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Acute undernutrition is not associated with excess of females at birth in humans: the Dutch Hunger Winter

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It has been suggested that maternal undernutrition results in adjustment of the sex ratio at birth, favouring females. We tested this hypothesis using births during the Dutch Hunger Winter of 1944–1945, an acute severe famine of seven months' duration. There was no evidence of an excess of female births among deliveries of human infants exposed to famine in any period in gestation. Indeed, among deliveries to women maximally exposed to famine prior to conception, there was an excess (odds ratio = 1.31, 95% CI 1.09–1.58; $p = 0.004$) of male offspring. Our data do not provide any support for acute and severe maternal undernutrition as a trigger for an increase in female conceptions or in male foetal deaths in human populations.

Keywords: famine; sex ratio; humans; gestation

1. INTRODUCTION

In most human populations there is a slight excess of males at birth. Facultative sex-ratio adjustment (alteration of the male-to-female ratio at birth in response to changes in the environment) has been clearly demonstrated in animal models (Huck *et al.* 1988; Meikle & Thornton 1995; Greeff & Ferguson 1999; Kruuk *et al.* 1999). The evolutionary rationale for this adjustment is conjectured to reflect the extra effort required to raise a male relative to a female (Trivers & Willard 1973), but the physiological mechanisms by which this facultative selection arises are unknown (Williams 1979; Brown & Silk 2002).

In humans, the male : female ratio appears to be declining in some, but not all developed countries in the period since World War II (Jongbloet *et al.* 2001), and the role of environmental pollutants in this trend is hotly debated (Lummaa *et al.* 1998; Vartiainen *et al.* 1999), as are the relative importance of other factors such as polygyny, the age and condition of the mother, household wealth and frequency of coitus (Gaulin & Robbins 1991; Lindström & Kokko 1998; Gutierrez-Adan *et al.* 2000; Koziel & Ulijaszek 2001). War induces a relative excess of male births (Graffelman & Hoekstra 2000); in both Germany (in World Wars I and II) and The Netherlands (in World War II, but not in World War I when The Netherlands was neutral), the proportion of males at birth was elevated (Bromen & Jockel 1997; Van den Broek 1997).

Although intriguing, such data do not provide clear directions towards the clarification of mechanisms because the precise exposure to famine is not well defined. Maternal nutritional status at the time of conception might play a role (Williams & Gloster 1992; Andersson & Bergstrom 1998). Gibson & Mace (2003) recently reported that better nutritional status of non-pregnant women, as measured by arm-muscle area (AMA), was strongly associated with a higher probability of the most recent live birth being male in Ethiopia, but that study was limited by a small sample size (a subsequent analysis of a national sample in Ethiopia (Stein *et al.* 2003) failed to replicate the findings) and the possibility of reverse causality.

For the sex ratio at birth to be related to the nutritional status of the mother, there has to be either selective fertilization of the ovum or selective attrition of the conceptus. Cross-sectional studies of the offspring sex ratio at birth are unable to differentiate between these potential mechanisms, and hence it is not known whether either or both mechanisms operate, particularly in situations where nutritional status changes markedly over short periods. We used the unique circumstances of the Dutch Famine of 1944–1945 to test whether acute and severe undernutrition at defined periods before and during pregnancy cause variation in the sex ratio of the offspring.

2. MATERIAL AND METHODS

During the winter of 1944–1945, the urban centres of the western Netherlands experienced an acute famine as a result of a German embargo on rail transport and a particularly severe winter that led to freezing of the canals. Food rations, which had been stable at *ca.* 1800 kcal per person over the duration of the war, rapidly deteriorated in quantity and quality, and were less than 1000 kcal per person for seven months (figure 1). The famine ended with the Allied liberation of The Netherlands and massive distribution of food relief. The famine affected several indices of reproduction. It is estimated that 50% of women of reproductive age experienced amenorrhoea at the height of the famine (Burger *et al.* 1948) and fertility dropped dramatically (Stein *et al.* 1975), more strongly among the working classes who, one presumes, had fewer resources with which to purchase any limited additional food available. We have previously demonstrated that women who were pregnant when the famine commenced experienced weight loss over the course of their pregnancy (Stein *et al.* 1995), and their offspring experienced a mean reduction of *ca.* 300 g in birth weight relative to pre-famine levels (Lumey *et al.* 1993; see also Smith 1947; Sindram 1953), while gestational length was not markedly affected (Stein *et al.* 1975).

We abstracted birth records from three birthing institutions in the western Netherlands, all in urban areas affected by the famine. The two largest, in Amsterdam and Rotterdam, were midwifery training schools that admitted only low-risk pregnancies, and predominantly those of poorer women who lacked resources at home for a safe delivery. The third institution served poorer women and some better-off women who experienced emergencies during delivery. The three institutions continued to operate throughout the period, and the selection mix did not change markedly during the famine.

Based on weekly rations, using an approach described elsewhere (Lumey & Stein 1997), we defined births between 1 February and 30 June 1945 as exposed late in pregnancy, births from 1 May through 30 September 1945 as exposed in mid-pregnancy, and births from 1 August through 31 December 1945 as exposed early in pregnancy. Additionally, we considered the period from 1 November 1945 through 31 March 1946 to represent births occurring to mothers who were themselves undernourished at conception, even though the pregnancy might have been carried during a period of adequate food availability. Births in 1943 and in 1947 were considered unexposed. Thus, we are able to test the specific additional effect of nutritional stress on the mother, over and above any general effect that the continued war had caused. We compared the proportion of males in each exposure period with the proportion of males born in 1943 and 1947 using standard χ^2 approaches, and adjusted the coefficients for possible differences in maternal age at delivery

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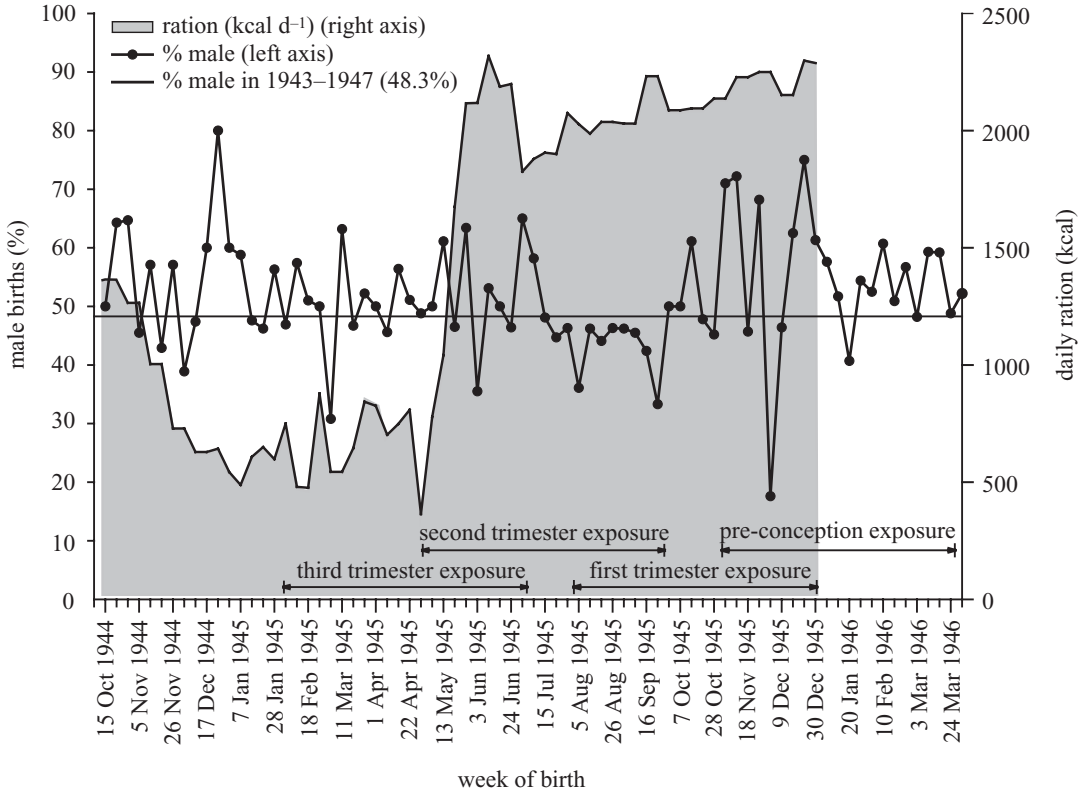

Figure 1. Rations distributed and percentage of male births at three birthing facilities in the western Netherlands, 1944–1946.

through binomial logistic regression. We hypothesized that the proportion of females would be elevated among births to women exposed in late gestation if acute famine resulted in selective miscarriage of male foetuses, and that the proportion of females would be elevated among births exposed at conception if acute famine resulted in lower conception and/or implantation rates for male embryos. Significance was declared at $p < 0.05$.

3. RESULTS

In the control periods (1943 and 1947), the proportions of births that were male were 47.4% and 49.2%, respectively ($p > 0.5$ by χ^2-test). Figure 1 depicts the percentage of male births in each week for the period from October 1944 through March 1946. Although there is clearly inter-weekly variation, as might be expected given the relatively small sample sizes (range of 10–57 deliveries per week), there is no evidence (table 1) of any systematic shift in sex ratios according to trimester of exposure to famine, except among births to women subject to famine exposure prior to conception, among whom the overall M : F ratio was elevated (odds ratio: 1.31, 95% CI: 1.09–1.48; $p = 0.004$). Adjustment for maternal age did not affect these findings.

4. DISCUSSION

Our data do not support the hypothesis that male foetuses are less likely to be conceived or to be successfully implanted or are at higher risk of attrition *in utero* as a consequence of variation in maternal nutrition. We used a well-described ecological measure of nutrition previously shown to be strongly related to changes in fecundability (Stein *et al.* 1975), maternal anthropometry (Stein *et al.* 1995) and foetal nutrition as measured by size at birth (Smith 1947; Sindram 1953).

For maternal nutrition to cause variation in the sex ratio at birth, one needs to postulate one of two mechanisms. First, there may be selective conception and/or implantation by sex. For facultative adjustment to be operating, such an effect should be maximally expressed if the woman is undernourished at the time of conception—if anything, we observed an excess of male births to women who were exposed maximally to famine immediately prior to conception. Second, it is possible that selective attrition of the foetus might occur. This may occur if undernutrition occurs while the woman is pregnant or may be 'programmed' by maternal nutritional status at or near conception. One study in Bangladesh has suggested that maternal nutrition impacts on the risk of miscarriage (Pebley *et al.* 1985), but a second, case-controlled study conducted in New York City was unable to replicate those findings (Stein & Kline 1991). In the present study we did not observe any effect of famine in mid or late gestation on the sex ratio. Furthermore, for attrition to be selective by foetal sex in the absence of a change in sex ratios at birth, there would have needed to be an excess of conceptions of females in the months prior to the onset of the famine. We consider this implausible, and it is discordant with other studies of the sex ratio during wartime, which suggest small excesses of males at birth.

Our data are based on births in three facilities in the western Netherlands, in a period in which only 10% of all Dutch births were delivered in institutions. The service provided by these institutions was maintained throughout the famine, and there is no evidence suggesting that the mix of patients changed markedly. While we have no data on miscarriages, we find it implausible, in a period before reliable methods were available for determining the sex of the foetus, that our birth series would be biased by the

Table 1. Association between exposure to famine at specified periods of gestation and the sex ratio at birth, among births in three institutions in the western Netherlands, 1943–1947.
(Note: second trimester exposure partly overlaps with both first and third trimester exposure. Peri-conceptional exposure partly overlaps with first trimester exposure. CI, confidence interval; reference, reference group.)

				unadjusted		age adjusted	
period of exposure	number of births	male (%)	sex ratio (M : F)	odds ratio	95% CI	odds ratio	95% CI
third trimeste (1 February to 30 June 1945)	906	50.6	1.024	1.03	0.97–1.10	1.03	0.97–1.09
second trimester (1 May to 30 September 1945)	872	48.6	0.946	1.01	0.92–1.10	1.01	0.91–1.10
first trimester (1 August to 31 December 1945)	652	49.5	0.980	1.05	0.86–1.29	1.04	0.85–1.27
peri-conceptional (1 November 1945 to 31 March 1946)	930	55.1	1.225	1.31	1.09–1.58	1.29	1.07–1.55
unexposed (1943 and 1947)	890	48.3	0.934	(reference)		(reference)	

foetal sex towards a selective admission for institutional delivery.

One must consider other methodological differences between our study and that of Gibson & Mace (2003). Our study is based on a larger sample size; their study included the most recent birth to only 324 women. Their study, in fact, does not measure the association between nutritional status in pregnancy and the sex of the offspring, as nutritional status was not measured prior to or during gestation, but at an interview of non-pregnant women during which previous pregnancy outcomes were ascertained. Indeed, a possible interpretation of their findings is that raising a male imposes a lower burden on the mother, as those who had given birth most recently to a boy had increased AMA and body mass index. Finally, their study reflects a state of chronic undernutrition not experienced by the women in The Netherlands, who were adequately (although clearly less generously than women in The Netherlands today) nourished until the onset of the famine. It is possible that the effects of chronic undernutrition differ from those of acute undernutrition.

In conclusion, we found no evidence that acute undernutrition in the context of adequate chronic nutritional status leads to facultative adjustments in favour of births to females in humans.

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