background actually undergo ritual circumcision, but our estimate that only 10.9% of these boys were circumcised by Danish doctors before their 10th birthday appears low. Recently, Muslim authorities in Denmark explained to the National Board of Health that Muslim circumcisions are often made by private practitioners in their clinics or in the boys' homes. One possible explanation for the apparent low overall circumcision rate in boys with a Muslim family background is that when payment occurs directly between parents and doctor, no public record will be available. The extent to which such arrangements take place, or similar ones involving non-Danish doctors or non-medical circumcisers, will determine the degree to which our 10.9% figure is an underestimate.

Among the much smaller group of Jews, the Chief Rabbi of Denmark reportedly performs all the approximately 15 orthodox Jewish circumcisions per year among boys with Jewish mothers.[35] Virtually all other Jewish circumcisions in Denmark are performed by doctors and are therefore most likely included in our data.

Importantly, any influence on our HR estimates arising from this kind of misclassification of cohort member's foreskin status, a type of misclassification that cannot plausibly depend on the boys' future risk of ASD, will most likely be towards the null. The statistically significant associations between ritual circumcision and ASD risk emerged despite the fact that some unknown proportion of circumcised boys were incorrectly considered to be genitally intact throughout follow-up. Our HR estimates for ASD are therefore most likely conservative.

In our main analysis, we followed the cohort of boys until April 2013, although we had no data on ritual circumcisions performed by Danish doctors after 2003. As with the missing circumcisions performed by religious circumcisers, such non-differential exposure misclassification will most likely produce conservative estimates of any real difference in ASD risk between circumcised and intact boys. Reassuringly, our robustness analysis in which we restricted the observation period to 1994–2003, when ritual circumcisions and ASD outcomes were covered, revealed a stronger association of ritual circumcision with ASD risk (HR = 1.62) than in the main analysis (HR = 1.46).

Ritual circumcisions in private practitioners' clinics were available only since 1996. Thus, boys who were circumcised in private clinics in 1994 or 1995 were inaccurately considered intact throughout follow-up. Again, any impact of such exposure misclassification would likely be non-differential, thus contributing to a conservative assessment of the link between circumcision and ASD risk. The observed 80–83% increase in ASD risk among 0- to 4-year-old circumcised boys is therefore unlikely to be an overestimate.

Limitations with respect to the outcome variables (ASD, hyperactivity disorder and asthma) also need consideration. To the extent outcomes were inaccurately or incompletely recorded in the national health registers, we might have missed some true cases, or wrongly included some irrelevant cases, as outcomes in the cohort. If outcomes were differentially under- or over-ascertained among either circumcised or intact boys within strata of cultural background, we cannot exclude the possibility of spurious results. However, we can think of no plausible mechanism through which culturally comparable boys with ASD, hyperactivity disorder or asthma would be systematically less or more likely to have their diagnoses recorded, or recorded correctly, in a manner depending on their foreskin status. Consequently, we consider potential under- or over-ascertainment problems for the outcomes likely to be non-differential, which tend to produce unaffected or conservative HR estimates. Reassuringly, 486 out of 499 ASD diagnoses (97%) in children born 1990–1999 and recorded in the Danish Psychiatric Central Register, the source of psychiatric data in the National Patient Register, were confirmed upon medical chart review.[42]

We lacked information about ASD and hyperkinetic disorder in the first year of life among cohort members born in 1994, because psychiatric data were only included in the National Patient Register from January 1995. However, this is an entirely theoretical concern, because the youngest case of ASD among the 57 circumcised boys with ASD was diagnosed at age 16 months, and hyperkinetic disorder is not a disease of infants either.

The way we dealt with cultural factors also needs comment. Most ritual circumcisions were in boys from Muslim families. To reduce any possible influence of cultural factors unrelated to the practice of ritual circumcision, we stratified all analyses on cultural background, using an algorithm capturing cohort members with at least one parent or grandparent born in a predominantly Muslim country. This algorithm categorised 7.8% of children in our cohort as having a likely Muslim cultural background. Applying the same algorithm to the entire Danish population on 1 January 2013, we identified a total of 243,175 Danish citizens (4.4%) as having a likely Muslim cultural background, which is in excellent agreement with the estimate of approximately 240,000 Danish Muslims calculated in a recent report by the Pew Research Center.[36] Therefore, it is likely that our cultural background variable categorised most children with a Muslim family background correctly, except those exceedingly few children whose Danish-born parents converted to Islam. Consequently, by stratifying on cultural background, we controlled for unmeasured cultural factors that might otherwise have produced spurious associations between circumcision and the outcomes studied.

An additional attempt was made to examine for possible unmeasured family factors that might explain the observed excess of ASD in circumcised boys. We studied ASD risk in sisters of boys undergoing ritual circumcision, assuming that any circumcision-unrelated family factor, whether cultural or genetic, would be equally associated with ASD risk in boys and girls. ASD risk was inconspicuous in sisters of ritually circumcised boys, suggesting that family factors other than circumcision *per se* would not explain the observed link with ASD risk in boys.

While no firm conclusions should be drawn at this point, several lines of evidence are compatible with a possible causal role of circumcision trauma in some cases of ASD. Recently, a strong positive correlation was reported between rates of infant male circumcision and ASD prevalence, with high rates of ASD in circumcising nations such as the United States and considerably lower rates in non-circumcising countries of Western Europe.[31] If circumcision-related pain and discomfort are sufficiently traumatic in some boys to be causally involved, then one would expect a lower average age at onset of ASD in countries with widespread neonatal circumcision than in countries where this practice is rare. In a study from the United Kingdom where infant circumcision is uncommon the estimated mean age at ASD diagnosis was 66 months.[43] This is considerably older than the corresponding average age of 39 months in Israel where most boys are circumcised on the eighth day according to Jewish tradition.[44]

Recently, a hypothesis linking prolonged paracetamol exposure *in utero* and early life to an increased risk of ASD development has received some attention.[45] So far, however, it has obtained only limited empirical support. The abovementioned study by Bauer and Kriebel, which demonstrated a strong, positive correlation between rates of neonatal circumcision and ASD, was actually carried out in an attempt to indirectly address the possible impact of paracetamol exposure in early life on ASD risk, under the questionable assumption that boys undergoing circumcision always receive paracetamol to curb the procedural or postoperative pain. Regardless of the authors' underlying thoughts, however, the study provided clear ecological support for a link between male circumcision in early life and ASD risk.[31] Unfortunately, we had no data available on analgesics or possible local anaesthetics used during ritual circumcisions in our cohort, so we were unable to address the paracetamol hypothesis directly.

A number of studies have linked obstetrical hazards to increased risk of ASD.[46] Based on national register data, our findings support the likely role of such early traumatic life experiences on ASD risk. Specifically, in univariate analyses, we observed increased rates of ASD in children with low birth weight, those born before 37 weeks of gestation, those with low Apgar scores, and those born by caesarean section, all of which are associated with elevated levels of neonatal stress. Of note, however, the robustness analysis with the most parsimonious statistical model that left all birth and perinatal characteristics out of the equation, produced HRs similar to those of the main model. The observed association of foreskin status with ASD risk therefore appears to be independent of already established birth and perinatal risk factors for ASD.

Possible mechanisms linking early life pain and stress to an increased risk of neurodevelopmental, behavioral or psychological problems later in life remain incompletely conceptualised. Circumcision was found in one preliminary report to be associated with increased risk of alexithymia in adult men,[47] a personality construct with reduced ability to identify and describe feelings,[48] and our findings suggest that circumcision may somehow trigger the development of ASD in a small fraction of young boys. These findings obviously do not prove the suggested associations. However, in combination with recent animal studies showing lifelong deficits in stress responses following exposure to just one single neonatal insult,[25] the observed strong correlation between circumcision and ASD prevalence,[31] and clinical observations of long-term changes in pain perception in circumcised infants,[4] our population-based findings should prompt other researchers to examine the possibility that circumcision trauma in infancy or early childhood might carry an increased risk of serious, yet hitherto unappreciated negative neurodevelopmental and psychological consequences.

Declarations

Competing interests: 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.

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Ethical approval: Study approved by Danish Data Protection Agency (approval no. 2009-41-4154).

Guarantor: MF

Contributorship: 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.

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References

1. Levy DM. Psychic trauma of operations in children. *Am J Dis Child* 1945; 69: 7–25.
2. Anand KJ and Hickey PR. Pain and its effects in the human neonate and fetus. *N Engl J Med* 1987; 317: 1321–1329.
3. Kouider S, Stahlhut C, Gelskov SV, Barbosa LS, Dutat M, de Gardelle V, et al. A neural marker of perceptual consciousness in infants. *Science* 2013; 340: 376–380.
4. Taddio A, Katz J, Ilersich AL and Koren G. Effect of neonatal circumcision on pain response during subsequent routine vaccination. *Lancet* 1997; 349: 599–603.
5. Victoria NC, Inoue K, Young LJ and Murphy AZ. Long-term dysregulation of brain corticotrophin and glucocorticoid receptors and stress reactivity by single early-life pain experience in male and female rats. *Psychoneuroendocrinology* 2013; 38: 3015–3028.
6. Sullivan MC, Msall ME and Miller RJ. 17-year outcome of preterm infants with diverse neonatal morbidities: part 1 – impact on physical, neurological, and psychological health status. *J Spec Pediatr Nurs* 2012; 17: 226–241.
7. Howard CR, Howard FM, Garfunkel LC, de Blieck EA and Weitzman M. Neonatal circumcision and pain relief: current training practices. *Pediatrics* 1998; 101: 423–428.
8. Lander J, Brady-Fryer B, Metcalfe JB, Nazarali S and Muttitt S. Comparison of ring block, dorsal penile nerve block, and topical anesthesia for neonatal circumcision: a randomized controlled trial. *JAMA* 1997; 278: 2157–2162.
9. American Academy of Pediatrics Task force on circumcision. Technical report: male circumcision. *Pediatrics* 2012; 130: e756–e785.
10. Paix BR and Peterson SE. Circumcision of neonates and children without appropriate anaesthesia is unacceptable practice. *Anaesth Intensive Care* 2012; 40: 511–516.
11. Howard CR, Howard FM, Fortune K, Generelli P, Zolnoun D, tenHoopen C, et al. A randomized, controlled trial of a eutectic mixture of local anesthetic cream (lidocaine and prilocaine) versus penile nerve block for pain relief during circumcision. *Am J Obstet Gynecol* 1999; 181: 1506–1511.
12. Butler-O'Hara M, LeMoine C and Guillet R. Analgesia for neonatal circumcision: a randomized controlled trial of EMLA cream versus dorsal penile nerve block. *Pediatrics* 1998; 101: E5.
13. Ng WT, Ng TK, Tse S, Keung WC and Wing LH. The use of topical lidocaine/prilocaine cream prior to childhood circumcision under local anesthesia. *Ambul Surg* 2001; 9: 9–12.
14. Irwin MG and Cheng W. Comparison of subcutaneous ring block of the penis with caudal epidural block for post-circumcision analgesia in children. *Anaesth Intensive Care* 1996; 24: 365–367.
15. Freeman JJ, Spencer AU, Drongowski RA, Vandeven CJ, Apgar B and Teitelbaum DH. Newborn circumcision outcomes: are parents satisfied with the results? *Pediatr Surg Int* 2014; 30: 333–338.
16. Gairdner D. The fate of the foreskin: a study of circumcision. *Br Med J* 1949; 2: 1433–1437.
17. Brady-Fryer B, Wiebe N and Lander JA. Pain relief for neonatal circumcision. *Cochr Datab Syst Rev* 2004; 4: CD004217.
18. Fletcher AB. Pain in the neonate. *N Engl J Med* 1987; 317: 1347–1348.
19. Franck LS. A new method to quantitatively describe pain behavior in infants. *Nurs Res* 1986; 35: 28–31.
20. Dixon S, Snyder J, Holve R and Bromberger P. Behavioral effects of circumcision with and without anesthesia. *J Dev Behav Pediatr* 1984; 5: 246–250.
21. Marshall RE, Porter FL, Rogers AG, Moore J, Anderson B and Boxerman SB. Circumcision: II. Effects upon mother-infant interaction. *Early Hum Dev* 1982; 7: 367–374.
22. Midmer DK. Pain perception in the neonate. *Can Fam Phys* 1989; 35: 1049–1054.
23. Williamson PS and Evans ND. Neonatal cortisol response to circumcision with anesthesia. *Clin Pediatr (Philadelphia)* 1986; 25: 412–415.

24. Fergusson DM, Boden JM and Horwood LJ. Neonatal circumcision: effects on breastfeeding and outcomes associated with breastfeeding. *J Paed Child Health* 2008; 44: 44–49.
25. Victoria NC, Inoue K, Young LJ and Murphy AZ. A single neonatal injury induces life-long deficits in response to stress. *Dev Neurosci* 2013; 35: 326–337.
26. Beggs S, Currie G, Salter MW, Fitzgerald M and Walker SM. Priming of adult pain responses by neonatal pain experience: maintenance by central neuroimmune activity. *Brain* 2012; 135: 404–417.
27. Hermann C, Hohmeister J, Demirakca S, Zohsel K and Flor H. Long-term alteration of pain sensitivity in school-aged children with early pain experiences. *Pain* 2006; 125: 278–285.
28. Walker SM, Franck LS, Fitzgerald M, Myles J, Stocks J and Marlow N. Long-term impact of neonatal intensive care and surgery on somatosensory perception in children born extremely preterm. *Pain* 2009; 141: 79–87.
29. Rattaz C, Dubois A, Michelon C, Viellard M, Poinso F and Baghdadli A. How do children with autism spectrum disorders express pain? A comparison with developmentally delayed and typically developing children. *Pain* 2013; 154: 2007–2013.
30. Lai MC, Lombardo MV and Baron-Cohen S. Autism. *Lancet* 2014; 383: 896–910.
31. Bauer AZ and Kriebel D. Prenatal and perinatal analgesic exposure and autism: an ecological link. *Environ Health* 2013; 12: 41.
32. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011; 39: 22–25.
33. Lynge E, Sandegaard JL and Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011; 39: 30–33.
34. Andersen JS, Olivarius NF and Krasnik A. The Danish National Health Service Register. *Scand J Public Health* 2011; 39: 34–37.
35. Danish National Board of Health. *Omskæring af Drenge [Report: Circumcision of Boys]*. See http://sundhedsstyrelsen.dk/publ/Publ2013/06jun/OmskaeringDrenge.pdf, 2013 (last checked 17 December 2014).
36. Pew Research Center Forum on Religion & Public Life. *The Future of the Global Muslim Population. Projections for 2010–2030. Pew Templeton Global Religious Futures Project*. See http://www.pewforum.org/files/2011/01/FutureGlobalMuslimPopulation-WebPDF-Feb10.pdf, 2011 (last checked 17 December 2014).
37. Mosaisk Troessamfund. *The Jewish Community in Denmark*. See http://www.mosaiske.dk/english/jewish-community-denmark, 2013 (last checked 17 December 2014).
38. Knudsen LB and Olsen J. The Danish Medical Birth Registry. *Dan Med Bull* 1998; 45: 320–323.
39. Cox DR. Partial likelihood. *Biometrika* 1975; 62: 269–276.
40. Lin DY, Wei LJ and Ying Z. Checking the Cox model with cumulative sums of martingale-based residuals. *Biometrika* 1993; 80: 557–572.
41. Frank L. Epidemiology. When an entire country is a cohort. *Science* 2000; 287: 2398–2399.
42. Lauritsen MB, Jørgensen M, Madsen KM, Lemcke S, Toft S, Grove J, et al. Validity of childhood autism in the Danish Psychiatric Central Register: findings from a cohort sample born 1990–1999. *J Autism Dev Disord* 2010; 40: 139–148.
43. Powell JE, Edwards A, Edwards M, Pandit BS, Sungum-Paliwal SR and Whitehouse W. Changes in the incidence of childhood autism and other autistic spectrum disorders in preschool children from two areas of the West Midlands, UK. *Dev Med Child Neurol* 2000; 42: 624–628.
44. Senecky Y, Chodick G, Diamond G, Lobel D, Drachman R and Inbar D. Time trends in reported autistic spectrum disorders in Israel, 1972–2004. *Isr Med Assoc J* 2009; 11: 30–33.
45. Becker KG and Schultz ST. Similarities in features of autism and asthma and a possible link to acetaminophen use. *Med Hypotheses* 2010; 74: 7–11.
46. Gardener H, Spiegelman D and Buka SL. Perinatal and neonatal risk factors for autism: a comprehensive meta-analysis. *Pediatrics* 2011; 128: 344–355.
47. Bollinger D and Van Howe RS. Alexithymia and circumcision trauma: a preliminary investigation. *Int J Mens Health* 2011; 10: 184–195.
48. Karukivi M, Hautala L, Kaleva O, Haapasalo-Pesu KM, Liuksila PR, Joukamaa M, et al. Alexithymia is associated with anxiety among adolescents. *J Affect Dis* 2010; 125: 383–387.