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The 2D:4D digit ratio is not a useful marker for prenatal famine exposure: Evidence from the Dutch Hunger Winter Families Study

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Abstract

Objectives—Digit lengths, and in particular the ratio of the 2nd (2D) to 4th (4D) digit (2D:4D), are stable in adulthood and have been linked to characteristics thought to have developmental origins, but little research has focused on early life determinants of these measures. We examined whether exposure to acute famine during specific periods of gestation was associated with 2D, 4D or the 2D:4D ratio.

Methods—We studied men and women (1) born in one of three hospitals in western Netherlands whose mothers were exposed to a limited period of famine immediately prior to or during the pregnancy (n=337); (2) born in the same hospitals to mothers not exposed to famine during the pregnancy (n=271) or same-sex siblings of individuals in groups 1 and 2 (n=295). We measured 2D and 4D on both hands using calipers and computed the 2D:4D ratio.

Results—Mean 2D and 4D lengths were 73.5 (SD 5.1) and 75.0 (5.4) mm respectively. The 2D:4D ratio was 0.981 (SD 0.030). Both 2D and 4D were associated with male gender and height (all $p<0.001$), and weakly with BMI. The 2D:4D ratio was 0.0070 (95% confidence interval 0.0017, 0.0123) lower among males as compared to females, and was not significantly associated with height (0.0002 per cm; 95% -0.0001, 0.0005). The 2D:4D ratio was not significantly associated with exposure to famine, overall (−0.0010, 95% CI 0.0030, 0.0050) or within any period of gestation.

Conclusions—The 2D:4D ratio is not significantly affected by prenatal exposure to famine and therefore is not a useful marker for generalized prenatal undernutrition.

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Keywords

Digit ratio (2D:4D); Netherlands; famine; epidemiology

Introduction

The ratio of the lengths of the second (index, 2D) digit to the fourth (ring, 4D) digit (2D:4D) is a sexually dimorphic trait, being lower in males than in females (Phelps, 1952; Manning, 2008). Sex-related differences in the 2D:4D ratio have been observed in fetuses (Garn et al, 1975) and in neonates and young children (McIntyre et al., 2005). The 2D:4D exhibits rank-order stability over childhood and little variation with age during adulthood (Manning 1998), and hence might constitute a stable marker over the life course of early-life exposures (Voracek and Loibl, 2009). The 2D:4D ratio is thought to result from the fetal testosterone surge during weeks 10–14 of gestation that causes sexual differentiation (Manning 2002). The 2D:4D ratio has been related to traits presumed to relate to testosterone level, such as adiposity (Fink et al., 2003), athleticism (Pokrywka et al., 2005), success in the stock market (Coates et al., 2009) – and even fecundity (Manning, 2002) and sexual orientation (Hall and Schaef, 2008).

Few studies have attempted to identify environmental factors that might affect the 2D:4D ratio. One study related the 2D:4D ratio at birth to elevated placental weight and shortened crown-to-heel length (Ronalds et al., 2002), but that study did not identify common early-gestational determinants. In a recent review, Voracek et al (2008) highlighted the lack of research on perinatal influences on the digit ratio.

We have previously shown that the fingertip ridge count, similarly fixed by mid-gestation (Babler 1991), is affected both by seasonal factors at the time of conception and by exposure to acute severe undernutrition at the time of conception (Kahn et al., 2008). If the 2D:4D ratio can be shown to be related to specific fetal exposures, it too might serve as a stable proxy for gestational exposures that might then be assessed at any stage over the life-course. We are aware of no studies that relate specific periconceptional or gestational exposures to the resulting 2D:4D ratio. Hence, its susceptibility to modification by environmental and other features of the pregnancy is unknown. We therefore assessed whether the 2D:4D ratio was related to maternal nutritional status, as measured using exposure to famine immediately prior or during the pregnancy, in a cohort of men and women born during and immediately after the Dutch famine of 1944–5.

Methods

Setting

The Dutch famine of 1944–45, which affected the western Netherlands, provides a rare opportunity to study the long term consequences of maternal undernutrition in defined stages of gestation (Stein et al., 1975; Lumey and van Poppel, 1994). Official rations, which by the end of the famine consisted almost exclusively of bread and potatoes, fell below 900 kcal per day by November 26, 1944, and were as low as 500 kcal per day by April 1945. The famine ceased immediately following liberation. This extraordinary period of deprivation affected fertility, weight gain during pregnancy and infant size at birth (Stein et al., 1975). The reduction in fertility was greater among manual compared to the non-manual occupational classes (Stein et al., 1975). The decline in mean birth weight of 300 g was restricted to exposure to maternal undernutrition during the third trimester (Smith, 1947; Stein et al., 1975; Stein et al., 2004b). Long term consequences of gestational exposure to famine have been reported for adiposity (Ravelli et al., 1976; Ravelli et al., 1999; Stein et al., 2007), blood pressure (Roseboom et al., 2001; Stein et al., 2006), and serum lipids (Roseboom et al., 2000; Lumey et al., 2009). It has also been suggested that women (but not men) exposed to famine early in gestation have enhanced reproductive fitness (Painter et al., 2008).

Population source and tracing

We identified 3307 live-born singleton births at three institutions in famine-exposed cities (the midwifery training schools in Amsterdam and Rotterdam and the university hospital in Leiden) (Lumey at al., 2007). We selected all 2417 births between February 1, 1945 and March 31, 1946 (infants whose mothers were exposed to the famine during or immediately preceding that pregnancy) and a sample of 890 births from 1943 and 1947 as hospital time controls (infants whose mothers did not experience famine immediately before or during this pregnancy). The sample of births in 1943 and 1947 included an equal number of births for each month, allocated across the three institutions according to their size.

Names and addresses at birth for these 3307 infants were provided to the Population Register in the municipality of birth with a request for tracing to their current address. 308 (9%) were reported to have died in the Netherlands and 275 (8%) to have emigrated. The Population Registry in Rotterdam declined to trace 130 individuals born out of wedlock and for 294 subjects (9%) a current address could not be located. Address information was obtained for 2300 individuals (70% of the birth series). The proportion of individuals identified as deceased was highest among births in 1943 (10.4%) and lowest among births in 1947 (6.0%). Other reasons for a failure to locate a current address differed little by year of birth or period of exposure to famine. Participants traced to a current address were similar to those who had died, emigrated, or had not been located with respect to birth weight, or length, placental weight, maternal age at delivery, and birth order (Lumey et al., 2007).

A letter of invitation signed by the current director of the institution in which they were born was sent to these 2300 individuals, together with a brochure describing the study and a response card. We mailed one reminder letter to non-responders. Initially, our study design called for the recruitment of same-sex sibling pairs only, and the lack of an available sibling was a reason for ineligibility. We received some reply to 58% of the initial letters and to 44% of the reminder letters; 347 individuals (20% of 1767 respondents) expressed willingness to participate together with a sibling. None of the siblings was included in the hospital birth series. Among the 1415 who responded but declined, 951 (67%) reported not having a same-sex sibling available for study. To increase the number of study subjects, we recontacted these 951 individuals, 381 of whom expressed willingness to participate. A higher positive response to our letters from women compared to men (36% vs. 29% overall) was consistent across all exposure categories.

We conducted telephone interviews, followed by a clinical examination at the Leiden University Medical Center. The standardized telephone interview (n=1031 completed; 718 from the birth series and 313 siblings) took approximately one hour. The clinical examination took approximately four hours (n=971 completed; 658 from the birth series and 313 siblings). All study protocols were approved by the Human Subjects Committees of all participating institutions. Study participants provided oral consent at the start of the telephone interview and written informed consent at the start of the clinical examination. All data were collected between 2003 and 2005.

Among the 2300 persons who were invited to join the study, we found no significant differences between those interviewed to those who were not in mean birth weight or length, placental weight, maternal age at delivery, or birth order (Lumey et al., 2004). Response to our invitation, however, was lower for those born in 1947 (25%) compared to all others

(35%). Eleven percent of those who were interviewed lived within 5 km of the examination site, versus 10% of those who were not interviewed, and 34% of those interviewed lived more than 45 km from the examination site versus 29% of those who were not interviewed.

Measurement of digit lengths

All examiners were research nurses and were trained for this study by one of us (HSK). Examiners measured 2D and 4D of both hands using a sliding caliper (VWR model 3415, West Chester PA) that was calibrated daily. Briefly, after removing rings and washing the hands, the study participant sat across a table from the examiner with the right elbow resting on the tabletop and the right palm facing upwards at about 45 degrees. The examiner identified the finger's basal crease as the major crease at the base of the digit that is proximal (nearest) to the palm. The participant was asked to extend the second finger to its full length. The fixed jaw of the caliper was placed on the on the mid-point of the basal crease. The sliding jaw of the caliper was extended past the end of the finger, then retracted until it lay gently at the midline distal tip of the fingertip skin and the digital readout was recorded to the nearest 0.01 mm. The measurement was then repeated for the fourth finger on the same hand, after which both fingers were measured again using the same protocol. After measuring 2D and 4D on the right hand, the protocol was repeated for the left hand. After collecting all 4 finger lengths in duplicate, finger(s) for which the measurements were discrepant by > 1.00 mm were measured two more times. For each finger we calculated the average of the measurements obtained, and we calculated the 2D:4D ratio as 2D divided by 4D.

We assessed handedness based on the response to three questions regarding preference for writing, dealing cards, and opening a bottle. Each question had a 1–3 response (left=1, either=2, right=3). We summed the responses, and categorized individuals scoring 7 or more as right handed, those scoring 6 points as ambidextrous, and those scoring 3–5 points as left handed.

Other variables

Information on schooling, smoking and alcohol intake were obtained by interview.

Anthropometric measures (height, weight, sitting height, and the waist, hip, supine sagittal abdominal diameter (SAD) and mid-thigh circumferences (MTC)) were obtained in duplicate during the clinic visit using standard protocols (Stein et al., 2007). We computed the body mass index (BMI; kg/m^2) as an overall measure of adiposity, the ratio of leg length to trunk length as a measure of linear proportionality, and the waist-hip ratio (WHR) and the ratio of the SAD to the MTC as measures of body fat distribution.

Exposure to famine

We used the date of last menstrual period (LMP) as noted in the hospital records to define the start of gestation unless it was missing or implausible. In those cases we inferred the LMP date from annotations on the birth record (e.g., a notation of 'term birth') or estimated gestational age from birth weight and date of birth, using cut-points from tables of gender-, parity- and birth weight-specific gestational ages from the combined birth records of the Amsterdam midwives school (1948–1957) and the University of Amsterdam Obstetrics Department (1931–1965) (Kloosterman, 1970). For each infant the most consistent and plausible estimate of gestation was selected and used together with date of birth to infer the LMP date.

We characterized exposure to famine during gestation by determining the gestational ages (in weeks after the LMP) during which the mother was exposed to an official ration of <900 kcal per day, namely between November 26, 1944, and May 12, 1945. We considered the mother exposed in gestational weeks 1–10, 11–20, 21–30, or 31-delivery if these gestational time windows were entirely included in this period. Thus, pregnancies with LMP's between November 26, 1944, and March, 4, 1945, were exposed in weeks 1–10; between September 18, 1944 and December 24, 1944 in weeks 11–20; between July 10, 1944, and October 15, 1944, in weeks 21–30; and between May 2, 1944 and August 24, 1944, in weeks 31 through delivery. By these definitions, a participant could have been exposed to famine during at most two adjacent 10-week periods. Individuals exposed in at least one of the 10-week periods were considered to have had any gestational famine exposure. Individuals with LMP between February 3, 1945 and May 11, 1945 were considered to have had peri-conceptional exposure as their mother had been exposed to famine for at least 10 weeks immediately prior to the estimated date of conception.

Statistical methods

We computed means and distributions, as appropriate. We computed the differences and correlations among 2D, 4D and the 2D:4D ratio between hands, and between members of the sibling pairs. We assessed the association of 2D, 4D and the 2D:4D ratio with handedness using analysis of variance.

We computed mean 2D and 4D as the average of the respective values across hands; where data for one hand was missing, we used the value for the other hand. We assessed the association of mean 2D, 4D and the 2D:4D ratio with gender and anthropometric measures using analysis of variance and correlation methods.

We assessed the differences in mean digit lengths attributable to exposure to famine using linear regression. In models focusing on any exposure to famine, the variables 'maternal exposure to famine prior to conception' and 'exposure to famine during any 10-week period of gestation' were entered simultaneously. In models focusing on exposure in defined periods, all four 10-week periods were entered as a set together with the term for exposure prior to conception and the overall significance of the set was tested using a 5 degree of freedom Wald Chi-square test. We examined additive interactions with gender. As there was no evidence of heterogeneity by gender (as defined by a p-value <0.05 for the interaction term) we present gender-pooled results throughout. We controlled for age at assessment (linear and squared terms), gender and the examiner in all models.

All statistical analyses were conducted with Stata software version 8.0 (Stata Inc, College Station TX). The two populations of controls were combined into a single reference group. We controlled for clustering at the family level using the cluster( ) option within Stata, which computes robust estimates using the Huber-White estimator. We report estimates and associated 95 percent confidence intervals. Statistical significance was declared at $p<0.05$.

Results

The 2D:4D ratio was available for 963 respondents. Digit length measures were obtained by a total of 12 examiners. Six examiners obtained measures on 1–3 subjects each, while the remaining six examiners obtained measures on 41 – 241 subjects each. We excluded data from 70 respondents because the examiner conducted 3 or fewer assessments (n=10) or the examiner reported one or more problems (contractures, calluses, etc.,) in obtaining the measure (n=60). Among the 893 remaining subjects (402 males, 491 females), the mean difference between the first and last measure ranged from −0.04 mm (D2 of the right hand) to 0.02 mm (D4 of the left hand) (all $p>0.05$ by t-test). Averaged across all examiners, the technical error of measurement (TEM), computed according to Voracek et al (2007), ranged from 0.62% of mean digit length (D4, right hand) to 0.72% D2, left hand). The examiners differed ($p<0.01$ by analysis of variance) in their TEM (range across examiners and digits 0.47% – 1.08%) and in their estimation of digit lengths (means across examiners: D2 72.2 – 74.4 mm; D4 72.7 – 76.3 mm, D2:D4 0.973 – 0.994; all $p<0.01$ by one-way analysis of variance). We therefore adjusted for examiner in all regression models. There were few differences in the characteristics of the study population across exposure groups (Table 1); the differences in birth weight and current body mass index have been reported previously (Lumey et al., 2007; Stein et al., 2007). 9.2 percent of respondents were left handed and 3.8 percent were ambidextrous. We combined these two groups for analysis.

2D and 4D lengths did not differ by hand (2D mean difference 0.09 mm, SD 1.68 mm; 4D mean difference 0.01 mm, SD 1.66 mm). Mean 2D and 4D lengths were 73.5 (SD 5.1) and 75.0 (5.4) mm respectively, and 2D and 4D were associated with gender and height (all $p<0.001$), and weakly with the body mass index even after adjusting for gender and height (Table 2).

The correlations between left and right hands within the whole sample of 893 individuals were 0.95 for 2D and 4D and 0.61 for the 2D:4D ratio; correlations within 274 sibling pairs were 0.60 for 2D, 0.58 for 4D and 0.27 for the 2D:4D ratio (all $p<0.001$).

The 2D:4D ratio was 0.981 (SD 0.030) and also did not differ by hand (mean difference 0.0009, SD 0.0292). The 2D:4D ratio was 0.0073 (95% CI 0.0028, 0.0129) lower among males than females, and was not associated with height (0.0002 per cm; 95% -0.0001, 0.0005) in sex-adjusted models (Table 2). In models controlling for gender and height, the 2D:4D ratio was positively associated with body mass index and with the ratio of leg length to trunk length. A test for heterogeneity by gender was not significant for any model.

In our basic specification, maternal exposure to famine prior to conception was not significantly associated with either 2D or 4D, whether exposure was considered as reflecting any period of exposure to famine (table 3) or when periods of potential exposure were considered individually (Table 4). We also considered models with additional adjustment for adult height. In these models, exposure to famine during weeks 11–20 of gestation was associated with 0.84 (95% CI 0.09, 1.58; $p=0.027$) mm longer 2D; no other period of famine exposure was associated with either digit length.

The 2D:4D ratio was not significantly associated with exposure to famine, whether considered as any exposure 0.0010, 95% confidence interval −0.0030, 0.0050; table 3) or as exposure during specific periods of gestation ($p>0.9$ for a 5-degree of freedom Wald test; table 4). Adjustment for adult height did not alter the estimates.

Discussion

We measured digit lengths using calipers in a large sample of men and women whose mothers had experienced marked exposure to famine in the period immediately prior to or during gestation. We did not observe any association between exposure to famine and either 2D or 4D lengths or the 2D:4D ratio.

The 2D:4D ratio is presumed to originate from the testosterone surge that accompanies sexual differentiation (Manning 2002). Consistent sex differences in the 2D:4D ratio have been demonstrated from early childhood through early adulthood in both cross-sectional (Manning et al., 1998) and longitudinal studies (McIntyre et al., 2005), and these differences persisted during the ages of puberty. Garn et al. studied sections from 56 human embryos and fetuses and found that the relative lengths of finger segments were unstable around gestational ages 10–13 weeks (the time window of transient fingertip volar pad development and distal elongation), but that the rankings and proportions of adult finger lengths were attained by about the 15th week of gestational age (Garn et al., 1975). Thus, despite the small number of fetuses examined in that study, it has been suggested that values of the 2D: 4D ratio observed in adulthood are likely to reflect digit-length ratios that were established before the middle of gestation (Manning 2002).

Unlike many studies of digit lengths, we used engineering calipers and trained measurers. Other common approaches include measurement of a palm-print (Ronalds et al., 2002) photocopies (Trivers et al., 2006; Coates et al., 2009) or x-rays (Paul et al., 2006), or self-measurement using a standard ruler (Manning and Peters, 2009). All measurements have their associated sources of error. The mean and variance of the 2D:4D ratio in our study was well within the general range seen in many other studies (reviewed in Manning (2002)). We did employ several examiners over the 2 years of field work, and the associated measurement error may have reduced study precision, but the TEM of our measures was <1.1% across all examiners.

As expected, the 2D:4D ratio was lower among males and both the 2D and 4D were strongly associated with gender and with height (even after adjusting for gender). Thus measurement error and the resulting attenuation of measures of association are unlikely to explain our null results for the 2D:4D ratio.

We observed that with additional adjustment for adult height the 2D was significantly longer in individuals exposed to famine in gestational weeks 11–20, with no evidence for heterogeneity by gender and no effect on the 2D:4D ratio. In our sample, while overall height was not related to exposure to famine, the ratio of the arm-to-leg length was somewhat elevated with exposure to famine in weeks 11–20 and 21–30 (Stein et al., 2007), and both 2D and 4D are related to the ratio of leg length to trunk length. The increase in 2D may reflect this overall change in body proportions.

One prior study identified two birth characteristics, namely an enlarged placenta and a shorter crown to heel length, as being positively associated with the 2D:4D ratio (Ronalds et al., 2002). While suggestive of common determinants, that study has not been replicated and may reflect chance associations. Furthermore, that study did not attempt to identify specific exposures that might explain the association, and we are not aware of any other studies that have attempted to identify prenatal determinants. Our own study, with its focus on a well-defined exposure, effectively rules out prenatal generalized undernutrition as a major determinant of the 2D:4D ratio, and hence of any phenotypic characteristics that share a developmental pathway with the 2D:4D ratio. In this light, a recent paper (de Rooij et al., 2009) that found no influence on sexual orientation among individuals exposed to the Dutch famine is confirmatory of the lack of a major effect of the Dutch famine (and by extension maternal undernutrition) on traits that may result from sexual differentiation.

We were unable to document any consistent heterogeneity by sex in the associations of D2, D4 or the 2D:4D ratio with maternal exposures. This is consistent with an overall null association of exposure to famine with the process of sexual differentiation. We have previously shown that the sex ratio at birth is not affected by famine exposure (Stein et al., 2004). Observations of heightened fertility among women conceived during the famine (Painter et al., 2008) may reflect a population-level measure of fertility given the widespread amenorrhea during the famine (Stein et al., 1975a), rather than a developmental response to the exposure.

In conclusion, we were unable to observe any association of the 2D:4D ratio with maternal exposure to famine during gestation. Taken together with a recent observation that the digit-length ratio is not a useful marker for individual quantitative differences in prenatal androgen exposure (Berenbaum 2009), and the limited potential for non-genetic factors to affect the ratio (Voracek and Dressler, 2009) we conclude that the 2D:4D ratio is not a useful marker for inferring generalized (macro- and micronutrient) gestational undernutrition.

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Table 1

Selected characteristics in 2003–2005 of Dutch individuals born in one of three hospitals in 1943–1947 and their siblings

	Males (n=402)				Females (N=491)			
	Hospital controls [a] (n=130)	Sibling controls (n=127)	Famine exposed [b] (n=145)		Hospital controls [a] (n=141)	Sibling controls (n=168)	Famine exposed [b] (n=182)	
	Mean ± SD or %	Mean ± SD or %	Mean ± SD or %	p- value [c]	Mean ± SD or %	Mean ± SD or %	Mean ± SD or %	p- value [c]
Birth weight (g)	3537 ± 447	n/a	3350 ± 486	<0.01	3376 ± 514	n/a	3253 ± 501	0.03
Age at assessment (years)	58.6 ± 1.5	57.2 ± 6.3	58.7 ± 0.4	<0.01	58.6 ± 1.6	57.0 ± 6.4	58.7 ± 0.4	<0.01
Completed secondary school (%)	79.2	81.9	76.6	0.55	66.7	58.9	55.5	0.12
Current smoker (%)	30.0	24.4	24.8	0.52	19.1	20.2	24.7	0.42
Regular alcohol consumption (%)	85.4	89.0	89.0	0.59	75.2	72.2	81.9	0.09
Height (cm)	178.2 ± 6.3	179.1 ± 5.9	177.4 ± 6.4	0.08	165.6 ± 6.4	166.6 ± 6.9	165 ±.4 6.7	0.25
Body mass index (kg/m^2)	27.9 ± 4.0	26.9 ± 3.3	28.1 ± 4.1	0.03	27.0 ± 4.6	27.0 ± 4.6	28.8 ± 5.6	<0.01
Length of second digit (left hand), mm	76.5 ± 4.1	77.5 ± 4.2	77.0 ± 4.4	0.21	70.6 ± 4.2	71.0 ± 4.3	70.6 ± 4.1	0.60
Length of second digit (right hand), mm	76.3 ± 4.1	77.0 ± 4.1	76.5 ± 4.3	0.32	70.7 ± 4.3	71.2 ± 4.5	70.8 ± 4.2	0.47
Length of fourth digit (left hand), mm	78.3 4 ±.7	79.0 ± 4.3	78.7 ± 4.3	0.52	71.8 ± 4.4	72.3 ± 4.4	71.8 ± 4.5	0.57
Length of fourth digit (right hand), mm	78.1 ± 4.7	78.8 ± 4.5	78.4 ± 4.2	0.54	71.9 ± 4.2	72.5 ± 4.8	72.0 ± 4.5	0.41
2D:4D ratio (left hand)	0.978 ± 0.033	0.982 ± 0.034	0.979 ± 0.033	0.62	0.983 ± 0.030	0.983 ± 0.028	0.985 ± 0.032	0.86
2D:4D ratio (right hand)	0.977 ± 0.036	0.979 ± 0.037	0.976 ± 0.033	0.75	0.983 ± 0.034	0.983 ± 0.035	0.984 ± 0.033	0.92
Wholly/predominantly right-handed (%)	82.9	86.6	83.5	0.68	94.3	88.6	86.8	0.08

[a] Born in the same institutions as exposed but not exposed to famine during gestation

[b] Mother was exposed to a daily ration of <900 kcal/day for at least 10 weeks during gestation

[c] By one-way analysis of variance or chi-square test (2 degrees of freedom), as appropriate.

[d] Not available for siblings

Table 2

Association of the lengths of the second (2D) and fourth (2D) digits and their ratio (2D:4D) with selected characteristics measured at follow-up, among 893 Dutch men and women assessed in 2003–05.

	2D (mm)	4D (mm)	2D:4D ratio
Gender [1] (male =1, female = 0)	1.59 (0.90, 2.28) *	2.16 (1.45, 2.86) *	−0.0070 (−0.0123, −0.0017) *
Height [2] (per cm)	0.36 (0.32, 0.39) *	0.35 (0.31, 0.39) *	0.0002 (−0.0001, 0.0005)
BMI [3] (per kg/m^2)	−0.023 (−0.071, 0.026)	−0.067 (−0.119, −0.015) *	0.0006 (0.0002, 0.0010) *
Ratio of leg length to trunk length [3]	6.50 (1.02, 11.98) *	9.81 (4.38, 15.23) *	−0.0402 (−0.0834, 0.0030)
Waist to hip ratio [3]	−0.50 (−4.94, 3.94)	−2.35 (−6.86, 2.16)	0.0242 (−0.0112, 0.0596)
Mid–thigh circumference [3] (per cm)	−0.041 (−0.088, −0.005) *	−0.073 (−0.121, −0.025) *	0.0004 (0.0001, 0.0008) *

Estimates are linear regression coefficients and associated 95 percent confidence intervals.

* $P<0.05$

[1] Adjusted for height, age, age squared, examiner and familial clustering.

[2] Adjusted for gender, age, age squared, examiner and familial clustering

[3] Adjusted for gender, height, age, age squared, examiner and familial clustering

Table 3

Association of digit lengths and the ratio of the second to fourth digits with exposure to the Dutch famine immediately preceding or during gestation, among 893 Dutch men and women assessed in 2003–05.

	Exposure immediately before conception	Exposure during gestation
2D (mm)	−0.61 (−1.46, 0.25)	−0.22 (−0.79, 0.35)
4D (mm)	−0.62 (−1.54, 0.31)	−0.30 (−0.90, 0.30)
2D:4D	−0.0001 (−0.0058, 0.0056)	0.0010 (−0.0030, 0.0050)

Estimates are linear regression coefficients and associated 95 percent confidence intervals.

Comparison group is combined hospital and sibling controls.

Models are adjusted for age, age squared, gender, examiner and familial clustering.

Table 4

Association of digit lengths and the ratio of the second to fourth digits with exposure to the Dutch famine immediately preceding or at specific periods during gestation, among 893 Dutch men and women assessed in 2003–05.

	Exposure immediately before conception	Exposure in gestational weeks 1–10	Exposure in gestational weeks 11–20	Exposure in gestational weeks 21–30	Exposure in gestational weeks 31- delivery	p-Value (Wald test, 5 degrees of freedom)
2D (mm)	−0.55 (−1.45, 0.34)	−0.38 (−1.49, 0.73)	0.37 (−0.54, 1.27)	−0.74 (−1.56, 0.07)	0.14 (−0.67, 0.95)	0.37
4D (mm)	−0.64 (−1.62, 0.32)	−0.13 (−1.28, 1.02)	0.16 (−0.73, 1.04)	−0.76 (−1.56, 0.05)	0.05 (−0.85, 0.95)	0.43
2D:4D ratio	0.0011 (−0.0050, 0.0072)	−0.0034 (−0.0107, 0.0039)	0.0025 (−0.0034, 0.0085)	0.0000 (−0.0058, 0.0059)	0.0016 (−0.0048, 0.0079)	0.91

Estimates are linear regression coefficients and associated 95 percent confidence intervals.

Comparison group is combined hospital and sibling controls.

Models are adjusted for age, age squared, gender, examiner and familial clustering.