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The Relation of Birth Weight and Adiposity Across the Life Course to Semen Quality in Middle Age

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Abstract

Background: Studies of body mass index and semen quality have reported mixed results, but almost all were cross-sectional and many were conducted in selected populations. Longitudinal studies in population-based cohorts are necessary to identify how timing and duration of excess adiposity may affect semen quality.

Methods: In 193 members of the Child Health and Development Studies birth cohort, we examined associations of birth weight and adiposity at six time points spanning early childhood and adulthood with sperm concentration, motility, and morphology at mean age 44 years, as well as with corresponding 2010 World Health Organization (WHO) subfertility reference levels.

Results: Birth weight for gestational age percentile was positively associated with square-root sperm concentration (regression coefficient B [95% confidence interval] = 0.02×10^3 sperm/ml [0.004, 0.04]). Overweight/obesity in men's 20s was associated with lower percent progressive

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motility (B =−5.2 [−9.9, −0.63]), higher odds of low motility (odds ratio (OR) = 2.4 [1.3, 4.4]), and higher odds of poor morphology (OR = 1.9 [0.94, 3.8]). Those who were overweight/obese in their 20s were also more likely to meet two or three WHO subfertility criteria (OR = 3.9 [1.6, 9.4]) compared with normal-weight men. Each additional adult decade in which a participant was overweight/obese was associated with higher odds of low motility (OR = 1.3 [0.96, 1.6]) and higher odds of meeting two or three WHO subfertility criteria (OR = 1.5 [1.0, 2.2]).

Conclusions: In our data, associations among adiposity and sperm concentration, motility, and morphology varied according to timing and duration of exposure, potentially reflecting different biological mechanisms that influence these semen parameters.

Keywords

Adiposity; Birth weight; Body mass index; Semen quality; Andrology; Male infertility

Adiposity has been identified as a potentially modifiable risk factor for poor semen quality. Numerous studies of body mass index (BMI), a convenient—albeit crude—measure of adiposity, and semen quality have been conducted around the world; all but two[1,2] have been cross-sectional, allowing only for inferences about current adiposity and sperm production. Although these analyses may capture the relation between BMI and spermatogenesis, this 74-day process[3] represents the culmination of a developmental trajectory that begins during fetal life and continues into adulthood. There remains a wide gap in our understanding of how birth weight, as well as adiposity in infancy, childhood, young adulthood, and middle age, may individually and cumulatively influence different aspects of semen quality.

Four meta-analyses of BMI and semen quality have been conducted with mixed results. Campbell et al.[4] compared obese men with normal-weight men and found lower progressive motility and normal morphology among the obese, but no difference in concentration. By contrast, Guo et al.[5] compared overweight and obese categories with normal and found obesity to be associated with lower concentration but found no associations between either category and motility. MacDonald et al.[6] treated BMI categories continuously and found no linear association with concentration or motility. Sermondade et al.[7] compared underweight, overweight, obese, and morbidly obese men to normal-weight men and found a J-shaped association with low sperm concentration.

The differences these studies suggest in the relations of BMI to various semen parameters are biologically plausible. Both underweight[8] and overweight/obesity[6] are associated with reduced testosterone, a crucial signal for sperm production, which could explain Sermondade et al.'s[7] finding of lower sperm concentration at either end of the BMI distribution. Overweight/ obesity is associated with increased inflammatory molecules in the testes,[9] which may affect sperm development, leading to the reduction in motility and morphology among those at the high end of the BMI spectrum that Campbell et al.[4] reported.

Dozens of prior empirical studies have also reported inconsistent results, likely stemming from differences among their samples' racial/ethnic composition, environmental exposures, fertility status, and distributions of age and BMI. In addition, studies had different

requirements for pre-ejaculatory abstinence, which could influence sperm concentration and motility,[10,11] and assessed morphology according to various criteria.[12] Motility and morphology also tend to be susceptible to interlaboratory variation.[13]

Fewer studies have examined associations of birth weight, a common proxy of fetal growth, [14] and/or childhood adiposity with semen quality. In a follow-up of male offspring from the Danish Healthy Habits for Two pregnancy cohort, neither birth weight nor prepubertal BMI (age 5–8 years) was associated with sperm concentration, motility, or morphology at age 18–21 years.[1] At the 20/21-year follow-up of the Western Australia Pregnancy Cohort (Raine) Study, neither prenatal growth trajectory, childhood growth pattern, nor BMI at age 20 years was associated with sperm concentration.[2] The Longitudinal Investigation of Fertility and the Environment Study also found no association between birth weight and semen parameters measured when participants were attempting conception.[15] By contrast, Olsen et al.[16] reported reduced sperm concentration among men who were born between 3,000 and 3,999 g compared with those with lower or higher birth weights, and more abnormally shaped sperm in those with birth weight <3,000 g; Auger et al.[17] found higher birth weight to be associated with an increase in abnormally shaped sperm; and Boeri et al.[18] detected an association of low birth weight (≤2,500 g) with low motility and pathologic morphology, but not with low concentration.

To date, no study has explored whether birth weight and adiposity measures across the life course are related to sperm concentration, motility, and morphology and whether the risk of poor semen quality accumulates with increased duration of excess adiposity. We assessed associations of birth weight for gestational age and six adiposity measures spanning early childhood to adulthood with three semen outcomes measured in middle age, as well as with parameter-specific and combined measures of subfertility based on 2010 World Health Organization (WHO) reference levels. In a secondary analysis, we also considered whether cumulative duration of exposure to excess adiposity was related to semen quality. Because the majority of Sertoli cells, which are responsible for the transformation from primary spermatocyte to mature spermatozoa in the postpubertal testes, are laid down during the fetal period,[19–21] we hypothesized a positive association between birth weight and sperm concentration. Because sperm tail and head development occurs in the 74 days before ejaculation,[3] we hypothesized that motility and morphology would be negatively associated with current adiposity.

METHODS

Study Population

Our analysis includes 193 men (mean age 44 years, range: 38–47) from a 2005–2008 follow-up of the Child Health and Development Studies (CHDS) birth cohort. The CHDS enrolled 98% of eligible pregnant women who were members of the Kaiser Foundation Health Plan in and around Oakland, CA, between 1959 and 1966. Women were enrolled in early pregnancy, and child growth and medical information were collected at regular intervals through age 5 years.[22]

Between December 2005 and April 2008, participants were recruited into a follow-up study of male reproductive health. The recruitment pool included 3,809 men believed to meet the study's eligibility criteria: who lived within 100 miles of the Kaiser Oakland Clinic and had available data on birth length and weight, at least one same-day measured height and weight between age 6 months and 5.5 years, maternal prenatal interview data, and adequate stored maternal mid-pregnancy and postpartum serum for serological measures. Those with major congenital abnormalities were excluded. Extensive efforts were made to trace and contact the portion of eligible men whom we had funding to pursue (n = 1,202), including the use of credit reports, computer search engines, and multiple local and state-wide public records. Among the 654 (54%) who could be traced, 568 met eligibility criteria; of these, 338 (60%) consented to participate and provided interviews. Nine participants had been vasectomized; 196 (60%) of the remaining provided at least one semen sample (Figure).[23] Our analyses exclude three azoospermatic men.

The institutional review boards at Columbia University Medical Center, Kaiser Permanente, and the Public Health Institute approved this study.

Study Protocol

Participants in the follow-up study traveled to the Kaiser Oakland Clinic where they underwent a 1-hour in-person interview, were weighed, had their height and blood pressure measured, and provided semen samples followed by blood samples. Participants returned to the clinic approximately 2 weeks later to provide a second semen sample.[23]

Exposure Measures

Birth Weight for Gestational Age—Birth weight for gestational age percentiles (bw/ga) were calculated using continuous curves derived from U.S. natality datasets containing information on male singleton infants born to U.S. resident mothers in 1999–2000.[24] Although created long after the CHDS children were born, these are the first continuous curves available based on the entire U.S. population; prior curves only provided data for specific percentiles[25–28] and were sometimes based on exclusively white populations.[25,26] Despite any changes in the bw/ga curve over time, the rank order of participants' percentiles would remain consistent.

Adiposity—Because measures of adiposity are not standard across the life course, we created variables appropriate to the ages at which height and weight were measured. For the 4- and 12-month measures, we calculated weight-for-height percentiles (wt/ht) using a SAS program provided by the Centers for Disease Control and Prevention (CDC) based on data from the 2000 CDC 0–36 months male weight-for-age and height-for-age growth charts.[29] For the age 4-year measure, we used the CDC SAS program to calculate sex-specific BMI-for-age percentiles (ssBMI) based on the 2000 CDC male BMI-for-age growth charts. As with the bw/ga curves, the 2000 growth charts better reflect the racial/ethnic diversity of the CHDS cohort than previously available ones[30] and the relative percentiles are still relevant. We categorized child adiposity variables using the CDC cut points for under/normal weight (<85th percentile), overweight (≥85th and <95th percentile), and obesity (≥95th percentile).[31]

We calculated continuous BMI measures for three time periods in adulthood according to the standard formula. Measured weight and height at the time of semen collection yielded current BMI. We calculated BMI in participants' 20s and 30s from recalled weight and from height measured at the study visit, assuming that height is stable between early adulthood and middle age. We dichotomized adult BMI measures using the WHO cut point for under/normal weight (<25 kg/m^2) versus overweight/obese (≥25 kg/m^2).[32]

We created scores for cumulative duration of overweight/obesity across different segments of the lifespan by allocating one point for every time a subject was classified as overweight/obese (≥85th percentile or BMI ≥25 kg/m^2). Scores ranged from 0 to 6 points for total duration of excess adiposity across all six time points, and 0 to 3 for separate childhood and adulthood periods.

Outcome Measures

Participants were invited to provide two semen samples approximately 2 weeks apart following 2–5 days of ejaculatory abstinence. Semen analysis was performed according to a standard protocol: sperm concentration and percent motile sperm were assessed at the Kaiser Clinic within 1 hour of ejaculation and seminal smears were prepared and sent to the Andrology Laboratory at the University of California, Davis, where they were stained to determine percent normal morphology, classified according to strict criteria.[33] Details of the semen analysis[23] and quality controls used throughout the procedure[34] have been described previously. Among the 160 men who provided two samples, intraclass correlation coefficients indicated good reliability between measures,[23] so we averaged values across samples when two were available.

We modeled semen parameters both continuously and dichotomously using the 2010 WHO reference values for subfertility: sperm concentration <15 × 10^6 sperm/mL, percent progressive motility <32%, percent normal morphology (strict criteria) <4%.[35] We additionally created a three-level combined subfertility measure that categorized participants according to the number of parameters they had below the 2010 WHO reference values (0, 1, 2–3).

Covariates

Potential covariates identified by causal diagrams as possible confounders or sources of selection bias included race (white/black/other), birth weight (g), gestational age (days), maternal and paternal BMI (kg/m^2), maternal age (years), parity (nulliparous/parous), and prenatal smoking (yes/no). Potential covariates identified as possible predictors of the outcomes that might be used to improve model fit included participants' age at follow-up (years), annual income (<$50,000, $50–100,000, $100–150,000, >$150,000), smoking status (current/not current), alcohol consumption (average g/week during the past 12 months), exercise (average minutes/ week during the past 3 months), current hormone use (yes/no), current employment status (employed/unemployed), and subjective stress (continuous, using the Perceived Stress Scale[36]). In a prior analysis, the latter two were associated with semen outcomes in this cohort.[37] Abstinence time (hours) was considered as a calibration variable, as it has been shown to affect various semen parameters.[11]

Statistical Analyses

To describe the analytic sample and compare it to the source population of eligible male CHDS members, we calculated summary statistics for selected participant and parental characteristic variables. We also examined the empirical distributions of the three semen parameters. Whereas motility and morphology had approximately normal distributions, the distribution of sperm concentration was right-skewed and was symmetrized by square-root transformation. We used analysis of variance to compare means of continuous exposure and outcome variables according to levels of categorical covariates, Chi-square tests to detect group differences in categorical variables, and Spearman correlation coefficients to measure associations between continuous variables.

We ran three sets of regression models for each exposure–outcome pairing: (1) covariate unadjusted, (2) adjusted for abstinence time (if associated with outcome) and confounders (associated with both exposure and outcome in bivariate analyses), and (3) in a sensitivity analysis, additionally adjusted for variables associated only with the outcome. When the primary exposures were wt/ht at 4 and 12 months, we additionally adjusted for participants' age (days) at examination, as the timing of visits varied widely around the ages for which the growth curves were calibrated (92–150 and 180–540 days, respectively).

Using linear regression models, we assessed associations of both continuous and dichotomous predictors (based on age-specific cut points for overweight/obesity) with continuous semen outcomes. We then used logistic regression to assess associations of continuous and dichotomous predictors with dichotomized semen outcomes (based on WHO reference values). We applied the same strategy using multinomial logistic regression for the combined three-category WHO subfertility outcome variable. In secondary analysis, we regressed continuous and dichotomous semen outcomes on three cumulative overweight/obesity variables (total score and scores for childhood and adulthood). All analyses were performed in SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Descriptive Analyses

Participants who provided semen samples were similar to eligible nonparticipants in terms of gestational age and birth weight, and their mothers were comparable in terms of education, coffee consumption, and alcohol consumption. Mothers of participants who provided semen samples were older than mothers of eligible nonparticipants and more likely to be non-white and have had a prior live birth (eTable 1; http://links.lww.com/EDE/B565).

Participant and parental characteristics did not differ by current BMI category (Table 1). Participants had a mean sperm concentration of 74×10^6 sperm/mL (range: $2.1–430 \times 10^6$ sperm/mL), mean percent progressive motility of 40% (range: 0%–77%), mean percent normal morphology of 7.6% (range: 0%–20%), and mean current BMI of 29 kg/m^2 (range: 19–44 kg/m^2). The three semen parameters were positively correlated with one another (range of Spearman correlation coefficients: 0.37–0.52) (eTable 2; http://links.lww.com/EDE/B565). Also, 9.8% of participants were below the WHO reference level for low sperm concentration, 33% for low percent progressive motility, and 22% for low

percent normal morphology. Abstinence time was positively correlated with sperm concentration (eTable 3; http://links.lww.com/EDE/B565).

The distribution of adiposity measures shifted with age. At 4 months, 79% of participants were in the normal range (<85th percentile), 12% were overweight (≥85th and <95th percentile), and 9% were obese (≥95th percentile). At mean age 44 years, 23% of participants were in the normal range (BMI <25 kg/m^2), 41% were overweight (≥25 and <30 kg/m^2), and 35% were obese (BMI ≥30 kg/m^2) (eFigure 1; http://links.lww.com/EDE/B565). The three childhood adiposity measures were correlated (range of r: 0.45–0.58), as were the three adult adiposity measures (range of r: 0.69–0.84) (eTable 2; http://links.lww.com/EDE/B565).

In bivariate analyses, prenatal variables that were potential sources of selection bias or confounding were not associated with any semen outcome measures and were therefore not included in regression models. All concentration models included abstinence time, which was necessary to calibrate the outcome, and postnatal concentration models additionally included bw/ga, which was associated with the outcome and two childhood adiposity measures. When we added variables only associated with the outcomes to improve model fit, confidence intervals for the associations of interest did not change, so we present results from the simpler models.

Birth Weight Models

Bw/ga was positively associated with square-root sperm concentration: for every percentile increase in bw/ga, mean square-root concentration increased by 0.02×10^3 sperm/mL (95% confidence interval = 0.004, 0.04). Those with bw/ga ≥85th percentile had 1.1 (−0.39, 2.6) $\times 10^3$ sperm/mL higher square-root concentration compared with those with bw/ga <85th percentile, and the parameter estimate increased to 2.8 (−0.01, 5.6) $\times 10^3$ sperm/mL when comparing those with bw/ ga ≥95th percentile to those <95th percentile. Bw/ga was not associated with motility or morphology, or with odds of meeting any of the WHO subfertility criteria (Table 2).

Childhood and Adulthood Adiposity Models Concentration

None of the continuous adiposity measures in childhood or adulthood, including current BMI, was associated with sperm concentration. Overweight/obesity at age 4 years was negatively associated with concentration (B_{4yr} = −0.12 [−2.3, −0.03]). Neither continuous nor dichotomous adiposity measures were associated with increased odds of low sperm concentration (<15 million sperm/mL) at any time point (Table 3).

Motility

Childhood adiposity measures were not associated with percent progressive motility or odds of low motility. Participants who were overweight/obese in their 20s had 5.2 (−9.9, −0.63) points lower percent progressive motility compared with those who were normal weight. This association did not persist and current BMI was not associated with motility. In logistic models, we found the same pattern: overweight/obesity in participants' 20s was associated

with higher odds of low percent progressive motility (<32%) at mean age 44 years (OR_{20s} = 2.4 [1.3, 4.4]), but current adiposity was not (Table 3).

Morphology

Similar to our results for motility, childhood adiposity measures were not associated with percent normal morphology or poor morphology according to the WHO reference level. Participants who were overweight/obese in their 20s had higher odds of poor morphology compared with normal-weight men (OR_{20s} = 1.9 [0.94, 3.8]), but current BMI was not associated with morphology (Table 3).

Subfertility

Participants with BMI ≥25 kg/m^2 in their 20s and 30s had higher odds of meeting two or three WHO subfertility criteria compared with participants with BMI <25 kg/m^2 at the same ages (OR_{20s} = 3.9 [1.6, 9.4]; OR_{30s} = 2.2 [0.87, 5.7]). At the time of semen collection, there was no association between overweight/obesity and subfertility (OR_{44} = 1.1 [0.44, 3.0]) (Table 4).

Cumulative Duration Models

Results of models assessing relations between cumulative duration of excess adiposity and semen quality paralleled our findings in models with age-specific predictors. All regression coefficients for associations between childhood, adulthood, and total cumulative duration of overweight/ obesity measures and square-root sperm concentration had confidence intervals that included the null. We detected no associations between childhood or total cumulative duration of excess adiposity and progressive motility, but each additional adult time point at which participants were overweight/obese was associated with higher odds of low motility (OR_{adult} = 1.3 [0.96, 1.6]). These results were attenuated but in the same direction when restricted to participants with childhood data (OR_{adult} = 1.2 [0.89, 1.6]). Cumulative adiposity measures were not associated with morphology. However, increasing duration of excess adiposity in adulthood was associated with increased odds of meeting at least two WHO subfertility criteria (OR_{adult} = 1.5 [1.0, 2.2]), and the results persisted when restricted to participants with childhood data (OR_{adult} = 1.6 [1.0, 2.9]) (Table 5).

DISCUSSION

In our study of 193 adult male participants from the CHDS birth cohort, we did not find associations between BMI at mean age 44 years with sperm concentration, motility, or morphology. In longitudinal models, the relation of birth weight and adiposity at different ages to semen quality in middle age varied across the life course. Bw/ga was positively associated with sperm concentration, while excess adiposity in early adulthood was negatively associated with percent progressive motility and positively associated with odds of low motility and poor morphology. Overweight/obesity in participants' 20s and 30s was associated with increased odds of meeting at least two WHO subfertility criteria. The lack of associations we observed between current BMI and semen quality are consistent with some but not all prior studies. Discrepancies likely result from differences in study populations. For example, our study included few underweight participants, so was inadequately powered

to detect associations at the low end of the BMI spectrum that may have contributed to other researcher's results.

The positive association we detected between bw/ga and sperm concentration suggests that gestation may be an important developmental window for testicular Sertoli[20] and Leydig[38] cells, which control spermatogenesis. Sertoli cells, which are the first cells to differentiate in the fetal gonad, play an essential role in fetal and neonatal testicular development. In puberty, their role shifts to supporting the transformation of spermatocytes into spermatozoa, under the hormonal regulation of testosterone produced by nearby Leydig cells. Sertoli cells proliferate during both of these periods; following puberty, they reach functional maturity and no longer multiply.[20] Because each Sertoli cell can only support the testosterone-stimulated maturation of a fixed number of spermatocytes at a time,[19,21] prenatal conditions that support proliferation of Sertoli cells will increase sperm concentration later in life.[38,39]

Progressive motility was associated with adiposity in early adulthood in our study. Two biological mechanisms that may explain this finding involve oxidative stress and inflammatory cytokines. Oxidative stress due to obesity results in the buildup of excessive reactive oxygen species (ROS) in the testes,[9,40] which is associated with reduced sperm motility.[41–47] Oxidative stress can adversely affect motility by (1) compromising fluidity and integrity of the sperm plasma membrane[48–50] and (2) damaging mitochondrial DNA[51] and reducing production of ATP,[52,53] which is required to power and sustain flagellation.[53,54] A study of seminal ROS levels in men of proven fertility versus men with low sperm count only or in combination with low motility and/or low morphology found the highest levels of ROS in those with low sperm count and poor motility.[55] Seminal ROS levels were also negatively correlated with progressive motility in a group of male partners of couples attending an infertility clinic.[56]

In addition to increased ROS, obesity leads to elevated serum levels of inflammatory cytokines, including various interleukins (IL), interferon (IFN)-γ, and tumor necrosis factor (TNF)-α,[57,58] and has been associated with increased inflammatory markers in seminal fluid.[9] IFN-γ and TNF-α have been associated with reduced sperm motility in studies of men with genital tract infections and nonspecific inflammatory conditions.[59–63] Among 17 men affected by spinal cord injury, an inflammatory condition associated with low motility, the use of monoclonal antibodies to inactivate IL-6, IL-1β, and TNF-α in the seminal plasma improved sperm motility in all cases.[64] Furthermore, in vitro treatment of semen samples from obese men with resveratrol, an antioxidant and anti-inflammatory agent that has been shown to inhibit IL-6 and IL-1β in laboratory and animal studies,[65–67] improved motility.[68]

Our observation of a strong association between overweight/obesity in participants' 20s and reduced motility at follow-up but no association between current BMI and motility may be due to the cumulative effect of ROS and/or inflammatory cytokine exposure. Because most men gained weight between their 20s and follow-up (eTable 4; http://links.lww.com/EDE/B565), those who were already overweight/obese in their 20s were potentially exposed to excess ROS/inflammatory cytokines for a longer period of time before semen collection compared with men who became overweight/obese later in adulthood. The lack of

association at follow-up, despite the fact that more participants were overweight/obese at that point, may result from a reduced effect of ROS/inflammatory cytokines on motility in men who were overweight/obese for a shorter length of time.

Strengths

This study is the only one we know of that has explored the relation of adiposity over the life course to semen quality in middle age. The CHDS data set includes prospectively measured childhood height and weight as well as a rich array of covariates. Two semen samples were collected from most men, providing a better approximation of long-term average semen quality measures than one sample,[69] and semen collection and analysis followed a validated protocol,[70] minimizing outcome misclassification. Mean concentration and motility in our sample are comparable to those in studies conducted among men from the general population,[71–73] enhancing generalizability.

Limitations

In light of the multiple comparisons that this project entailed, we have focused on results that appeared consistent across various analytic approaches. The confidence intervals of many of our findings included the null, reflecting both our limited sample size, especially of participants with both excessive adiposity at younger ages and poor semen quality, and the possibility of residual confounding. We also lacked childhood adiposity measures in the potentially critical periods of puberty and adolescence. Because of the overall increase in U.S. child adiposity between 1970 and 2000,[74] our use of the 2000 CDC growth charts was likely a source of nondifferential exposure misclassification when we dichotomized our exposure measures, which would bias our results toward the null. Reliance on recalled weight during participants' 20s and 30s could also be a source of error. Because these recall errors are not likely to be associated with semen outcomes and studies of recalled weight among middle-age men in the United States[75] and United Kingdom[76] have found recalled weight to be highly correlated with measured past weight, any resulting bias would be minimal and nondifferential. Finally, our data set did not include measures of seminal ROS, inflammatory cytokines, or sperm DNA fragmentation, all of which have been implicated in poor semen quality.[40,77,78] Nor did it include measures of epigenetic changes to sperm DNA, which have been associated both with obesity[79] and with poor semen quality,[80,81] and which may convey adverse reproductive outcomes associated with obesity to future generations.[82]

Our findings add nuance and complexity to the debate over the relation between adiposity and semen quality. Additional life course studies of adiposity and semen quality in larger cohorts are warranted to confirm these results and expand them to include the important developmental periods of puberty and adolescence. Future studies would ideally use a measure of adiposity that distinguishes between fat and lean mass, assess seminal ROS and inflammatory cytokines, and analyze both nuclear and mitochondrial sperm DNA to assess potential biological mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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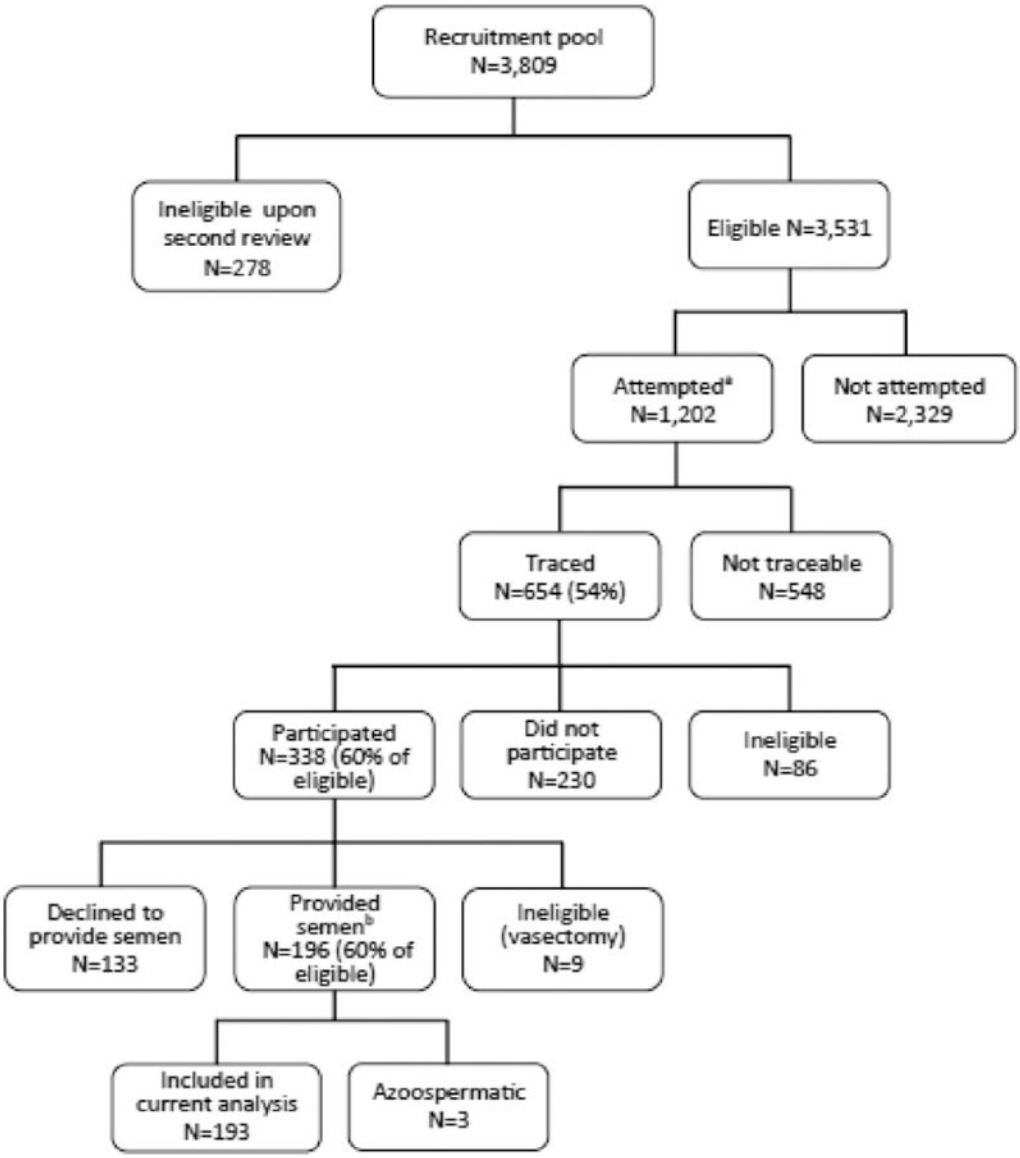

FIGURE.

Participants in the 2005–2008 follow-up to the Child Health and Development Studies included in the current analysis.

[a] Attempted contact

[b] 160 participants provided two samples, 36 provided one

TABLE 1.

Characteristics of the Study Sample by Current BMI Category

	BMI <25 kg/m^2 (n = 44) Mean (SD)	25 ≤ BMI < 30 kg/m^2 (n = 78) Mean (SD)	BMI ≥30 kg/m^2 (n = 67) Mean (SD)	*P*	Total (n = 193[a]) Mean (SD)
Participant at follow-up					
Sperm concentration (×10^6/mL)	68 (54)	76 (68)	74 (53)	0.78	74 (59)
% progressive motility	40 (16)	42 (16)	38 (16)	0.26	40 (16)
% normal morphology	6.9 (3.7)	7.7 (4.1)	8.0 (4.7)	0.40	7.6 (4.2)
Age (years)	44 (1.6)	44 (1.8)	44 (1.6)	0.94	44 (1.7)
Alcohol (g/wk)	88 (121.4)	100 (160)	56 (96)	0.12	82 (130)
Perceived stress scale	12 (5.6)	12 (5.9)	14 (6.2)	0.11	12 (5.9)
Exercise (mins/wk)	520 (870)	530 (730)	570 (780)	0.93	540 (780)
Abstinence time (hr)	97 (43)	100 (98)	113 (100)	0.55	103 (88)
	n (%)	**n (%)**	**n (%)**	***P***	**n (%)**
Participant at follow-up					
Race				0.76	
White	27 (61)	43 (55)	36 (54)		110 (570)
Black	10 (23)	17 (22)	19 (28)		46 (24)
Other	7 (16)	18 (23)	12 (18)		37 (19)
Income (×US$1,000)				0.56	
≤50	12 (27)	21 (28)	21 (35)		55 (31)
50–99	15 (34)	26 (35)	23 (38)		64 (36)
100–149	6 (14)	16 (21)	9 (15)		31 (17)
≥150	11 (25)	12 (16)	7 (12)		30 (17)
Smoking				1.0	
Current	8 (18)	14 (18)	11 (18)		33 (18)
Never/ever	36 (82)	64 (82)	51 (82)		152 (82)
Hormone use				0.42	
Yes	0 (0)	1 (1.3)	2 (3.3)		3 (1.7)
No	42 (100)	75 (99)	59 (97)		180 (98)

Epidemiology. Author manuscript; available in PMC 2020 March 04.

	BMI <25 kg/m^2 (n = 44) Mean (SD)	25 ≤ BMI < 30 kg/m^2 (n = 78) Mean (SD)	BMI ≥30 kg/m^2 (n = 67) Mean (SD)	*P*	Total (n = 193[a]) Mean (SD)
Employment				0.69	
Employed	37 (84)	69 (89)	52 (84)		159 (86)
Unemployed	7 (16)	9 (12)	10 (16)		26 (14)
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	***P***	**Mean (SD)**
Participant at birth					
Birthweight (g)	3,258 (540)	3,456 (442)	3,407 (620)	0.14	3,389 (536)
Gestational age (days)	280 (17)	277 (18)	279 (17)	0.60	279 (17)
Birthweight percentile	37 (28)	51 (25)	45 (29)	0.03	45 (29)
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	***P***	**Mean (SD)**
Parental					
Maternal age (years)	29 (26)	28 (5.7)	29 (6.1)	0.74	28 (5.9)
Maternal BMI (kg/m^2, n = 148)	22 (3.0)	22 (2.3)	23 (3.7)	0.02	22 (3.1)
Paternal BMI (kg/m^2, n = 128)	24 (3.6)	24 (3.5)	25 (2.7)	0.36	24 (3.2)
	n (%)	**n (%)**	**n (%)**	***P***	**n (%)**
Parental					
Maternal parity				0.32	
Nulliparous	4 (9.1)	14 (18)	13 (19)		33 (17)
Parous	40 (91)	64 (82)	54 (81)		160 (83)
Maternal prenatal smoking				0.34	
Yes	13 (30)	20 (26)	12 (18)		46 (24)
No	31 (70)	56 (74)	54 (82)		143 (76)

[a] Includes 4 participants who were missing BMI data.

TABLE 2.

Associations of Birth Weight for Gestational Age Percentile (bw/ga) with Semen Outcomes at Mean Age 44 Years

	Sperm Concentration[a] ($\times 10^3$/mL) *B*[b] (95% CI)	**<15 Million Sperm/mL OR[b] (95% CI)**
bw/ga	n = 193	
Continuous	0.02 (0.004, 0.04)	0.99 (0.98,1.0)
≥85th vs. <85th percentile	1.1 (−0.39, 2.6)	1.1 (0.39, 3.3)
≥95th vs. <95th percentile	2.8 (−0.01, 5.6)	*c*
	Percent Progressive Motility *B* (95% CI)	**<32% Progressive Motility OR (95% CI)**
bw/ga	n = 193	
Continuous	0.03 (−0.05, 0.11)	0.99 (0.98. 1.0)
≥85th vs. <85th percentile	2.1 (−5.3, 9.5)	0.66 (0.23, 1.9)
≥95th vs. <95th percentile	−2.9 (−17, 11)	1.4 (0.23, 8.5)
	Percent Normal Morphology *B* (95% CI)	**<4% Normal Morphology OR (95% CI)**
bw/ga	n = 192	
Continuous	−0.01 (−0.03, 0.02)	1.0 (0.99, 1.0)
≥85th vs. <85th percentile	0.50 (−1.5, 2.5)	1.2 (0.40, 3.4)
≥95th vs. <95th percentile	2.8 (−0.98, 6.5)	*c*

[a] Square-root transformed.

[b] Adjusted for abstinence time.

[c] Model diverged.

TABLE 3.

Associations of Child and Adult Adiposity Measures with Semen Outcomes at Mean Age 44 Years

	Sperm Concentration[a] (×10³/mL) *B*[b] (95% CI)	<15 Million Sperm/mL OR[b] (95% CI)	Percent Progressive Motility *B* (95% CI)	<32% Progressive Motility OR (95% CI)	Percent Normal Morphology *B* (95% CI)	<4% Normal Morphology OR (95% CI)
wt/ht 4 months[c]	n = 153	n = 153	n = 153	n = 153	n = 152	n = 152
Continuous	0.0005 (−0.02, 0.02)	1.0 (0.98, 1.0)	0.03 (−0.07, 0.14)	1.0 (0.98, 1.0)	0.01 (−0.02, 0.03)	1.0 (0.99, 1.0)
≥85th vs. <85th percentile	0.33 (−0.97. 1.6)	0.60 (0.13, 2.9)	−1.6 (−8.9, 5.6)	0.93 (0.36, 2.4)	1.2 (−0.54, 2.9	0.70 (0.26, 1.9)
wt/ht 12 months[c]	n = 152	n = 152	n = 152	n = 152	n = 151	n = 151
Continuous	0.01 (−0.01, 0.03)	1.0 (0.98, 1.0)	0.02 (−0.07, 0.12)	1.0 (0.99, 1.0)	0.01 (−0.02, 0.03)	1.0 (0.99, 1.0)
≥85th vs. <85th percentile	−0.14 (−1.3, 0.99)	1.6 (0.56, 4.8)	1.4 (−6.2, 9.1)	0.77 (0.28, 2.2)	0.48 (−0.91, 1.9)	1.3 (0.61, 2.9)
ssBMI 4 years	n = 160	n = 160	n = 160	n = 160	n = 159	n = 159
Continuous	0.003 (−0.02, 0.02)	1.0 (0.98, 1.0)	−0.01 (−0.10, 0.08)	1.0 (0.99, 1.0)	0.004 (−0.02, 0.03)	1.0 (0.99, 1.0)
≥85th vs. <85th percentile	−0.12 (−2.3, −0.03)	1.7 (0.55, 5.0)	−3.3 (−8.9, 2.3)	1.4 (0.67, 2.8)	−0.24 (−1.7, 1.3)	1.4 (0.60, 3.1)
BMI in 20s	n = 185	n = 185	n = 185	n = 185	n = 184	n = 184
Continuous	−0.01 (−0.14, 0.13)	0.97 (0.84, 1.1)	−0.44 (−1.1, 0.23)	1.1 (0.98, 1.2)	0.08 (−0.10, 0.26)	1.0 (0.94, 1.1)
≥25 vs. <25 kg/m^2	−0.38 (−1.3, 0.54)	1.4 (0.54, 3.6)	−5.2 (−9.9, −0.63)	2.4 (1.3, 4.4)	−0.23 (−1.5, 1.0)	1.9 (0.94, 3.8)
BMI in 30s	n = 185	n = 185	n = 185	n = 185	n = 184	n = 184
Continuous	−0.06 (−0.16, 0.05)	0.95 (0.84, 1.1)	−0.30 (−0.84, 0.23)	1.1 (0.99, 1.1)	0.02 (−0.12, 0.17)	1.0 (0.97, 1.1)
≥25 vs. <25 kg/m^2	0.04 (−0.90, 0.98)	0.89 (0.34, 2.3)	0.02 (−4.7, 4.8)	1.4 (0.73, 2.6)	0.76 (−0.50, 2.0)	1.2 (0.59. 2.5)
Current BMI	n = 189	n = 189	n = 189	n = 189	n = 188	n = 188
Continuous	−0.10 (−0.10, 0.08)	0.92 (0.83, 1.0)	−0.30 (−0.75, 0.15)	1.0 (0.98, 1.1)	0.06 (−0.06, 0.18)	1.0 (0.97, 1.1)
≥25 vs. <25 kg/m^2	0.13 (−0.96, 1.2)	0.45 (0.16, 1.2)	0.38 (−5.1, 5.8)	1.3 (0.60, 2.6)	0.92 (−0.51, 2.4)	1.2 (0.51, 2.6)

[a] Square-root transformed.

[b] Adjusted for bw/ga and abstinence time.

[c] Additionally adjusted for age (days) at examination.

TABLE 4.

Associations of Birth Weight and Adiposity Measures Across Childhood and Adulthood with WHO Subfertility Criteria

	2 or 3 WHO Subfertility Criteria Versus None OR[a] (95% CI)	1 WHO Criterion Versus None OR[a] (95% CI)
bw/ga	n = 192	
Continuous	1.0 (0.98, 1.0)	1.0 (0.99, 1.0)
≥85th vs. <85th percentile	0.79 (0.21, 3.0)	0.77 (0.24, 2.5)
wt/ht 4 months[b]	n = 152	
Continuous	1.0 (0.98, 1.0)	1.0 (0.99, 1.0)
≥85th vs. <85th percentile	0.54 (0.16, 1.8)	0.64 (0.24, 1.7)
wt/ht 12 months[b]	n = 151	
Continuous	1.0 (0.99, 1.0)	1.0 (0.99, 1.0)
≥85th vs. <85th percentile	1.6 (0.67, 4.0)	1.5 (0.68, 3.4)
ssBMI 4 years	n = 159	
Continuous	1.0 (0.98, 1.0)	1.0 (0.99, 1.0)
≥85th vs. <85th percentile	1.4 (0.53, 3.8)	1.2 (0.54, 2.9)
BMI in 20s	n = 184	
Continuous	1.1 (0.97, 1.2)	1.0 (0.91, 1.1)
≥25 vs. <25 kg/m^2	3.9 (1.6, 9.4)	1.1 (0.52, 2.2)
BMI in 30s	n = 184	
Continuous	1.1 (1.0, 1.2)	0.99 (0.91, 1.1)
≥25 vs. <25 kg/m^2	2.2 (0.87, 5.7)	0.56 (0.28, 1.1)
Current BMI	n = 188	
Continuous	1.1 (0.98, 1.1)	0.99 (0.92, 1.1)
≥25 vs. <25 kg/m^2	1.1 (0.44, 3.0)	0.96 (0.42, 2.2)

[a]Adjusted for bw/ga percentile and abstinence time.

[b]Additionally adjusted for age (days) at examination.

Epidemiology. Author manuscript; available in PMC 2020 March 04.

TABLE 5.

Cumulative Duration Models

	n	Sperm Concentration[a] (×10³/mL) *B*[b] (95% CI)	<15 Million Sperm/mL OR[b] (95% CI)
Total overweight/obese points	127	−0.10 (−0.45, 0.25)	1.1 (0.78, 1.6)
Child overweight/obese points (≥85th percentile)	132	−0.29 (−0.84, 0.27)	1.3 (0.78, 2.2)
Adult overweight/obese points (BMI ≥25 kg/m^2)	184	−0.04 (−0.43, 0.35)	0.93 (0.63, 1.4)
Adult overweight/obese points (BMI ≥25 kg/m^2)[c]	127	0.06 (−0.44, 0.57)	0.98 (0.60, 1.6)
	n	**Progressive Motility *B* (95% CI)**	**<32% Progressive Motility OR (95% CI)**
Total overweight/obese points	127	−0.29 (−1.9, 1.3)	1.1 (0.91, 1.4)
Child overweight/obese points (≥85th percentile)	132	−0.38 (−3.0, 2.2)	1.1 (0.80, 1.6)
Adult overweight/obese points (BMI ≥25 kg/m^2)	184	−0.84 (−2.8, 1.1)	1.3 (0.96, 1.6)
Adult overweight/obese points (BMI ≥25 kg/m^2)[c]	127	−0.34 (−2.7, 2.0)	1.2 (0.89, 1.6)
	n	**Percent Normal Morphology *B* (95% CI)**	**<4% Normal Morphology OR (95% CI)**
Total overweight/obese points	126	0.28 (−0.15, 0.70)	1.1 (0.87, 1.4)
Child overweight/obese points (≥85th percentile)	131	0.25 (−0.45, 0.94)	1.1 (0.72. 1.6)
Adult overweight/obese points (BMI ≥25 kg/m^2)	183	0.19 (−0.32, 0.71)	1.2 (0.89, 1.6)
Adult overweight/obese points (BMI ≥25 kg/m^2)[c]	126	0.43 (−0.19, 1.0)	1.2 (0.82, 1.7)
	n	**2 or 3 WHO Subfertility Criteria Versus None OR[b] (95% CI)**	**1 WHO Criterion Versus None OR[b] (95% CI)**
Total overweight/obese points	126	1.3 (0.95, 1.7)	0.90 (0.70, 1.2)
Child overweight/obese points (≥85th percentile)	131	1.1 (0.68, 1.7)	1.0 (0.70, 1.5)
Adult overweight/obese points (BMI ≥25 kg/m^2)	183	1.5 (1.0, 2.2)	0.92 (0.69, 1.2)
Adult overweight/obese points (BMI ≥25 kg/m^2)[c]	126	1.6 (1.0, 2.7)	0.83 (0.58, 1.2)

[a] Square-root transformed.

[b] Adjusted for birth weight for gestational age percentile and abstinence time.

[c] Restricted to participants with childhood measures.