Sex ratio at birth following prenatal maternal exposure to severe life events: a population-based cohort study

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BACKGROUND: A reduction in the sex ratio at birth has been linked to maternal condition during and before pregnancy. A recent study reported an association between maternal exposure to severe life events and sex ratio at birth using the Danish national register. We attempted to replicate that study using a new Danish cohort.

METHODS: Mothers of all singleton live births (n = 1.35 million births) in Denmark, between 1 January 1980 and 31 December 2002, were linked to data on their children and partners. The old cohort consisted of babies born between 1980 and 1992 (n = 699 362), whereas the new cohort consisted of babies born between 1993 and 2002 (n = 633 451). We defined exposure as death or serious illness in older children and partners in the first trimester or in the 6 months before conception. Sex ratio at birth was defined as the proportion of male live births.

RESULTS: During the study period, there were 1 349 099 singleton live births (692 870 boys and 656 229 girls). The sex ratio at birth in the new cohort was 0.5134. In the new cohort, prenatal exposure to severe life events was not associated with a reduction in the sex ratio at birth [relative risk = 1.00 (95% confidence interval: 0.95–1.05)].

CONCLUSIONS: In the new cohort, we did not find strong evidence that, in a stable western population, prenatal exposure to severe life events is associated with a reduction in the sex ratio at birth.

Key words: epidemiology / pregnancy / sex ratio

Introduction

In a homogeneous, stable human population, the sex ratio at birth, or the secondary sex ratio (defined as number of males divided by the number of females), is commonly found to be around 1.05; or 105 boys born for every 100 girls. It varies between, and within, populations over time (Ansari-Lari and Saadat, 2002) and is susceptible to a number of influences and, as such, may act as an indicator of maternal (parental) condition in a population. For example, a reduced sex ratio has been reported with parents who smoke (Fukuda et al., 2002), who have maternal metabolic disorder, e.g. diabetes (James, 1998), with aged mothers (Orvos et al., 2001) or aged fathers (Jacobsen et al., 1999). Previous studies have also reported reduced male births with periconceptional exposure to war (Ansari-Lari and Saadat, 2002), smog (Lyster, 1965), 11th September attacks (Catalano et al., 2005a), severe life events (Hansen et al., 1999), psychological distress (Obel et al., 2007) and earthquakes (Fukuda et al., 1998). However, not all studies have supported these findings (Stein et al., 2004; Polasek et al., 2005). In stressed populations, poor maternal condition (Cagnacci et al., 2004) and paternal stress may decrease the sex ratio at birth through a reduction of female embryogenic loss (Boklage, 2005), a reduction of male conceptions through reduced semen quality (Fukuda et al., 1996) or an increase in male fetal loss (Catalano et al., 2006).

Hansen et al. (1999) reported a significant decrease in the sex ratio of the offspring of mothers who were exposed to person-level stress
in the form of death or serious illness in older children and/or partners during the first trimester, or up to 17 months before conception. The authors utilized the Danish National Registers and included all singleton births in Denmark from 1 January 1980 until 31 December 1992. We decided to replicate the study with an extra decade of data (1993–2002). We hypothesized that maternal exposure to severe life events before conception or during the first trimester of pregnancy would reduce the sex ratio at birth, i.e. decrease the proportion of male births.

**Methods**

We identified all mothers who delivered singleton live babies, with known gestational age in Denmark between 1 January 1980 and 31 December 2002 using the Danish Medical Birth Register (Knudsen and Olsen, 1998). The mothers were linked to their partners and older children using the personal identification number; partner was defined as the legal father of the child. Partners and older children were linked to the Civil Registration System (Pedersen et al., 2006) and National Hospital Register (Anderson et al., 1999) to identify if and when they died or were diagnosed (first diagnosis only) with cancer (ICD-8 codes 140–207 and ICD-10 C00–C97) or acute myocardial infarction (ICD-8 410 and ICD-10 I21, I22). Offspring were excluded from the data analyses if their mothers had no links to their partners.

The date of first exposure was defined as the date of death or the first hospital admission among children or partner leading to illness diagnosis. Date of conception (the first day of last menstrual period) was identified using the date of birth and gestational duration. The date of first exposure was categorized by timing: up to 6 months before conception and first trimester (0–12 weeks). If more than one event occurred during the same pregnancy, priority was given to the earliest event.

Sex ratio at birth was defined as the proportion of male live births. Logistic binomial regression in Stata software was used to estimate the relative risk (RR) of male birth in relation to exposure. Analyses were carried out for the whole cohort and for the old cohort (1980–1992) and new cohort (1993–2002) separately. We fitted a statistical interaction to test whether the effect of severe life events on the sex ratio was statistically different in the old and new cohorts. To look for further time trends, further analyses were performed by dividing the whole cohort into eight separate smaller cohorts. All models were adjusted for parity (five categories), maternal age and paternal age (six categories: <20, 20–25, 26–29, 30–34, 35–39 and >40 years) and year of birth (1 year categories). A RR >1.0 indicates an increase in the sex ratio, whereas an RR <1.0 indicates a decrease in the sex ratio.

The Danish Data Protection Agency and the Danish National Board of Health gave permission to conduct this study.

**Results**

The initial cohort consisted of mothers of 1 349 099 (692 870 boys and 656 229 girls) singleton, live births with known gestational age. A total of 11 745 (0.87%) offspring were excluded from the data analyses due to missing links to their fathers. The final cohort consisted of mothers of 1 337 354 offspring (686 804 boys and 650 550 girls). There were 701 981 births in the old cohort (1980–1992) and 635 373 in the new cohort (1993–2002). The observed sex ratio was 0.5136 during 1980–2002, 0.5137 in the old cohort and 0.5134 in the new cohort. Mothers of 4059 babies were exposed to death or serious illness in children or spouses in the 6 months before conception or during the first trimester (2397 in the old cohort and 1662 in the new cohort) (Table I). The exposed mothers were older and had higher parity.

The sex ratio in the offspring of exposed mothers declined to 0.4974 compared with 0.5136 in the unexposed giving an adjusted RR of 0.97 [95% confidence interval (CI): 0.94–1.00], which was not significant at the 5% level; P = 0.05 (Table I). Furthermore, there was no statistically significant reduction in the 6 months before conception or during the first trimester. When we divided the cohort into two periods, 1980–1992 and 1993–2002, the results showed that the sex ratio declined significantly to 0.4869 in the exposed offspring during the first period 1980–1992 [adjusted RR = 0.95 (95% CI: 0.91–0.99)]. In the offspring of mothers exposed during the first trimester, the sex ratio declined to 0.4365 [adjusted RR = 0.85 (95% CI: 0.74–0.98)].

In the old cohort (1980–1992), the sex ratio in the exposed population was 0.5126 [adjusted RR = 1.00 (95% CI: 0.95–1.05)] and exposure in the first trimester was associated with a non-significant increased sex ratio of 0.5366 [adjusted RR = 1.04 (95% CI: 0.93–1.17)]. A statistical interaction term between the exposure variable and a variable that represented the old and new cohorts was added to the model in order to test whether the effect of exposure on sex ratio in the two cohorts was significantly different. The interaction term showed that the effect of exposure in the first trimester during the 1980–1992 period was significantly different compared with the effect in the 1993–2002 period (P = 0.026). We also examined the effect of exposure to events in each relative separately (partner or child) and in general the results were similar. The lowest sex ratio was in relation to severe life events during the first trimester in partners (sex ratio = 0.4309) and older children (sex ratio = 0.4444) in the 1980–1992 cohort.

We explored the results further by dividing the cohort into 3-year periods and analyzed each cohort separately (the last cohort included births in 2 years only). There was no consistent pattern beyond the earlier observed difference. Maternal exposure to severe life events in the 6 months before conception was associated with a statistically significant decrease in the sex ratio in the first period [adjusted RR = 0.90 (95% CI: 0.82–0.99)] (1980–1982), third [adjusted RR = 0.89 (95% CI: 0.81–0.98)] (1986–1988) and fifth [adjusted RR = 0.88 (95% CI: 0.80–0.97)] (1992–1994) cohorts but not the others. There was also a significant decrease in the sex ratio of offspring of women exposed to severe life events in the first trimester in the second [adjusted RR = 0.62 (95% CI: 0.42–0.94)] (1983–1985) cohort.

**Discussion**

We found little evidence for an association between the secondary sex ratio and maternal exposure to severe life events during the first trimester or in the 6 months before pregnancy in a 23-year Danish population cohort. The sex ratio was reduced in relation to maternal exposure to severe life events, mainly in the first trimester, but not significantly. We were able to replicate the findings from the previous study, but these associations could not be extended to the new cohort.

There were some differences between the present study and that of Hansen et al. Hansen et al. (1999) excluded all children who had
We used a conservative definition of stress, restricted to life events before conception and they adjusted for more potential confounders. We limited the definition of partner to legal fathers, whereas their definition included legal fathers and cohabiting partners. However, we were able to identify 99.13% of the legal fathers. Despite these minor differences between the two studies, our estimates were virtually identical to those reported by Hansen et al. when using the same cohort (1980–1992). At first sight, the estimates reported by Hansen et al. for the 1980–1992 period appear to be slightly smaller than the present results for the same period (0.91 versus 0.95). This difference was due to their use of the odds ratio (OR) to summarize effect size rather than RRs, which is more appropriate in a study where the outcome of interest (male birth) is very common, because in this case, the OR exaggerates the RR (Greenland, 1979). In fact, calculating the unadjusted RR of male births from their data showed that the RR is 0.956 (95% CI: 0.92–0.99), which is the same as the unadjusted RR in the present study 0.954 (95% CI: 0.91–0.99).

Another difference between the two studies was that they adjusted for more variables than the current study. However, the unadjusted OR from Hansen et al.’s data was 0.915 (95% CI: 0.85–0.99), which is identical to the adjusted OR that they reported. This suggests that there was no imbalance in confounders between the exposed and unexposed groups and therefore no actual confounding in the unadjusted result. Given that we studied the same population a decade later, it seems likely that this is true in our study also and therefore we judge our adjustments to be adequate.

We used a conservative definition of stress, restricted to life events that were both severe and objectively measurable for two reasons. First, we wished to secure a robust definition of our prenatal maternal stress exposure and secondly, because it was the same definition used by Hansen et al. Although it is true that in some cases bereavement is not a severely stressful event, in most cases we would argue that it does represent a good proxy variable for psychological stress, especially if the death is of a child or partner. Less catastrophic and more common events (such as work related and financial problems) may also cause stress but would make clear and well timed definition of exposure more difficult. It may be that our comparison is effectively between high and low stress groups.

The difference we observed in the sex ratio between the two time periods could in part be explained by the economic recession in Denmark between early 1980s and early 1990s (Mortensen et al., 2008). Recent research linked unemployment, which is common in recession times, with higher risk of male fetal loss and consequently a reduction in the sex ratio (Catalano et al., 2005b). Van den Berg et al. (2009) suggested that economic recession causes hardship and stress; they reported a higher rate of mortality among individuals born in Denmark in recession time and that those who survive until age 35 live, on average, 10 months less than those born in better conditions (Van den Berg et al., 2009). In the present study, economic recession in Denmark was not associated with a reduced sex ratio in the old cohort (the sex ratio in the old cohort was 0.5137). However, it is possible that severe life events acted synergistically with the economic recession to reduce the sex ratio in the exposed mothers in the old cohort.

The sex ratio at birth may be less sensitive to maternal stress in healthy stable populations such as the Danish population. Observations in non-human primate populations suggest that there is an adaptive variation in secondary sex ratio according to maternal condition or stress, but that this may only be observed in populations in poor general health with high selective pressure (Clutton-Brock and Iason, 1986; Kruuk et al., 1999). Finally, it is possible that the significant findings reported by Hansen et al., despite their statistical

<table>
<thead>
<tr>
<th>Exposure and period of cohort</th>
<th>Number of births</th>
<th>Boys (%)</th>
<th>Unadjusted sex risk ratio (95% CI)</th>
<th>Adjusted* sex risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980–2002 cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexposed</td>
<td>1 333 295</td>
<td>0.5136</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>Exposed in any exposure period</td>
<td>4059</td>
<td>0.4974</td>
<td>0.97 (0.94–0.999)</td>
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<tr>
<td>Exposed before conception</td>
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<td>0.4990</td>
<td>0.97 (0.94–1.004)</td>
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<td>Exposed first trimester</td>
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<td>0.4859</td>
<td>0.95 (0.86–1.04)</td>
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<tr>
<td>1980–1992 cohort</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>699 584</td>
<td>0.5138</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>Exposed in any exposure period</td>
<td>2397</td>
<td>0.4869</td>
<td>0.95 (0.91–0.99)</td>
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<tr>
<td>Exposed before conception</td>
<td>2145</td>
<td>0.4928</td>
<td>0.96 (0.92–1.001)</td>
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<td>0.4365</td>
<td>0.85 (0.74–0.98)</td>
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<td>1993–2002 cohort</td>
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<tr>
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<td>0.5134</td>
<td>1.00</td>
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<tr>
<td>Exposed in any exposure period</td>
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<td>Exposed first trimester</td>
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<td>0.5366</td>
<td>1.04 (0.93–1.17)</td>
<td>1.04 (0.93–1.17)</td>
</tr>
</tbody>
</table>

*Adjusted for maternal age, paternal age, year of birth and parity.
significance, were due to random fluctuations: we would expect 1 in 20 tests of a null hypothesis to give a statistically significant result; hence the need for repeat studies.

**Funding**

This study was funded by Tommy’s the Baby Charity and the Stanley Medical Research Institute.

**References**


Submitted on February 11, 2009; resubmitted on March 10, 2009; accepted on March 16, 2009.