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Intrauterine famine exposure and body proportions at birth: the Dutch Hunger Winter

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Background Fetal programming of adult disease may be a long-term effect of fetal nutrition. Expected short-term effects include changes in body size and proportions at birth. The specific responses of fetal growth to acute undernutrition at varying points in pregnancy are still unclear.

Methods We abstracted all birth records of infants born in two midwife training schools in the western Netherlands between 1 October 1944 and 31 March 1946, and compared infants whose mothers were exposed to the Dutch famine of 1944–1945 during specific trimesters of pregnancy with control infants born in 1943. We considered birthweight (BWT), crown-to-heel length (CHL), head circumference (HC), and ratio and regression-adjusted measures of these parameters.

Results BWT, CHL, and HC declined with famine exposure late in pregnancy. Changes in WT for CHL paralleled changes in WT alone in size and direction. Results for HC were inconsistent, varying by choice of body size adjustor (WT or CHL), and by method of adjustment (ratio or regression). BWT, CHL, and HC did not change with first trimester famine exposure.

Conclusion Even under famine conditions, birth size and body proportions vary only with late pregnancy exposure. HC for body size has the added disadvantage that late pregnancy exposure effects vary drastically with choice of measure. We do not recommend the use of birth size or body proportions as a proxy for fetal nutritional status in the study of adult disease.

Keywords Birth size, body proportions, famine, The Netherlands, newborn, pregnancy

Fetal programming of adult disease may be a long-term effect of fetal nutrition in gestation.[1] The most widely available indicator of nutrition at birth is birthweight, but weight clearly provides only a limited perspective on fetal growth in the preceding 9 months.[2] Measures of length and proportionality (Table 1) might provide additional information, and have been examined, with conflicting results.[3–5] The use and interpretation of birth size and proportion in relation to fetal programming assumes that birth size and proportion indeed reflect specific fetal responses to specific variations in maternal nutritional status. For example, it has been suggested that under adverse nutritional conditions, fetuses maintain head size at the expense of body size ('head sparing') and that this has specific implications for adult disease risk.[6] We here provide empirical data on the relation between prenatal undernutrition at defined periods of gestation and birth size and body proportions, comparing births of mothers exposed to the Dutch famine of 1944–1945 with unexposed controls, born in 1943.

Methods

Study population

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 which led to freezing of the canals. Food rations, which had been stable at ~1800 kcal/person over the duration of the war, rapidly deteriorated in quantity and quality, and were below 1000 kcal/person for 7 months. The famine ended abruptly with the Allied liberation of The Netherlands and massive distribution of food relief. It is estimated that 50% of women of reproductive age experienced amenorrhoea at the height of the famine.[7] Fertility dropped dramatically,[8] more strongly among the working classes who, one presumes, had fewer resources with which to purchase any limited additional

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Table 1 Selected measures of body proportions at birth examined for their association with chronic disease later in life

Measure	Comments
Direct measures	
Weight	Most widely available routinely obtained measure; aggregate measure of growth in fetal life
Length (crown to heel)	Routinely recorded in many settings
Head circumference	Not routinely recorded in many settings; presumed to reflect brain growth in fetal life
Abdominal circumference	Rarely recorded in routine settings; presumed to reflect visceral tissue development in fetal life, predominantly liver
Placental weight or diameter	Recorded in some settings; presumed to reflect fetal nutrient and oxygen supply
Ratio measures	
Head circumference/weight	Presumed to reflect head sparing
Head circumference/length	Length/head circumference has also been reported
Length/abdominal circumference	Rarely available
Weight/length	Presumed to reflect a failure to deposit fat late in gestation
Ponderal index (kg/m^3)	$m/kg^{1/3}$ has also been reported
Placental weight (or diameter)/ birth weight	Presumed to reflect the relation between fetal demand and maternal supply

food available. We have previously demonstrated that women pregnant when the famine started experienced weight loss over the course of their pregnancies,[9] and that their offspring experienced a mean reduction of ~300 g in birthweight (BWT),[10–12] while gestational length was not markedly affected.[8]

We abstracted BWT, crown-to-heel length (CHL), and head circumference (HC) on singleton live births from birth records maintained at two midwife training schools in the western Netherlands, both in urban areas affected by the famine. All available records between 1 October 1944 and 31 March 1946 were abstracted, as well as a systematic sample of approximately 15 records per month per institution from 1943. (Stein *et al.*,[8] in their previous examination of this issue, had abstracted a 50% sample of birth records from one of these institutions, with a slightly different coverage period.) Based on weekly rations, using an approach described elsewhere,[13] we defined births between 1 February and 30 June 1945 as third trimester exposed, births between 1 May and 30 September 1945 as second trimester exposed, and births between 1 August and 31 December 1945 as first trimester exposed. Births between 1 November 1945 and 31 March 1946, to mothers maximally exposed to famine prior to conception, were defined as peri-conceptional exposed. There is a partial overlap between exposure in the third and second trimesters, between exposure in the second and first trimesters, and between exposure in the peri-conceptional period and the first trimester. Births in 1943 were considered unexposed.

Analytical methods

Statistical results are presented for the 1826 births between 1 October 1944 and 31 March 1946 (783 in Amsterdam, 1043 in Rotterdam) with BWT, CHL, and HC. We computed the BWT/CHL, HC/CHL, and HC/BWT ratios. We also adjusted BWT for CHL, HC for CHL, and HC for BWT using a regression approach, with the adjusted value being the residual from linear regression models run on site-specific reference groups of births in 1943. This method yields an adjusted value uncorrelated with body size. All measures were converted to Z-scores with respect to the site-specific reference group; thus the reference group always has mean = 0 and SD = 1. Trimester-specific famine effects on the direct measures, ratios, and regression residuals were tested for significance against the 1943 birth data with t-tests.

Results

For the period 1 October 1944 through 31 March 1946 plus 1943, BWT was available for 2353 births, of whom 2312 (98.3%) had CHL and 1840 (78.2%) had HC. Missing HC data appeared to result from two distinct processes. Periods of complete absence of HC data were interspersed within otherwise near-complete data. Specifically, no HC data were available for Amsterdam between 1 February and 20 March 1945, between 22 October and 31 December 1945, between 18 and 30 January 1946, between 5 and 15 March 1946, and between 1 and 4 January 1943. There were no analogous gaps in data collection in Rotterdam. Outside these periods, HC was sporadically missing in Amsterdam and Rotterdam, HC being 97.8% complete in Amsterdam and 81.6% complete in Rotterdam. The proportion of records obtained from Amsterdam varied between 40.2% for peri-conceptional exposure to 52.5% for second trimester exposed. BWT, CHL, and HC were comparable between sites, within exposure groups, with the following exceptions: BWT in first and second trimester exposure groups (difference 133 g; 95% CI: 29, 243 g; $P = 0.013$ and 99 g (95% CI: 21, 177 g; $P = 0.013$, respectively) and CHL in the peri-conceptional exposure group (−0.58 cm; 95% CI: −0.99, −0.16 cm; $P = 0.006$)(Table 2).

BWT, CHL, and HC decreased following third trimester exposure (Table 3). The magnitude of the maximal decline was consistent across the three measures, centering at approximately 0.6 SD for third trimester exposure. The decrease in BWT, CHL, and HC immediately followed the decline in rations (Figure 1). Recovery was also rapid, BWT reaching pre-famine levels within weeks of the end of the famine.

Third trimester exposure effects on BWT were consistent regardless of whether BWT was expressed as direct measure, as a ratio measure (BWT/CHL) or as a residual after regression on CHL (Table 3), although the magnitude of the decline was less marked when the residual method was used. Results for HC adjusted for birth size were inconsistent, depending on choice of body size adjustor, BWT, or CHL, and method of adjustment (Table 3).

Second trimester exposure effects on BWT, direct measure, ratio measure, and residual measure, were similar to third trimester effects, but roughly half as big (0.3 SD). The second trimester decline in CHL was no longer significant. As with third trimester exposure, HC results varied by choice of

Table 2 Size at birth according to exposure to famine in specific trimesters among births in midwife training schools in Amsterdam and Rotterdam, 1943–1946

	Reference births 1943		**Third trimester births 1 February 1945–30 June 1945**		**Second trimester births 1 May 1945–30 September 1945**		**First trimester births 1 August 1945–31 December 1945**		**Peri-conceptional births 1 November 1945–31 March 1946**	
	Amsterdam $n = 161$ Mean (SD)	Rotterdam $n = 163$ Mean (SD)	Amsterdam $n = 236$ Mean (SD)	Rotterdam $n = 299$ Mean (SD)	Amsterdam $n = 304$ Mean (SD)	Rotterdam $n = 275$ Mean (SD)	Amsterdam $n = 135$ Mean (SD)	Rotterdam $n = 173$ Mean (SD)	Amsterdam $n = 183$ Mean (SD)	Rotterdam $n = 268$ Mean (SD)
Birthweight (g)	3383 (462)	3461 (466)	3098 (442)	3148(443)	3231 (473)	3329 (485)*	3359 (448)	3495 (492)*	3408 (451)	3461 (532)
Length (cm)	50.8 (1.8)	50.6 (1.8)	49.8 (2.0)	49.9 (2.3)	50.4 (2.2)	50.6 (2.3)	50.8 (2.1)	50.4 (2.2)	50.8 (1.9)	50.3 (2.4)**
Head circumference (cm)	35.5 (1.7)	35.5 (1.8)	34.5 (1.6)	34.5 (1.7)	35.0 (1.6)	35.1 (1.7)	35.4 (1.6)	35.5 (1.7)	35.3 (1.6)	35.3 (2.1)

Systematic sample of ~15 births/month at each institution in reference period, all births during famine.

Famine exposure defined as a mean ration <1000 kcal/day over the trimester.

Period of second trimester exposure overlaps with both first and third trimester exposure; period of peri-conceptional exposure overlaps with 1st trimester exposure.

* $P < 0.05$; ** $P < 0.01$ by t-test.

Table 3 Change in z-score of selected measures of size at birth following exposure to famine during specific trimesters of pregnancy, relative to births in the same hospitals without exposure to famine in gestation. Births in midwife training schools in Amsterdam and Rotterdam, 1943–1946

	Third trimester versus reference Mean (95% CI)	Second trimester versus reference Mean (95% CI)	First trimester versus reference Mean (95% CI)	Peri-conceptional versus reference Mean (95% CI)
Direct measures				
Birthweight	−0.65 (−0.78, −0.51)	−0.31 (−0.45, −0.17)	0.02 (−0.14, 0.18)	0.02 (−0.13, 0.17)
Length	−0.46 (−0.61, −0.30)	−0.13 (−0.29, 0.03)	−0.04 (−0.21, 0.13)	−0.11 (−0.27, 0.05)
Head circumference	−0.59 (−0.73, −0.46)	−0.26 (−0.39, −0.13)	−0.04 (−0.19, 0.12)	−0.13 (−0.28, 0.02)
Ratio measures				
Birthweight/length	−0.64 (−0.77, −0.50)	−0.33 (−0.47, −0.19)	0.03 (−0.12, 0.18)	0.05 (−0.09, 0.20)
Head circumference/length	−0.26 (−0.41, −0.11)	−0.16 (−0.30, −0.01)	0.00 (−0.17, 0.17)	−0.05 (−0.21, 0.10)
Head circumference/birthweight	0.54 (0.39, 0.69)	0.27 (0.12, 0.41)	−0.02 (−0.18, 0.15)	−0.05 (−0.20, 0.11)
Residual measures				
Birthweight predicted from length	−0.45 (−0.59, −0.32)	−0.30 (−0.43, −0.16)	0.05 (−0.10, 0.21)	0.13 (−0.02, 0.27)
Head circumference predicted from length	−0.43 (−0.57, −0.29)	−0.22 (−0.36, −0.08)	−0.03 (−0.19, 0.13)	−0.10 (−0.25, 0.05)
Head circumference predicted from birthweight	−0.28 (−0.42, −0.14)	−0.11 (−0.24, 0.03)	−0.06 (−0.22, 0.11)	−0.17 (−0.33, 0.02)

All measures expressed as z-scores, calculated with respect to 1943 births, using city-specific means and SDs. Residuals based on city-specific 1943 regressions. Period of second trimester exposure overlaps both first and third trimester exposure; period of peri-conceptional exposure overlaps with 1st trimester exposure.

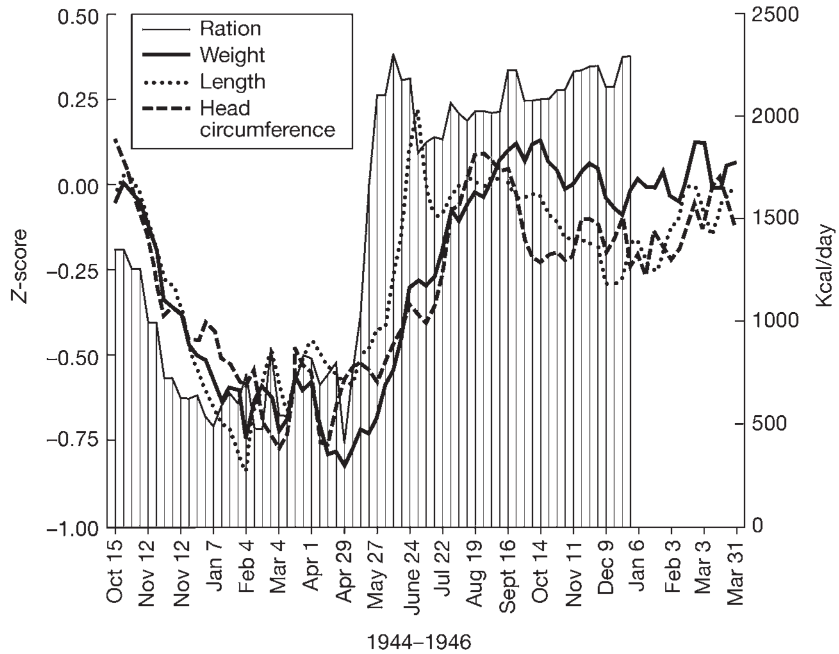

Figure 1 Weekly caloric rations and averages of z-scored linear measures of weight, length, and head circumference at birth, for births in two institutions in the Western Netherlands, 1944–1946. Moving averages across individual births were used to smooth the plots. The reference population (births in 1943) has a mean Z-score of 0.

measure; most decreasing, some increasing, some remaining stable in comparison with 1943 births.

First trimester famine exposure was not associated with changes in BWT, CHL, or HC. There was possibly a very small (0.1 SD) decrease in CHL and HC with peri-conceptional famine exposure.

Discussion

Our study extends previous work on linear size at birth among populations exposed to the Dutch famine,[14] and provides additional new information on body proportion parameters. Our study includes the largest series available to date of HC and is the first to systematically evaluate the effect of acute severe famine on head size in relation to other body measures at birth. As has been demonstrated before in studies of the Dutch Famine,[8–12] our data indicate that BWT is a sensitive and consistent indicator of third trimester famine exposure, but is not affected by undernutrition confined to early exposures.

Earlier reports did not systematically assess quantitative changes in body proportions. Our results show that inferences about the effect of famine on 'body proportions' depend on the choice of proportionality measure. For instance, second trimester exposure to famine may suggest 'head-sparing' if HC is adjusted for body size using BWT in the ratio method. Adjustment by BWT with the regression method yields a small, non-significant decline in HC. Adjustment by CHL, with either the ratio or regression method also results in declines in HC. Ratios are not recommended as a means of 'controlling for' the denominator.[15] In our data, BWT and HC/BWT are correlated ($r = -0.91$) and HC and HC/BWT are correlated ($r = -0.26$). Consequently, HC/BWT behaves as the reciprocal of BWT. We therefore do not interpret the third and second trimester exposed increases in the HC/BWT ratio as evidence for 'head sparing'.

The very small decline in CHL and HC after peri-conceptional famine exposure may be of interest. We observed a decline in CHL among women born at the same time in the Wilhemina Gasthuis, Amsterdam.[9] Recent work in sheep models has suggested that acute undernutrition in the period immediately preceding conception can trigger preterm delivery.[16] While it is tempting to ascribe the human findings to the same phenomenon, we caution that the observed effect size is small and that the estimation of gestational age is especially problematic among this group, who were conceived at a time when amenorrhoea was widely prevalent.[7]

Many indices of body size at birth are unavailable except under special circumstances (e.g. the birth series reported by Yajnik *et al*.[5]). Our results are based on routinely collected data, albeit obtained under the stressful circumstances of war. It is possible that BWT was measured more accurately than either CHL or HC. It has been suggested that routine measures of CHL are unreliable.[17] This is likely to be less of a concern in the institutions from which we obtained our data. Both were training centres for midwives, whose instructors would presumably insist on high degrees of consistency. At any rate, estimates of famine exposure effects would be reduced to the extent that an 'assumed', rather than actual, size was recorded.

We conclude that third trimester famine exposure depresses BWT, CHL, and HC, with a weaker and less-consistent pattern after second trimester exposure; that there are no discernible effects from first trimester exposure and only a hint of an effect after peri-conceptional exposure. Changes in BWT persisted after adjustment for CHL. Changes in HC became inconsistent after adjustment for body size, depending on both choice of body size adjustor and method of adjustment. We do not recommend the use of the HC:BWT ratio, as it is entirely driven by changes in BWT.

Even under famine conditions, birth size and body proportions vary only with late pregnancy exposure. HC for body size has the added disadvantage that late pregnancy exposure effects vary drastically with choice of measure. We do not recommend the use of birth size or body proportions as a proxy for fetal nutritional status in the study of adult disease.

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KEY MESSAGES

- Late pregnancy famine exposure is associated with reductions in weight, length, and head circumference at birth. First trimester famine exposure is not.
- Changes in weight, length, and head circumference result in changes in body proportion.
- Changes in weight for length parallel changes in weight alone in both size and direction. Changes in head circumference for body size are inconsistent, varying with choice of body size adjustor (weight or length), and with method of adjustment (ratio or regression).

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