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Male birthweight, semen quality and birth outcomes

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STUDY QUESTION: What are the relations among birthweight (BW), semen parameters and birth outcomes in a population-based sample?

SUMMARY ANSWER: BW is unrelated to semen parameters, which are in turn unrelated to birth outcomes.

WHAT IS KNOWN ALREADY: In clinical settings, there has been suggestion that semen parameters are related to BW when comparing fertile and infertile men; however, findings have been less clear in more general populations.

STUDY DESIGN, SIZE, DURATION: Questionnaire data and semen samples were collected at baseline from 427 male participants of the population-based Longitudinal Investigation of Fertility and the Environment (LIFE) prospective cohort study from 2005 to 2009, who were followed prospectively to assess pregnancy outcomes among 226 singleton births.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Men of at least 18 years of age who were married or in a committed relationship and trying to conceive were eligible for participation; physician-diagnosed infertility was an exclusion criterion. Participants were recruited from two geographic areas and semen samples were analyzed for 34 quality parameters categorized as general, motility, morphology, sperm head and sperm chromatin structure using methods including computer-aided semen analysis integrated visual optical system and sperm chromatin structure assay. Linear and mixed models were used for statistical analysis of the relations between men's BW, semen parameters, and BW, gestational age at delivery, birth length, head circumference and ponderal index of singleton births.

MAIN RESULTS AND THE ROLE OF CHANCE: No association was observed between male BW and semen parameters or birth outcomes. Few associations were observed between semen parameters and birth outcomes, and the observed statistically significant associations were isolated and without a consistent pattern that would suggest an association between BW and birth outcomes.

LIMITATIONS, REASONS FOR CAUTION: Men's BW was self-reported and may be subject to some imprecision. Semen analysis was performed the day after collection, an approach that impacts the assessment of motility and that may limit inference from our analyses of motility measures. In addition, inclusion criteria for selection into the cohort limits generalizability to generally healthy couples trying to conceive and without known subfertility.

WIDER IMPLICATIONS OF THE FINDINGS: Despite suggestions from prior studies of male *in utero* exposures impacting BW and male reproductive health, there appears to be little support for such relations in this generally healthy population.

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Introduction

Increasingly, interest has focused on the possibility that prenatal and preconception exposures may impact reproductive outcomes in later life. The longstanding developmental origins of adult health and disease hypothesis have received support from recent research of non-genetic influences on offspring, including epigenetic changes (Barouki et al., 2012; Juul et al., 2014). Data suggest an influence of the uterine environment on reproductive health in offspring, through various processes (Jensen et al., 2004; Ravnborg et al., 2011; Dupont et al., 2012). In animal studies, Sertoli cell development and, potentially, sperm production, are affected by maternal nutrition during pregnancy (Olsen et al., 2000; Genovese et al. 2010). Paternal lifestyle, behavior and environmental exposure may impact offspring as well (McPherson et al., 2014; Soubry et al., 2014). However, evidence from epidemiologic studies of peri-conceptional effects on offspring reproductive function is limited and equivocal (Power et al., 2003; Dupont et al., 2012).

Birthweight (BW) is an easily measurable variable that may reflect the influence of factors that impact fetal growth and development, and predict long-term health outcomes (Barker, 2004; Risnes et al., 2011). Evaluating relations of men's BW with measures of reproductive health in adulthood provides an approach to assess how early life exposures affect sexual maturation and gametogenesis, as reflected by measures of semen quality, for example. However, limited data are available evaluating links between BW, as a marker of fetal development, and semen quality characteristics, as measures of male reproductive function; among the few such studies, results are ambiguous. Associations between BW and subsequent unexplained infertility and/or semen quality measures have been observed in some studies (Faure et al., 2015; Francois et al., 1997), but not all (Olsen et al., 2000; Ozturk et al., 2001; Ramlau-Hansen et al., 2010). Complicating interpretation of these studies is variation in the study populations when assessing the relation between BW and adult male reproductive health, which have included men seeking treatment for infertility (Francois et al., 1997), male partners in couples with primary idiopathic subfertility (Faure et al., 2015) and males volunteering for studies of semen quality (Olsen et al., 2000). Less still is known regarding relations among BW and semen quality in the general population.

The Longitudinal Investigation of Fertility and the Environment (LIFE) study used a population-based approach to recruit couples trying to conceive and followed participants for pregnancy outcomes. The LIFE study provides an opportunity to evaluate the relations among BW and semen quality in a non-clinic based preconception cohort. In addition, the availability of information on outcomes of observed pregnancy provides a unique opportunity to also consider relations of BW and semen quality as markers of fetal development and male reproductive health with measures of fetal development in offspring. Our primary aims, therefore, were to evaluate first the relation of BW with semen quality characteristics and second the relations of BW and semen quality measures with offspring characteristics, in a sample from the general population.

Materials and Methods

Study sample

The current analysis was performed using the prospective LIFE study, the details of which have been previously published (Buck Louis et al., 2011). In brief, a total of 501 couples discontinuing contraception to conceive a pregnancy were recruited from 16 counties at study sites in Michigan and Texas, USA, from 2005 to 2009. A total of 501 male partners were enrolled for the study, of whom 473 (94%) provided a semen sample at baseline for semen analysis. BW information was available for 427 (90%) of these men. Among men contributing at least 1 semen sample, 226 had singleton births and this subset of men comprises the study population for this work. Eligible men were aged at least 18 years, in a committed relationship, and capable of communication in English or Spanish. Men with physician-diagnosed infertility were ineligible for participation. Participants completed informed consent prior to enrollment, and the study protocol was approved by the Institutional Review Boards at all participating institutions.

Data collection

A research team member visited eligible couples in their homes and enrolled participants following a negative pregnancy test. A baseline questionnaire was administered, querying demographics, health-related behaviors, medical history and reproductive histories. Male participants provided for analysis one (n = 473) or two (n = 378) semen specimens using home collection kits; one at baseline and one after 30 days, as previously described in detail (Buck Louis et al., 2015). In brief, participants were asked to abstain from ejaculation for 2 days and then to masturbate without lubricant into a glass specimen container, with an attached thermometer that monitors temperatures during the 24-h collection-to-analysis window. The semen specimens were shipped in a specially prepared insulated container with cold packs to the study's andrology laboratory.

Women were instructed in the use of the Clearblue Easy™ Fertility Monitor to time intercourse more effectively, and allowing for us to capture the date of ovulation. Women were followed until delivery when they completed and returned birth announcements that captured date and sex of birth, BW in grams and birth length (BL) in centimeters and head circumference (HC) in centimeters. We defined gestational age (GA) from the date of ovulation, estimated as the date the fertility monitor recorded LH peak to the reported delivery date. Preterm delivery was defined as GA <245 days (35 weeks) from the date of ovulation (conventionally defined as 37 weeks from last menstrual period date in the absence of ovulation data (WHO, 1977)), which is an accurate proxy for timing of conception related to the limited period of viability of the oocyte (Wilcox et al., 1995). Low BW (LBW) was defined as <2500 g (WHO, 1977). Ponderal index (PI), an indicator of fetal growth proportionality (Landmann et al., 2006), was defined as $100 \times (BL/BW^3)$.

Semen quality assessment

After overnight shipment to the National Institute for Occupational Safety and Health's andrology laboratory, specimen volume was measured and temperature was verified (−0.5–15°C), and samples were inspected for turbidity, color and liquefaction. The sperm quality analysis assessed 34 parameters categorized as general, motility, morphology, sperm head and sperm chromatin structure. All semen quality parameters were evaluated in the first specimen, and volume, viability, total count, concentration, motility and sperm head morphometry were further evaluated in the second specimen. If no sperm was present in either sample men were advised to seek clinical care for azoospermia. Briefly, sperm viability was evaluated by the hypo-osmotic swelling (HOS) assay (Schrader et al., 1990; Jeyendran et al., 1992). The hyperactivated motility (HTM)-integrated visual optical system (IVOS) computer-aided semen analysis (CASA) platform with video playback (Hamilton Thorne Biosciences, Beverly, MA, USA) was employed to assess eight measures of motility in a 20-μm-depth micro chamber slide (Leja, Nieuw-Vennep, Netherlands). Following preparation of four IDENT™-stained slides per specimen, the HTM-IVOS CASA platform was used to determine total sperm count and concentration, and the IVOS METRIX system (Hamilton Thorne

Biosciences) was used to determine sperm morphology (14 measures) and sperm head morphometry (6 measures). We used the third edition of the World Health Organization (WHO) morphologic criteria (i.e. 'traditional' criteria) and Kruger's Tygerberg criteria (i.e. 'strict' criteria) to evaluate overall sperm morphology (Cooper *et al.*, 2010; World Health Organization, 2010). The DNA fragmentation index (DFI) and percentage high stainability were assessed by sperm chromatin structure assay (SCSA®) using a Coulter Epics Elite Flow Cytometer (SCSA Diagnostics, Brookings, SD, USA) (Evenson *et al.*, 2013). Additional details regarding semen sample analysis have been published previously (Buck Louis *et al.*, 2011).

Statistical analysis

Male participant characteristics and semen quality parameters, dichotomized using clinical cut points based on WHO standards (Cooper *et al.*, 2010), were compared by self-reported BW. These BWs were converted from pounds and ounces to grams and categorized as <2500 g, 2500–4000 g and >4000 g. Statistical comparisons were made with ANOVA for continuous variables and Chi-square tests for categorical variables.

To evaluate how BW is related to measures of semen quality in adulthood, we used linear mixed models, as some participants contributed multiple semen samples. For these models, BW was standardized by its SD so that regression coefficients represent the change in outcome associated with a one-SD change in BW. Semen parameter-specific Box-Cox transformations were used to achieve normality of semen quality parameters assessed by Shapiro Wilk W statistics (Handelsman, 2002) and normality assumptions were confirmed by examining residual plots. Details of these transformations have been published previously (Buck Louis *et al.*, 2015). Azoospermic men ($n = 5$) were excluded from analysis. For these linear models, influences of semen quality and potential confounding factors identified *a priori* were included as covariates: these included male age (years), smoking status (unexposed, passive exposure, current smoking based on serum cotinine measures), study site (MI or TX, USA), race (white non-Hispanic, black non-Hispanic, Hispanic, other) and BMI (kg/m^2).

We used linear regression models to assess how semen quality parameters are related to offspring BW, GA at delivery, HC, BL, and PI, each in separate models, and used continuous semen quality variables as predictors. These models were run unadjusted as well as with adjustment for covariates as described previously, including paternal age, smoking status, study site, race and BMI. Models were run excluding BMI for concerns regarding causal pathways, but yielded very similar results to those with BMI, and thus only models adjusting for BMI are shown. In addition, we considered the possibility that relations of semen quality measures with offspring characteristics might vary by offspring sex and performed analyses separately for male ($n = 110$) and female ($n = 116$) offspring.

We defined statistical significance as $P < 0.05$ and SAS v.9.3 (SAS Institute, Inc., Cary, NC, USA) was used for statistical analysis.

Results

Characteristics of the 427 LIFE male participants with data available are shown in Table I, by paternal BW group. A total of 18 men (4%) reported having been born with an LBW (<2500 g), and 16% ($n = 67$) reported BWs >4000 g, with the majority ($n = 342$, 80%) having BWs between 2500 and 4000 g. BMI was observed to vary with BW ($P = 0.06$), with slightly lower BMI among men with normal BW compared with those reporting either low BW or high BW. Low BW was more common among black non-Hispanics (17.6%) and Hispanics (13.5%) than among white participants (2.9%). In comparisons of dichotomous semen quality parameters, we found no statistical differences among BW groups, with the exception of DFI, which was significantly higher ($P = 0.03$) in men with low BW (22%, $n = 4$) compared with men reporting normal BW (6%, $n = 20$) or high BW (7.6%, $n = 5$), though numbers for this comparison were very limited.

Results from linear mixed models of measures of semen quality in samples provided by participants ($n = 427$) and associations with BW are shown in Table II. A statistically significant association was observed between BW and % megalo head ($\beta = -0.05.3$, $P = 0.05$) in adjusted models. No other semen parameter was statistically significantly associated with BW in either unadjusted or multivariable models. Similar results were observed in models that characterized BW in groups and compared semen quality measures between LBW ($n = 18$), normal BWT ($n = 342$) and high BWT ($n = 67$) (results not shown). Low sample numbers precluded comparison of dichotomized semen quality parameters in multivariable models of continuous or categorized BW.

Results of models of continuous pregnancy outcomes (including offspring BW, GA at delivery, HC, BL and PI) among singleton births ($n = 226$), in association with paternal semen quality parameters from the first semen sample, are shown in Table III. In these analyses, earlier GA at delivery (weeks) was associated with percentage acrosome area of sperm head ($\beta = -0.08$ weeks, $P = 0.01$), and with measures of percentage normal morphology (strict criteria, $\beta = -0.03$ weeks, $P = 0.05$; traditional criteria, $\beta = -0.03$ weeks, $P = 0.03$) and percent coiled tail ($\beta = 0.03$ weeks, $P = 0.05$). Sperm concentration ($\beta = 0.001$, $P = 0.04$) and percentage HOS test ($\beta = 0.005$, $P = 0.05$) were associated with PI (Table III). No other semen parameters were associated with GA at delivery and no significant associations were observed in models of BW, HC or PI. Results of analyses conducted separately by offspring sex were largely similar to those among all singleton births, and are described in the Supplementary Tables and Supplementary Data.

Results of linear models of characteristics of singleton offspring ($n = 226$) as related to paternal BWs are shown in Table IV. For all characteristics evaluated, results were non-significant and, except for offspring BW, point estimates were close to zero.

Discussion

BW is an easily measured variable that has been suggested by some to be related to male reproductive health (Francois *et al.*, 1997; Faure *et al.*, 2015). In this analysis of 427 male participants in the LIFE study, we evaluated BW as a predictor of 34 different semen parameters and assessed associations with pregnancy outcomes among 226 singleton births. As expected, race-based disparities in LBW were observed (Hamilton *et al.*, 2015). However, male participant BWs were associated only with a single morphology parameter (percentage megalo head), and not with other evaluated semen parameters. Similarly, semen quality measures were not meaningfully related to pregnancy outcomes in this cohort. The recruitment strategy for the LIFE study utilized population-based sampling frameworks to target couples discontinuing contraception for the purposes of becoming pregnant and excluded couples with diagnosed infertility. By design, our study limited consideration of relations among BW, semen parameters and pregnancy outcomes to a relatively unselected sample of men. It remains possible that *in utero* exposures may impact adult male reproductive health. However, among this population-based sample of men without known infertility, our results do not provide evidence to support

Table I Characteristics of the male Longitudinal Investigation of Fertility and the Environment (LIFE) study participants ($n = 427$) by BW category.

	Male participant BW						
	<2500 g ($n = 18$)		2500–4000 g ($n = 342$)		>4000 g ($n = 67$)		P[a]
	Mean (SD) or n (%)		Mean (SD) or n (%)		Mean (SD) or n (%)		
Age (years)	31.9	(5.5)	32.0	(5.1)	30.8	(3.6)	0.36
BMI (kg/m^2)	30.5	(3.7)	29.3	(5.0)	30.6	(5.1)	0.06
Race/ethnicity							<0.001
White, non-Hispanic	10	(55.6%)	277	(81.5%)	61	(91.0%)	
Black, non-Hispanic	3	(16.7%)	11	(3.2%)	3	(4.5%)	
Hispanic	5	(27.8%)	30	(8.8%)	2	(3.0%)	
Other	0	(0%)	22	(6.5%)	1	(1.5%)	
College education	16	(88.9%)	318	(93.8%)	60	(89.6%)	0.37
Household income (US$)							0.28
<$50,000	5	(27.8%)	40	(11.9%)	10	(15.4%)	
$50 000–$69 999	4	(22.2%)	64	(19.1%)	10	(15.4%)	
$70 000+	9	(50.0%)	232	(69.1%)	45	(69.2%)	
Health insurance	15	(83.3%)	313	(92.1%)	62	(92.5%)	0.41
Smoking status (serum cotinine in ng/ml)							0.41
Unexposed (<10)	13	(72.2%)	270	(80.4%)	53	(79.1%)	
Passive exposure (10–100)	2	(11.1%)	15	(4.5%)	1	(1.5%)	
Active smoking (>100)	3	(16.7%)	51	(15.2%)	13	(19.4%)	
Semen quality parameters[b]							
Volume <1.5 ml	3	(16.7%)	36	(10.5%)	6	(9.0%)	0.64
Concentration <15 million/ml	1	(5.6%)	25	(7.3%)	10	(14.9%)	0.11
Total count <39 million	0	(0.0%)	29	(8.5%)	9	(13.4%)	0.17
Vitality <58%	3	(16.7%)	50	(14.7%)	12	(17.9%)	0.78
Normal morphology <30% (WHO)	12	(66.7%)	144	(45.3%)	28	(45.2%)	0.21
Normal morphology <4% (Strict)	0	(0.0%)	12	(3.8%)	3	(4.8%)	0.64
DNA fragmentation index <30%	4	(22.2%)	20	(6.0%)	5	(7.6%)	0.03

BW, birthweight.
[a]P-values from ANOVA, chi-square or Fisher's exact test as appropriate.
[b]Dichotomous semen quality parameters based on World Health Organization (WHO) reference values (Cooper *et al.*, 2010).

relations of BW with semen parameters or characteristics of offspring in singleton pregnancies.

Our findings are consistent with most prior studies of paternal BW and measures of male reproductive health or semen quality and offspring's birth outcomes. Among 296 Danish men recruited for a study of pregnancy planners in an occupational cohort, no relation was observed between BWs or PI collected from midwife records and semen characteristics, including concentration, volume and normal morphology (Olsen *et al.*, 2000). Our results concur for these measures of semen quality, and further considered many additional semen parameters with similar findings. A case–control study of $n = 126$ with unexplained infertility (cases) and $n = 76$ with normal semen parameters (controls) also observed no significant association with BW (Ozturk *et al.*, 2001). There was no relation between low semen quality and shorter GA or LBW for >4200 infertility clinic and population-based deliveries in Norway, between 1976 and 1994 (Irgens *et al.*, 2001).

In contrast to our results, a case–control study reported by Francois (1997) observed higher standardized BWs in a group of 128 men with normal semen analysis compared with 32 cases with unexplained subfertility. No differences, however, were observed comparing BWs of the men with normal semen analysis with those with explained subfertility ($n = 28$). Reasons for the discrepant findings between explained and unexplained subfertility are not clear, although confounding variables were not considered by the authors (Francois *et al.*, 1997). More recently, Faure (2015) compared BWs in 92 men with diagnosed subfertility with those in 91 fertile men and evaluated associations of BW with semen parameters among the subfertile men. Whereas Francois reported lower BWs among subfertile men compared with those with normal semen analysis (Francois *et al.*, 1997), Faure (2015) observed a significantly higher mean BW among subfertile men than among fertile men (3561 versus 3303 g, $P < 0.001$), and among the subfertile men BW was correlated with sperm fragmentation ($r = 0.19$, $P = 0.004$) and total sperm count ($r = 0.09$, $P = 0.03$). Explanations for the

Table II Results of linear mixed models of self-reported BW of LIFE study male participants ($n = 427$) as a predictor of semen parameters.

Dependent semen quality variable	Regression coefficient for BW (per 100 grams) [95% CI]					
	Unadjusted			Adjusted		
	Coeff.	95% CI	P	Coeff.	95% CI	P
General characteristics						
Volume (ml)	**6.6**	**(0.0, 13.2)**	**0.05**	5.2	(−1.7, 12.1)	0.14
Sperm concentration ($\times 10^6$/ml)	0.5	(−25.1, 26.1)	0.97	−2.6	(−29.6, 24.4)	0.85
Total sperm count ($\times 10^6$/ejaculate)	22.2	(−15.6, 59.9)	0.25	13.8	(−25.8, 53.4)	0.49
Hypo-osmotic swollen (%)	43.4	(−44.1, 131.0)	0.33	−9.6	(−99.7, 80.6)	0.83
Sperm motility (24 h)						
Average path velocity (mm/s)	57.4	(−50.5, 165.3)	0.30	2.1	(−111.7, 115.9)	0.97
Straight line velocity (mm/s)	42.7	(−45.6, 131.0)	0.34	−0.2	(−93.4, 93.0)	0.99
Curvilinear velocity (mm/s)	126.5	(−60.4, 313.4)	0.18	36.1	(−161.5, 233.7)	0.72
Amplitude head displacement (mm)	3.8	(−8.2, 15.9)	0.53	−1.7	(−14.3, 10.9)	0.79
Beat cross frequency (Hz)	17.5	(−41.9, 77.0)	0.56	6	(−56.7, 68.8)	0.85
Straightness (%)	−33.4	(−195.4, 128.7)	0.69	−112.3	(−282.7, 58)	0.20
Linearity (%)	−46	(−152, 60.1)	0.39	−92.9	(−204.1, 18.3)	0.10
Percent motility (%)	13.1	(−11.5, 37.6)	0.30	1.3	(−24.4, 27)	0.92
Sperm head measurements						
Length (mm)	−0.3	(−0.8, 0.2)	0.21	−0.3	(−0.9, 0.2)	0.23
Area (mm^2)	−3.6	(−11.6, 4.4)	0.38	−6.2	(−14.6, 2.2)	0.14
Width (mm)	0.2	(−1.4, 1.9)	0.77	−0.5	(−2.2, 1.3)	0.61
Elongation factor (%)	23.8	(−26.2, 73.8)	0.35	9.9	(−43, 62.8)	0.71
Perimeter (mm)	−2.4	(−7.0, 2.2)	0.31	−3.2	(−8.1, 1.6)	0.19
Acrosome area of head (%)	38.3	(−7.4, 83.9)	0.10	27.3	(−20.4, 75.0)	0.26
Morphology						
Strict criteria (%)	27.7	(−13.4, 68.7)	0.19	16.6	(−25.8, 59.1)	0.44
Traditional normal (%)	79.2	(−42.7, 201.0)	0.20	52.9	(−73.1, 178.9)	0.41
Amorphous (%)	−2.7	(−12.7, 7.2)	0.59	−2.7	(−13.3, 7.9)	0.62
Round (%)	0.8	(−4.4, 6.1)	0.75	3.4	(−2.0, 8.9)	0.22
Pyriform (%)	−6.1	(−14.1, 1.9)	0.14	−6	(−14.5, 2.4)	0.16
Bicephalic (%)	3.6	(−1.8, 9.0)	0.19	2.7	(−3.0, 8.4)	0.36
Taper (%)	−5.9	(−12.4, 0.6)	0.08	−3.4	(−10.2, 3.4)	0.33
Megalo head (%)	−3.9	(−8.8, 1.0)	0.12	**−5.3**	**(−10.5, −0.1)**	**0.05**
Micro head (%)	−1.1	(−5.6, 3.4)	0.62	−0.1	(−4.8, 4.6)	0.96
Neck/midpiece abnormalities (%)	−2.4	(−6.0, 1.2)	0.19	−1.2	(−4.9, 2.6)	0.54
Coiled tail (%)	−0.9	(−5.2, 3.4)	0.68	−0.2	(−4.6, 4.3)	0.94
Other tail abnormalities (%)	−3	(−8.3, 2.3)	0.27	−2.9	(−8.5, 2.6)	0.30
Cytoplasmic droplet (%)	2.3	(−8.3, 13.0)	0.67	2.9	(−8.3, 14.1)	0.61
Immature sperm (#)	−2.8	(−11.2, 5.6)	0.51	−2.9	(−11.8, 6.0)	0.52
Sperm chromatin stability assay						
DNA fragmentation index (%)	−0.7	(−5.9, 4.5)	0.78	0.5	(−4.9, 5.9)	0.85

Notes: Findings in boldface are significant ($P < 0.05$). Adjusted model included age (years), smoking status (unexposed, passive exposure, current smoker), site (MI or TX, USA), race (white non-Hispanic, black non-Hispanic, Hispanic, other) and BMI (kg/m^2).

contrary findings of these studies regarding whether higher or lower paternal BW is related to subfertility in adulthood are not apparent. However, given the observed weak associations of BW with selected semen parameters among the subfertile men that were reported in Faure (2015) relations of measures of paternal fetal development with those of reproductive function in adulthood may only be apparent in clinically affected individuals. Unlike these case–control studies making comparisons based on semen analysis results, we utilized a prospective

Table III Semen analysis parameters as predictors of characteristics in offspring ($n = 226$): results of linear regression models among LIFE study fathers with singleton births.

Semen analysis variable	Linear regression coefficients [95% CI] for offspring characteristics from adjusted models				
	BW (g)	GA at delivery (weeks)	HC (cm)	BL (cm)	PI*
General characteristics					
Volume (ml)	−8.36 (−48.8, 32.09)	0.10 (−0.06, 0.26)	−0.06 (−0.26, 0.14)	−0.09 (−0.31, 0.13)	0.01 (−0.02, 0.03)
Sperm concentration ($\times 10^6$/ml)	−0.06 (−1.26, 1.15)	0.00 (−0.01, 0.00)	0.00 (−0.01, 0.01)	−0.01 (−0.01, 0.00)	0.00 (0.00, 0.00)
Total sperm count ($\times 10^6$/ejaculate)	0.03 (−0.33, 0.40)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Hypo-osmotic swollen (%)	1.33 (−6.23, 8.88)	−0.02 (−0.05, 0.01)	0.02 (−0.02, 0.06)	−0.03 (−0.07, 0.01)	0.00 (0.00, 0.01)
Sperm motility (24 h)					
Average path velocity (mm/s)	0.54 (−4.73, 5.82)	0.01 (−0.01, 0.03)	−0.01 (−0.04, 0.02)	0.00 (−0.03, 0.03)	0.00 (0.00, 0.00)
Straight line velocity (mm/s)	0.27 (−6.18, 6.72)	0.00 (−0.02, 0.03)	−0.01 (−0.04, 0.03)	0.00 (−0.03, 0.04)	0.00 (0.00, 0.00)
Curvilinear velocity (mm/s)	0.99 (−2.11, 4.10)	0.01 (−0.01, 0.02)	0.00 (−0.02, 0.01)	0.00 (−0.02, 0.02)	0.00 (0.00, 0.00)
Amplitude head displacement (mm)	16.70 (−32.97, 66.37)	−0.07 (−0.27, 0.13)	−0.14 (−0.39, 0.12)	−0.03 (−0.31, 0.24)	0.01 (−0.02, 0.05)
Beat cross frequency (Hz)	1.45 (−8.01, 10.91)	0.01 (−0.03, 0.05)	0.01 (−0.03, 0.06)	0.01 (−0.05, 0.06)	0.00 (−0.01, 0.01)
Straightness (%)	2.30 (−1.13, 5.73)	0.01 (−0.01, 0.02)	0.00 (−0.01, 0.02)	0.00 (−0.02, 0.02)	0.00 (0.00, 0.00)
Linearity (%)	2.86 (−2.23, 7.95)	0.02 (0.00, 0.04)	0.00 (−0.02, 0.03)	0.01 (−0.02, 0.04)	0.00 (0.00, 0.00)
Percent motility (%)	−2.21 (−7.53, 3.12)	−0.02 (−0.04, 0.01)	0.00 (−0.03, 0.02)	−0.01 (−0.04, 0.01)	0.00 (0.00, 0.00)
Sperm head measurements					
Length (mm)	−87.13 (−341.64, 167.39)	0.33 (−0.70, 1.35)	−0.05 (−1.36, 1.26)	0.17 (−1.25, 1.59)	−0.13 (−0.29, 0.03)
Area (mm^2)	18.78 (−60.76, 98.31)	0.04 (−0.28, 0.37)	0.18 (−0.22, 0.58)	0.11 (−0.33, 0.55)	−0.01 (−0.06, 0.04)
Width (mm)	246.11 (−136.97, 629.18)	0.11 (−1.46, 1.67)	1.15 (−0.81, 3.10)	0.95 (−1.23, 3.13)	0.07 (−0.17, 0.32)
Elongation factor (%)	8.96 (−4.05, 21.98)	−0.01 (−0.07, 0.04)	0.03 (−0.03, 0.10)	0.02 (−0.06, 0.09)	0.01 (0.00, 0.01)
Perimeter (mm)	3.80 (−136.69, 144.29)	0.05 (−0.52, 0.62)	0.17 (−0.55, 0.88)	0.17 (−0.61, 0.95)	−0.03 (−0.12, 0.05)
Acrosome area of head (%)	−11.23 (−25.06, 2.60)	−0.08 (−0.13, −0.02)	−0.07 (−0.14, 0.00)	−0.07 (−0.14, 0.01)	0.00 (−0.01, 0.01)
Morphology					
Strict criteria (%)	−0.87 (−8.16, 6.42)	−0.03 (−0.06, 0.00)	−0.02 (−0.06, 0.02)	−0.02 (−0.06, 0.02)	0.00 (0.00, 0.01)
Traditional normal (%)	−1.79 (−7.72, 4.15)	−0.03 (−0.05, 0.00)	−0.01 (−0.04, 0.02)	−0.02 (−0.05, 0.02)	0.00 (0.00, 0.00)
Amorphous (%)	2.24 (−4.34, 8.82)	0.02 (−0.01, 0.05)	0.00 (−0.03, 0.04)	0.02 (−0.02, 0.06)	0.00 (−0.01, 0.00)
Round (%)	5.07 (−46.06, 56.2)	0.11 (−0.09, 0.32)	0.03 (−0.22, 0.27)	0.00 (−0.29, 0.28)	0.00 (−0.03, 0.04)
Pyriform (%)	−7.15 (−19.17, 4.87)	0.00 (−0.05, 0.05)	−0.02 (−0.09, 0.04)	0.00 (−0.06, 0.07)	0.00 (−0.01, 0.00)
Bicephalic (%)	17.87 (−21.41, 57.16)	−0.04 (−0.20, 0.12)	0.14 (−0.05, 0.33)	0.07 (−0.15, 0.29)	0.00 (−0.02, 0.03)
Taper (%)	9.84 (−15.73, 35.4)	0.06 (−0.04, 0.17)	−0.06 (−0.20, 0.08)	−0.04 (−0.19, 0.11)	0.01 (0.00, 0.03)
Megalo head (%)	22.48 (−13.91, 58.87)	0.01 (−0.14, 0.16)	0.04 (−0.16, 0.23)	0.13 (−0.07, 0.33)	0.00 (−0.02, 0.02)
Micro head (%)	30.98 (−20.63, 82.59)	0.18 (−0.04, 0.39)	−0.17 (−0.47, 0.14)	−0.03 (−0.35, 0.28)	0.03 (−0.01, 0.06)
Neck/midpiece abnormalities (%)	3.21 (−4.25, 10.68)	0.03 (0.00, 0.06)	0.02 (−0.02, 0.06)	0.02 (−0.02, 0.06)	0.00 (0.00, 0.00)
Coiled tail (%)	3.28 (−3.26, 9.82)	0.03 (0.00, 0.05)	0.02 (−0.01, 0.06)	0.02 (−0.02, 0.06)	0.00 (0.00, 0.00)
Other tail abnormalities (%)	−6.54 (−28.95, 15.87)	−0.06 (−0.15, 0.03)	0.03 (−0.09, 0.15)	−0.05 (−0.18, 0.07)	0.01 (−0.01, 0.02)
Cytoplasmic droplet (%)	10.82 (−2.41, 24.05)	0.02 (−0.04, 0.07)	0.00 (−0.07, 0.07)	0.05 (−0.03, 0.12)	0.00 (−0.01, 0.01)
Immature sperm (#)	8.82 (−5.24, 22.88)	0.00 (−0.06, 0.06)	0.04 (−0.03, 0.11)	0.02 (−0.06, 0.10)	0.00 (0.00, 0.01)
Sperm chromatin stability assay					
DNA fragmentation index (%)	2.23 (−4.19, 8.64)	0.01 (−0.02, 0.04)	0.00 (−0.04, 0.04)	0.03 (−0.01, 0.06)	0.00 (−0.01, 0.00)
High DNA stainability (%)	13.70 (−0.27, 27.68)	0.03 (−0.02, 0.09)	0.03 (−0.05, 0.10)	0.05 (−0.03, 0.13)	0.00 (−0.01, 0.01)

GA, gestational age; HC, head circumference; BL, birth length; PI, ponderal index.
Notes: Adjusted model included age (years), smoking status (unexposed, passive exposure, current smoker), site (MI or TX, USA), race (white non-Hispanic, black non-Hispanic, Hispanic, other) and BMI (kg/m^2).
*Ponderal index = $100 \times BL/BW^3$.

Table IV Linear regression of relation of BW of fathers as a predictor of characteristics of singleton births in LIFE ($n = 226$).

Characteristic	Unadjusted			Adjusted		
	Coeff.	95% CI	P	Coeff.	95% CI	P
BW (SD)[a]	−14.04	(−78.01, 49.93)	0.67	−26.13	(−97.25, 44.99)	0.47
GA at delivery (weeks)	−0.12	(−0.40, 0.15)	0.38	−0.19	(−0.48, 0.11)	0.21
HC (cm)	0.01	(−0.33, 0.34)	0.97	0.04	(−0.32, 0.40)	0.84
BL (cm)	−0.13	(−0.49, 0.24)	0.50	−0.26	(−0.66, 0.15)	0.22
PI ($100 \times BL/BW^3$)	−0.003	(−0.045, 0.039)	0.90	0.005	(−0.041, 0.051)	0.83

Notes: Adjusted model included age (years), smoking status (unexposed, passive exposure, current smoker), site (MI or TX, USA), race (white non-Hispanic, black non-Hispanic, Hispanic, other) and BMI (kg/m^2).
[a]Divided by the SD of BW to yield units of SDs.

cohort design and restricted participation to those without diagnosed infertility; accordingly, although subfertile men with previously undiagnosed infertility may have been included in our sample, the recruitment strategy for LIFE under-represents subfertility by design and our conclusions are generalizable only to similar populations without diagnosed infertility.

The large sample size and prospective design capturing incident pregnancies and births are strengths of our study that allowed for high statistical power and consideration of temporality (Hill, 1965). For analyses of semen quality measures as outcomes and associations with male participant BW, we had 80% power to detect correlations as low as 0.13. Our assessment of relations among BW, subsequent semen quality and birth outcomes was highly comprehensive, incorporating 34 measures of overall quality, motility, morphology, sperm head morphometry and DNA stability. As a result, we are less likely to have failed to detect associations than if we had used composite semen quality measures.

Despite widespread recognition of paternal impacts on embryo development (Tesarik, 2005), placentation (Frost and Moore, 2010) and pregnancy outcomes (Bray *et al.*, 2006), ours is only the second investigation of semen quality and birth outcomes. Our use of a population-based cohort adds to previously reported results evaluating reproductive outcomes according to semen quality in males attending an infertility clinic (Irgens *et al.*, 2001). We also collected detailed covariate data, allowing for incorporation of important confounding variables into adjusted analyses, and for stratification by offspring's sex, although these had limited impact on results.

A number of limitations are of note. Related to our use of a non-clinical population, we implemented a next day semen analysis approach. Next day, semen analysis provided valid and reliable data for most indicators in prior studies, as some sperm survive for >24 h; however, the approach impacts assessment of motility, which may limit inference from our analyses of motility measures (Stovall *et al.*, 1994; Royster *et al.*, 2000; Morris *et al.*, 2003). In addition, our use of self-reported BWs of male participants rather than confirmed medical records is a likely source of measurement error. Studies comparing BW as self-reported by women in adulthood with recorded BWs in medical records have observed imperfect agreement, with correlation coefficients ranging from 0.59 to 0.83 (Sanderson *et al.*, 1998; Jaworowicz *et al.*, 2010; Wodskou *et al.*, 2010; Cairns *et al.*, 2011). Less is known about self-report by men. Such errors in BW due to self-report are unlikely to be related to outcomes and so would represent a potential bias toward the null. Also of note, consideration of 34 semen parameters provides a highly comprehensive assessment of associations, but comprised a total of 204 adjusted primary analyses, of which 3.4% were statistically significant at $P < 0.05$. Statistical power was maximized by not adjusting for multiple comparisons, but chance findings cannot be ruled out. To the best of our knowledge, this study offers the most complete assessment to date of associations of BWs with semen quality measures.

The LIFE study is among the largest to consider influences of semen quality, and provided the opportunity to evaluate hypotheses in a population-based sample. We did not observe associations between BW and semen parameters or with offspring characteristics. Whereas prior investigations of clinically infertile populations raised questions regarding potential preconception-based impacts on offspring's birth outcomes, we see little evidence to corroborate the association in a general population sample. In conjunction with the results of prior studies, our data suggest that paternal BW is not an important predictor of semen quality and that semen quality is not an important predictor of birth outcomes in fertile couples. However, given the novelty of these data and the limitations in our analysis, our results require confirmation in a future study.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

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Authors' roles

B.W. and M.B. made substantial contributions to design, analysis and interpretation of data, drafting the article and gave final approval of the version to be published. Z.C. and S.K. made substantial contributions to analysis and interpretation of data, revising the article critically for important intellectual content, and gave final approval of the version to be published. G.B.L. made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data, revising the article critically for important intellectual content, and gave final approval of the version to be published.

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Conflict of interest

The authors report no competing interests.

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