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Secular trends in semen parameters among men attending a fertility center between 2000 and 2017: identifying potential predictors.

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Abstract

Background: Multiple meta-analyses have shown sperm count declines in Western countries spanning eight decades. Secular trends in other parameters remain unclear, as are potential predictors of these trends.

Objective: To analyze secular trends in semen quality and to evaluate whether factors previously found to be related to semen quality were responsible for these patterns.

Methods: This is a prospective study including 936 men of couples seeking infertility treatment who provided 1,618 semen samples at a single center (2000-2017). Self-reported demographic, nutritional and reproductive characteristics were collected using standardized questionnaires. Urinary concentrations of bisphenol A, parabens and phthalates were quantified by isotope-dilution tandem mass spectrometry. Semen samples were analyzed for volume, sperm

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concentration, count, motility and morphology following WHO guidelines. We estimated the differences in semen parameters over time by fitting generalized linear mixed models with random intercepts to account for repeated samples while adjusting for abstinence time. We also adjusted for demographic, nutritional and environmental factors to investigate these as potential predictors of time trends.

Results: Sperm concentration and count declined by 2.62% per year (95% CI −3.84, −1.38) and 3.12% per year (95% CI: −4.42, −1.80), corresponding to an overall decline of 37% and 42%, respectively, between 2000 and 2017. Decreasing trends were also observed for total motility (per year: −0.44 percentage units, 95% CI −0.71, −0.17) and morphologically normal sperm (per year: −069 percentage units, 95% CI −0.116, −0.023). These decreases reflected relative percentage declines of 15% and 16% over the 17 year study period, respectively. When reproductive factors were included in the model, the downward trends in sperm concentration and sperm count were attenuated by 29% and 26%, respectively, while the trends in motility and morphology were attenuated by 54% and 53%, respectively. Also, the downward trends in both sperm concentration and sperm morphology over time were attenuated by 19% when including the DEHP and non-DEHP metabolites, respectively.

Conclusions: Sperm concentration, total count, motility and morphology significantly declined between 2000 and 2017 among subfertile men. These negative trends were attenuated when considering simultaneous changes in reproductive characteristics and urinary phthalates during the course of the study.

Keywords

Semen parameters; secular trends; phthalates; predictors; male infertility

1. Introduction

Male factors, defined according to World Health Organization (WHO) reference values for semen quality, account for 40% of infertility cases (Legare et al. 2014). In addition, poor semen quality has been also associated with higher risk of common chronic diseases (Eisenberg et al. 2016; Latif et al. 2017) and mortality (Eisenberg et al. 2014; Jensen et al. 2009), highlighting their public health importance beyond fertility and reproduction. Whether semen quality parameters have declined has been a matter of ongoing research and debate since 1992, when Carlsen *et al* published a meta-analysis showing a decline in semen quality in Western countries starting in the late 1930s (Carlsen et al. 1992). Others have replicated these findings both in meta-analyses (Swan et al. 1997) and primary analyses from single centers (Feki et al. 2009; Splingart et al. 2011; Sripada et al. 2007). Furthermore, decreasing semen parameters have coincided with an increasing frequency of male reproductive disorders (Skakkebaek et al. 2016). More recently, a rigorous systematic review and meta-regression of 185 studies (42,935 men) excluding subfertile and infertile men confirmed a significant decline in sperm concentration and total sperm count between 1973 and 2011 (Levine et al. 2017).

Despite the consistency across multiple meta-analyses, two major gaps remain in this literature. First, there is little data regarding long-term trends in sperm motility and

morphology, important markers of sperm function. Second, while many authors have suggested that these consistent downward trends may be the result of concomitant changes in “environmental factors,” no study to date has formally tested this hypothesis. To address these gaps, we took advantage of an ongoing study recruiting men attending a single fertility center, in which we have used standardized and rigorous methods to assess a wide range of participant characteristics and lifestyle factors. We analyzed data from men recruited between 2000 and 2017 to investigate the secular trends in semen parameters, and evaluate whether demographic, reproductive, nutritional and environmental factors previously related to semen quality, contributed to the observed secular trends in semen quality.

2. Methods

2.1 Study population

Participants were men in couples seeking infertility treatment at the Massachusetts General Hospital (MGH) between 2000 and 2017. Men, aged 18 to 56 years, and without a history of vasectomy were eligible to participate in the study which aimed to identify environmental determinants of fertility (Meeker et al. 2011; Messerlian et al. 2018). Approximately 50% of those contacted by the research nurses were enrolled. Semen quality did not differ between men who enrolled in the study and men who did not enroll (Hauser et al. 2005). After the study procedures were explained and all questions were answered, participants signed an informed consent form. The study was approved by the Human Subject Committees of the Harvard T.H. Chan School of Public Health and MGH. Between 2000 and 2004, each man provided one semen sample. Starting in 2005, consent procedures changed, allowing access to all diagnostic semen samples of men consenting. The final study sample included 936 men who provided a total of 1,618 semen samples, after excluding 22 men who were azoospermic and 15 who did not provide a semen sample. Of these, in 1,482 semen samples morphologically normal sperm was assessed.

2.2 Assessment of potential predictors

The participant’s date of birth was collected at entry, and weight and height were measured by trained study staff. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. The participants completed a nurse-administered questionnaire that contained additional questions on lifestyle factors, reproductive health, and medical history. Time spent in leisure time physical and sedentary activities was assessed using a validated questionnaire (Wolf et al. 1994). Starting in 2007, diet was assessed using an extensively validated food frequency questionnaire (FFQ) (Yuan et al. 2017) and two data-derived dietary patterns, the ‘Prudent’ and the ‘Western’, were calculated based on reported food intakes using principal component analysis (Gaskins et al. 2012). Urine samples were collected the same day the semen samples were collected. Urinary concentrations of bisphenol A (BPA), methylparaben (MPB), propylparaben (PPB), mono-n-butyl phthalate (mBP), mono-isobutyl phthalate (miBP), monoethyl phthalate (mEP), monobenzyl phthalate (mBzP), mono-2-ethylhexyl phthalate (mEHP), mono-2-ethyl-5-hydroxyhexyl phthalate (mEHHP), mono-2-ethyl-5-oxohexyl phthalate (mEOHP), mono-2-ethyl-5-carboxypentyl phthalate (mECPP) were quantified using tandem mass spectrometry and adjusted for specific gravity as described in detail elsewhere (Hauser et al.

2016; Silva et al. 2007; Ye et al. 2005). For these chemicals, the percentage of urine samples below the limit of detection (LOD) ranged from 1 to 12, with the exception of mEHP that 22% of the urines had concentrations <LOD.

2.3 Semen assessment

Semen samples were collected on site at MGH in a sterile plastic specimen cup following a recommended 48-hour abstinence period (Meeker et al. 2010; Minguez-Alarcon et al. 2017). Of the 936 men in the study, 648 (69%) contributed 1 semen sample, 128 (14%) contributed 2 samples, 63 (7%) contributed 3 samples, and 97 (10%) contributed 4 or more samples (range=4-11). Semen volume (mL) was measured by an andrologist using a graduated serological pipet. Sperm concentration (mil/mL) and motility (% motile) were assessed using a computer-aided semen analyzer (CASA; 10HTM-IVOS, Hamilton-Thorne Research, Beverly, MA). To measure semen concentration and motility, 6 μl of semen was placed into a pre-warmed (37°C) and disposable Leja Slide (Spectrum Technologies, CA, USA). A minimum of 200 sperm cells from at least four different fields were analyzed from each specimen. Total sperm count (mil/ejaculate) was calculated by multiplying sperm concentration by semen volume. Motile spermatozoa were defined as according to the World Health Organization (WHO) four-category scheme: rapid progressive, slow progressive, non-progressive, and immotile (World Health Organization 2010). Sperm morphology (% normal) was assessed on two slides per specimen (with a minimum of 200 cells assessed per slide) via a microscope with an oil-immersion 100× objective (Nikon, Tokyo, Japan). Strict Kruger scoring criteria was used to classify men as having normal or below normal morphology (Kruger et al. 1988). Andrologists were trained in semen analysis and participated in rigorous daily and weekly internal quality control (QC) and external monitoring of within and between observer variation over all the entire study period as required to maintain CLIA certification and accreditation by the College of American Pathologists

2.4 Statistical analysis

Demographic, reproductive, nutritional, urinary concentrations of environmental chemicals, and semen quality parameters were presented using median ± interquartile ranges (IQRs) or percentages. Differences in these factors across years of the study period were evaluated using linear regression models, and random subject effects were used to account for repeated measurements within the same man for abstinence time and environmental factor models. Sperm concentration and total count had skewed distributions and were natural log-transformed before analysis to more closely approximate a normal distribution. Multivariable generalized linear mixed models with to estimate the differences in semen parameters across the years, adjusting for abstinence time (days). Specifically, we used the model

$$y_{ij} = \alpha + \beta x_{ij} + v_i + e_{ij}$$

where y_{ij} represents individual semen analyses for each man (i) at different times (j), x_{ij} represents the vector of covariates for each man at different times, v_i represents the random

intercept for each individual and e_{ij} represents the random error term. The independent variable, year, was used as categorical to report the marginal means per year and continuous to calculate the decrease per year. To allow for better interpretation of the results, population marginal means (Searle et al. 1980) were presented at the mean level for continuous covariates and the weighted frequency for categorical variables. Potential non-linear trends over time were also explored by including year (expressed as year-2000) as a quadratic variable in the models. We evaluated the robustness of the findings by: 1) restricting analyses to one semen sample (first sample) per man, 2) excluding from analyses all samples below the WHO reference limits, and 3) excluding men who did not complete the FFQ and therefore they had missing nutritional data.

To investigate whether secular trends in semen quality were explained by factors previously related to semen quality in this population, we included each of these factors individually as covariates in the regression models (one at a time, and also in groups). The relative change was calculated as a percentage for each semen parameter, comparing the slope estimate between the adjusted model and the crude model, restricting to just those men with available data for the specific factor(s) evaluated. Statistical analyses were performed with SAS (version 9.4; SAS Institute Inc., Cary, NC, USA).

3. Results

Participants were mostly white (85%), 31% had ever smoked and they had a median (interquartile range [IQR]) age of 35.7 (32.7, 39.6) years and BMI of 27.1 (24.8, 29.9) kg/m^2 (Table 1). More than half (56%) of the men reported undergoing a previous infertility exam and 77 (10%) had a history of varicocele. Most men's semen quality parameters were above the WHO 2010 reference levels, although the proportion of men with values below these limits (Cooper et al. 2010) was greater than 10% for all semen parameters (Supplemental Table S1). Some participant characteristics changed significantly over the study period (Table 1). Over the 17 years of enrollment, there was a slight decrease in having a history of previous infertility exam (−0.17% per year) and in the duration of abstinence (−0.10 days per year). Demographic as well as nutritional characteristics (BMI, physical activity, intake of alcohol and caffeine, and summary measures of diet quality) remained stable over time (Table 1). Similarly, urinary concentrations of parabens remained stable over the study period. In contrast, urinary concentrations of BPA and most phthalate metabolites decreased significantly over the study period with the exception of miBP, which increased significantly, and mBP and mCPP which remained stable (Table 1).

Sperm concentration, total count, total motility and percent morphologically normal sperm decreased significantly over the study period (2000-2017) (Table 2, Figure 1). In models adjusted for abstinence time, sperm concentration and total sperm count declined by 2.62% per year (95% CI −3.84, −1.38) and 3.12% per year (95% CI: −4.42, −1.80), corresponding to an overall decline of 37% and 42%, respectively, between 2000 and 2017 (Figure 1). Decreasing trends were also observed for total motility (per year: −0.44 percentage units, 95% CI −0.71, −0.17) and morphologically normal sperm (per year: −0.069 percentage units, 95% CI −0.116, −0.023) (Figure 1. These decreases reflected relative percentage declines of 15% and 16% over the 17 year study period, respectively. Ejaculate volume

remained stable over the study period (Table 2). There was no evidence of non-linearity in the time trends in semen quality (data not shown).

We tested the robustness of our findings in a series of sensitivity analyses. Downward trends were still observed for sperm concentration, total count, motility and morphology when analyses were restricted to the first semen sample per man, when samples with values below WHO 2010 reference limits were excluded, and in analyses restricted to men who had completed dietary assessments (Supplemental Table S2). The downward trends for all parameters were of similar magnitude in the analyses restricted to men with diet data, steeper in analyses restricted to one sample per man, and less steep when excluding men below WHO 2010 reference limits.

Lastly, we investigated whether demographic, reproductive, nutritional and environmental exposures previously related or hypothesized to be related to semen quality could explain the secular trends in semen quality. When reproductive factors were included in the model, the downward trends in sperm concentration and sperm count were attenuated by 29% and 26%, respectively, while the trends in motility and sperm morphology were attenuated by 54% and 53%, respectively (Table 3). Most of the attenuation resulted from an increase in the proportion of men with a previous infertility exam (Supplemental Table S3). The observed trends were also attenuated when including urinary concentrations of phthalates in the models. Specifically, the downward trends in both sperm concentration and morphology over time were attenuated by 19% when including the DEHP and non-DEHP metabolites, respectively (Table 3). When individual metabolites were examined, urinary mECPP accounted for most of the contribution of DEHP metabolites towards decreasing sperm concentration, and urinary concentrations of miBP and mCPP accounted for most of the contribution of non-DEHP metabolites to the decreasing trend in morphologically normal sperm (Supplemental Table S3). The observed trends in sperm counts (sperm concentration and total count) were not substantially attenuated by including any of the demographic, nutritional or other environmental exposures considered (BPA and parabens). (Table 3, Supplemental Table S3).

4. Discussion

We observed significant downward trends in sperm concentration, total count, total motility and morphologically normal sperm in semen samples of men attending a fertility center in Boston, MA between 2000 and 2017. Yearly decrease in semen parameters were attenuated up to 54% when including reproductive characteristics in the models. The downward trends in sperm concentration and morphology also were attenuated by 19% when including urinary phthalate concentrations in the models. Including several demographic, nutritional and other environmental factors previously related to semen quality in this and other studies (Chavarro et al. 2010; Cutillas-Tolin et al. 2015; Gaskins et al. 2014; Gaskins and Chavarro 2018; Meeker et al. 2010; Meeker et al. 2011), did not substantially change the secular trends in this study population of men attending a fertility center. If replicated, these results may help to reduce economic burden of male infertility and the associated morbility and mortality in men (Eisenberg et al. 2014; Eisenberg et al. 2016; Hauser et al. 2015; Latif et al. 2017).

Our results are consistent with three meta-analyses, collectively covering the period between 1934 and 2013, that have documented downward trends in sperm concentration and total sperm county. In the first of these meta-analyses on 61 studies, which excluded subfertile men, Carlsen *et al* reported a decline in total sperm concentration of 1% per year between 1940 and 1990 (Carlsen et al. 1992). Swan and colleagues (Swan et al. 1997) extended this meta-analysis by including 101 studies and reported a downward trend in sperm concentration (0.94 mil/mL per year). More recently, Levine *et al* conducted an even larger meta-analysis including 185 studies and 42,935 men, again excluding subfertile and infertile men. This meta-analysis confirmed significant declines in sperm concentration and total sperm count between 1973 and 2011 (−0.75% per year and 28.5% overall, for both outcomes (Levine et al. 2017), which were particularly pronounced among Western men.

While compelling, these meta-analyses were limited in their ability to examine secular trends in sperm motility and morphology. They also excluded studies conducted in fertility centers and were unable to adjust for potential time trends in factors that may impact semen quality. In contrast, our single fertility center study, albeit smaller in sample size, was able to consider sperm motility and morphology and adjust for some environmental and nutritional trends. Other studies have also explored trends using data on infertile couples and included measures of motility and morphology. Overall declines in sperm concentration and morphology were reported among French male partners of women with bilateral tubal blockage between 1989 and 2005, although no decrease in motility was observed (Rolland et al. 2013). Sperm concentration also decreased significantly among men seeking evaluation for infertility in Vienna between 1986 and 2003, but no secular trends were observed for motility or normal morphology (Lackner et al. 2005). No evidence of deteriorating semen quality based on sperm counts were found among infertile men in Northeastern Spain between 1960 and 1996 (Andolz et al. 1999) or among Swedish men in infertile couples between 1985 and 1995 (Berling and Wolner-Hanssen 1997). In addition, one recent study including over 6,000 young men attending the military system in Copenhagen (Denmark) found, overall, no persistent temporal trends in semen quality, testicular volume or levels of follicle-stimulating hormone over the 21 years studied (1996-2016) (Priskorn et al. 2018).

Studies evaluating secular trends in semen quality conclude that such trends may be explained by poorly specified environmental factors (Carlsen et al. 1992; Levine et al. 2017; Swan et al. 1997). However, to our knowledge, no study to date has tested the hypothesis that specific environmental factors are explanations for a downward trend in semen quality. Including environmental factors, such as BPA and parabens, and energy/nutritional factors that we have previously found related to or hypothesized to impact semen quality in our cohort (Chavarro et al. 2010; Gaskins et al. 2014; Meeker et al. 2010; Meeker et al. 2011) did not substantially change the downward trends in semen parameters. However, the downward trends in sperm concentration and normal morphology were attenuated when including urinary concentrations of phthalates in the models. Our results do not rule out the possibility that these consistent trends in semen quality may be explained by yet to be determined environmental factors.

The most salient strength of the study was our ability to evaluate multiple environmental correlates of semen quality as potential contributors to the downward trends in semen

quality, which has not been addressed in any previous study and that was made possible by the long-term, consistent and standardized assessment of environmental, nutritional and lifestyle factors in our study. In addition and in contrast to the meta-analyses, we were able to evaluate long-term trends in sperm motility and morphology. Although there are important strengths imparted by studying an infertility clinic population, the choice of study population also represents a limitation. It is uncertain whether our findings can be generalized to men in the general population and in non-Western countries. However, our findings are comparable to those observed in studies which excluded men with known fertility issues. This may be because men in our study tended to have good semen quality compared to international reference standards (World Health Organization 2010) and fertile men (Levine et al. 2017) and findings remained unchanged when samples below WHO reference limits were excluded. Another limitation is the lack of data on all potential predictors in all study participants over the study period, which prevented us from evaluating potential contributors to the trends in semen quality simultaneously adjusting for all potential predictors.

5. Conclusion

Overall declines in sperm concentration, total count, total motility and morphologically normal sperm were observed among men attending a fertility center in Boston between 2000 and 2017. These decreases in temporal trends were attenuated when reproductive characteristics and urinary phthalate concentrations were considered in the models. Further research is needed to confirm these results in our study and others, given their potential public health consequences for fertility and overall male health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

1) Sperm concentration and total count declined 37% and 42%, respectively, between 2000 and 2017 among men attending a fertility center in Boston.

2) Total motility and morphologically normal sperm declined 15% and 16% over the 17 year study period, respectively.

3) When reproductive factors were included in the model, the downward trends in sperm concentration and sperm count were attenuated by 29% and 26%, respectively, while the trends in motility and morphology were attenuated by 54% and 53%, respectively.

4) The downward trends in both sperm concentration and sperm morphology over time were attenuated by 19% when including the DEHP and non-DEHP metabolites, respectively.

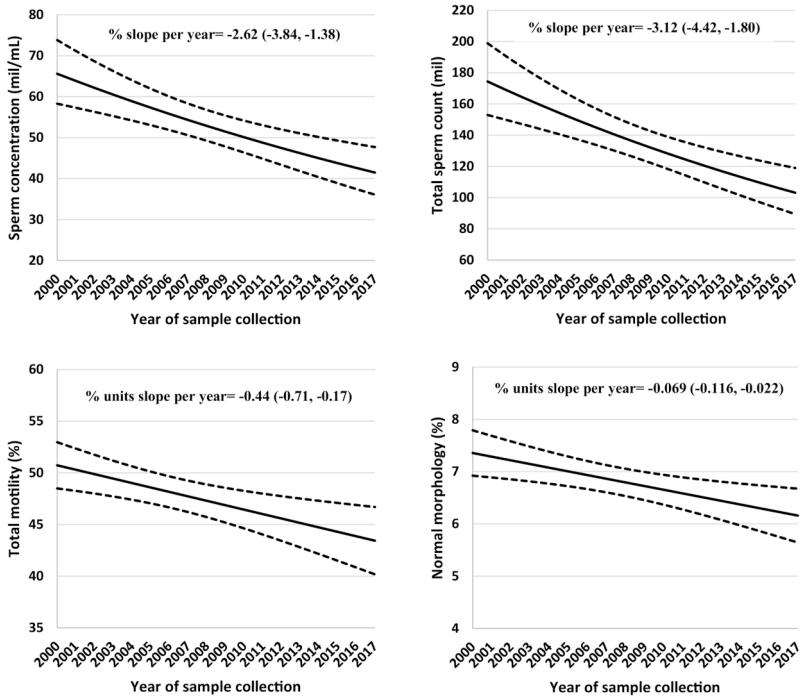

Figure 1. Secular trends in sperm concentration, total sperm count, sperm motility and normal morphology among men attending a fertility center in Boston between 2000 and 2017.

The solid lines represent the adjusted mean for semen parameters by year of sample collection, the dotted lines are the upper and lower 95% confidence intervals for the adjusted means. Adjusted means are presented for average abstinence time (2 days). N=936 men and 1,618 semen samples for all parameters except sperm morphology, which was assessed in 1,482 semen samples.

Table 1.

Demographic, reproductive history and other lifestyle characteristics among men attending a fertility center in Boston between 2000 and 2017.

	Sample size	Total cohort median (IQR) or N (%)	Change per year β, p-value	
Demographics				
Age, years	936	35.7 (32.7, 39.6)	0.04	0.26
Race, % White	936	798 (85)	0.02	0.26
Ever smoked, %	936	290 (31)	−0.02	0.25
Reproductive characteristics				
Previous infertility exam (yes), %	915	514 (56)	−0.17	<.0001
Ever made partner pregnant (yes), %	906	358 (40)	0.01	0.37
Varicocele (yes), %	786	77(10)	0.02	0.42
Abstinence time, days	1,618	2.42 (2.00, 3.33)	−0.10	<.0001
Nutritional factors				
BMI, kg/m^2	936	27.1 (24.8, 29.9)	0.01	0.65
Physical activity, hrs/day	436	4.00 (0.27, 9.34)	0.17	0.31
Prudent pattern[a]	276	−0.20 (−0.72, 0.56)	0.04	0.09
Western pattern[a]	276	−0.14 (−0.64, 0.54)	−0.02	0.33
Alcohol intake, g/day	276	9.64 (3.07, 19.7)	−0.03	0.94
Caffeine intake, mg/day	276	160 (71.2, 271)	2.40	0.40
Environmental factors				
Urinary concentrations, ng/mL:				
BPA	1,108	1.12 (0.67,2.00)	−0.06	0.07
MPB	1,066	20.3 (8.70, 63.8)	1.34	0.53
PPB	1,066	1.84 (0.52, 10.5)	−0.29	0.40
mEP	1,378	52.3 (19.5, 170)	−29.8	<.0001
mBP	1,378	10.3 (5.6, 17.9)	−3.59	0.18
miBP	1,023	6.34 (3.50, 11.1)	0.55	0.0007
mCPP	1,023	2.70 (1.31, 6.98)	0.72	0.19
mBzP	1,378	3.67 (1.80, 7.22)	−0.63	<.0001
mEHP	1,378	2.66 (1.12, 7.00)	−1.76	<.0001
mEHHP	1,154	13.3 (6.44, 32.9)	−11.7	<.0001
mEOHP	1,154	7.93 (3.82, 20.1)	−7.38	<.0001
mECPP	931	17.6 (9.00, 39.1)	−20.0	<.0001

Abbreviations: BMI, Body Mass Index; BPA, bisphenol A; BPB, methylparaben; PPB, propylparaben; mBP, mono-n-butyl phthalate; miBP, mono-isobutyl phthalate; mEP, monoethyl phthalate; mBzP, monobenzyl phthalate; mEHP, mono-2-ethylhexyl phthalate; mEHHP, mono-2-etliyl-5-hydroxyhexyl phthalate; mEOHP, mono-2-ethyl-5-oxohexyl phthalate; mECPP, mono-2-ethyl-5-carboxypentyl phtlialate; mCPP, mono-3-carboxypropyl phtlialate.

[a]The dietary patterns do not have units since they are calculated using principal component analysis (Gaskins et a., 2012).

Table 2.

Predicted marginal means (95% CI) for semen parameters[a] over time among 936 men (contributing 1,618 semen samples) attending a fertility center in Boston between 2000 and 2017.

Year of sample collection	N (samples)	Ejaculate Volume (mL)	Sperm Concentration (mil/mL)	Total Sperm Count (mil/ejaculate)	Total Motility (%)	Normal Morphology[b] (%)
2000	151	2.69 (2.46, 2.92)	72.8 (60.5, 87.6)	168 (137, 206)	52.0 (48.3, 55.6)	7.49 (6.74, 8.25)
2001	130	3.09 (2.81,3.38) *	58.5 (47.4, 72.2)	157 (126, 196)	49.3 (45.1, 54.6)	7.17 (6.42, 7.93)
2002	93	3.43 (3.05, 3.81) *	65.5 (52.0, 82.5)	187 (148, 236)	49.8 (45.1, 54.6)	7.17 (6.29, 8.05)
2003	73	3.28 (2.86, 3.71) *	64.3 (50.3, 82.1)	182 (141,232)	48.3 (43.4, 53.2)	7.16 (6.28, 8.03)
2004	55	3.58 (3.08,4.07) *	56.9 (42.6, 75.9)	174 (132, 231)	48.8 (43.8, 53.8)	8.27 (7.01, 9.53)
2005	30	2.97 (2.37, 3.58)	57.8 (40.5, 82.5)	151 (107, 214)	51.2 (44.8, 57.5)	5.47 (3.96, 6.99) *
2006	76	3.13 (2.85, 3.41) *	71.3 (54.7, 92.9)	203 (152, 270)	47.9 (41.5, 54.4)	6.26 (5.12, 7.40) ≠
2007	71	2.95 (2.62, 3.28)	47.9 (39.5, 58.0) *	123 (98.9, 152) *	48.4 (43.5, 53.3)	6.35 (5.45, 7.25) ≠
2008	121	2.90 (2.65, 3.16)	53.3 (46.3, 61.3) *	140 (119, 164)	45.8 (42.0, 49.5) *	5.40 (4.75, 6.05) *
2009	139	2.71 (2.49, 2.93)	52.9 (45.2, 61.9) *	128 (110, 150) *	45.4 (41.9, 49.0) *	6.72 (5.87, 7.57)
2010	134	2.73 (2.50, 2.96)	51.4 (44.5, 59.4) *	124 (106, 144) *	43.6 (39.5, 47.6) *	6.39 (5.66, 7.11) *
2011	113	2.74 (2.51, 2.96)	48.4 (41.2, 56.8) *	119 (99.7, 140) *	42.3 (38.0, 46.6) *	6.34 (5.58,7.09) *
2012	73	2.87 (2.60, 3.14)	46.8 (37.4, 58.4) *	118 (92.1, 151) *	41.6 (36.0, 47.1) *	6.31 (5.50, 7.12) *
2013	97	2.73 (2.49, 2.97)	42.2 (35.4, 50.2) *	99.2 (80.0, 123) *	41.2 (37.7, 44.7) *	6.69 (5.84, 7.54)
2014	77	2.89 (2.59, 3.19)	45.8 (38.7, 54.1) *	117 (96.2, 143) *	48.5 (44.3, 52.8)	7.58 (6.86, 8.29)
2015	72	2.62 (2.25, 2.99)	41.7(33.7, 51.5) *	91.9 (72.1, 117) *	48.2 (43.1, 53.2)	6.21 (5.32, 7.09) *
2016/2017	113	2.92 (2.61, 3.22)	49.0 (39.8, 60.2) *	122 (98.0, 153) *	45.8 (41.1, 50.6) *	6.08 (5.36, 6.91) *

Abbreviations: ml, milliliters; mil, million.

[a] Adjusted for abstinence time (days).

[b] Morphologically nonnal sperm was assessed in 1,482 semen samples.

* p-value≤0.05 when compared against samples obtained in 2000.

≠ p-value<0.10 when compared against samples obtained in 2000.

Table 3.

Decrease in sperm parameters (per year) over time after adjusting for different factors among men attending a fertility center in Boston between 2000 and 2017.

Models	N (men /samples)	Sperm concentration (mil/mL) % 95% CI	Total sperm count (mil) % 95% CI	Total motility (%) % units 95% CI	Normal morphology (%) %units 95% CI
Main analysis	936 / 1,618	−2.62(−3.84, −1.38)	−3.12(−4.42, −1.80)	−0.44(−0.71, −0.17)	−0.069(−0.116, −0.022)
+ Demographics	936 / 1,618	−2.70 (−3.92, −1.47)	−3.10 (−4.39, −1.79)	−0.43 (−0.70, 0.17)	−0.069 (−0.116, −0.022)
+ Reproductive	764 / 1,408	−1.84 (−3.26, −0.40)	−2.09 (−3.62, −0.55)	−0.31 (−0.61, −0.01)	−0.025 (−0.076, 0.026)
+ Energy balance	436 / 1,118	−2.41 (−4.80, 0.03)	−3.30 (−5.81,−0.73)	−0.21 (−0.74, 0.32)	0.055 (−0.038, 0.148)
+ Diet quality	276 / 765	−2.57 (−5.55, 0.50)	−2.47 (−6.00, 1.20)	−0.49 (−1.18, 0.21)	0.051 (−0.069, 0.171)
+ BPA	596 / 1,108	−2.46 (−4.40, −0.85)	−2.23 (−4.01, −0.43)	−0.27 (−0.61, 0.08)	−0.063 (−0.129, 0.002)
+ Parabens	576 / 1,066	−2.49 (−4.08, −0.88)	−2.24 (−4.03, −0.43)	−0.26 (−0.61, 0.09)	−0.067 (−0.133, −0.001)
+ DEHP	419 / 931	−1.57 (−4.16, 1.08)	−2.95 (−5.69, −0.13)	0.03 (−0.51, 0.57)	0.008 (−0.098, 0.114)
+ non-DEHP	511 / 1,023	−2.13 (−4.04, 0.18)	−3.43 (−5.45, −1.36)	−0.18 (−0.62, 0.26)	−0.017 (−0.096, 0.063)

Main analysis: abstinence time.

Demographics: main analysis + age, race and smoking.

Reproductive characteristics: main analysis + previous infertility exam, ever made partner pregnant, varicocele.

Energy balance: main analysis + BMI and physical activity.

Diet quality: main analysis + Prudent and Western diet patterns.

BPA: main analysis + BPA

Parabens: main analysis + MPB+PPB

DEHP: main analysis + mEHP+mEHHP+mEOHP+mECPP

Non-DEHP: main analysis + miBP+mBP+mBzP+mEP+mCPP

Note: Each model included the semen samples with available data for all the covariates in that specific model.

Abbreviations: BMI, Body Mass Index; BPA, bisphenol A; DEHP, di(2-ethylhexyl)phthalate; MPB, methylparaben; PPB, propylparaben; mBP, mono-n-butyl phthalate; miBP, mono-isobutyl phthalate; mEP, monoethyl phthalate; mBzP, monobenzyl phthalate; mEHP, mono-2-ethylhexyl phthalate; mEHHP, mono-2-ethyl-5-hydroxyhexyl phthalate; mEOHP, mono-2-ethyl-5-oxohexyl phthalate; mECPP, mono-2-ethyl-5-carboxypentyl phthalate; mCPP, mono-3-carboxypropyl phthalate.