

A North American prospective study of depression, psychotropic medication use, and semen quality

Jennifer J. Yland, M.S.,^a Michael L. Eisenberg, M.D.,^{b,c} Elizabeth E. Hatch, Ph.D.,^a Kenneth J. Rothman, Dr.P.H.,^{a,d} Craig J. McKinnon, Ph.D.,^a Yael I. Nillni, Ph.D.,^{e,f} Greg J. Sommer, Ph.D.,^g Tanran R. Wang, M.P.H.,^a and Lauren A. Wise, Sc.D.^a

^a Department of Epidemiology, Boston University School of Public Health, Boston, Massachusetts; ^b Department of Obstetrics and Gynecology, Stanford University School of Medicine, Stanford, California; ^c Department of Urology, Stanford University School of Medicine, Stanford, California; ^d RTI Health Solutions, Research Triangle, North Carolina; ^e Department of Psychiatry, Boston University School of Medicine, Boston, Massachusetts; ^f National Center for PTSD, Women's Health Sciences Division at VA Boston Healthcare System, Boston, Massachusetts; and ^g Sandstone Diagnostics, Inc., Pleasanton, California.

Objective: To evaluate the associations of a history of diagnosed depression, current depressive symptoms, and recent use of psychotropic medications with semen quality and to consider mediation of the association between depression and semen quality by medication use.

Design: Prospective cohort study.

Setting: United States.

Patient(s): The patients were 329 men aged ≥ 21 years (566 semen samples) who participated in a semen-testing substudy of Pregnancy Study Online. Pregnancy Study Online is an ongoing, web-based preconception cohort study of couples attempting to conceive. At baseline, participants reported information about depression diagnosis, depressive symptoms using the Major Depression Inventory, medication use in the last 4 weeks, and selected covariates.

Intervention(s): None.

Main Outcome Measure(s): The men used an at-home semen-testing kit (Trak; Sandstone Diagnostics, Inc., Pleasanton, California) to measure semen volume, sperm concentration, and motile sperm concentration. We calculated percent motility, total sperm count in the ejaculate, and total motile sperm count.

Result(s): Forty-nine men (15%) reported a history of depression diagnosis, and 41 (12%) reported recent use of psychotropic medications. A history of depression diagnosis was associated with a 4.3-fold increase in the risk of low semen volume (<1.5 mL) (95% CI 1.16, 16). A 5-unit increase in Major Depression Inventory score was associated with a 1.38-fold increase in the risk of low semen volume (95% CI 0.92, 2.1). The results for other semen parameters were inconsistent. Recent use of psychotropic medications was associated with worse semen quality, and this association was confounded by a history of depression diagnosis. The observed association between depression and semen volume showed little mediation by psychotropic medication use.

Conclusion: A history of diagnosed depression and severe depressive symptoms at enrollment were associated with low semen volume. (Fertil Steril® 2021;116:833–42. ©2021 by American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

Key Words: Depression, psychotropic medications, semen analysis

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Major depressive disorder (depression) affects about 15% of males in the United States (1) and is a leading cause of disability worldwide (2). Depression is characterized by changes in cognitive

or physical symptoms lasting for at least 2 weeks, including low mood, sadness, despair, anhedonia, fatigue, and changes in eating and sleeping. It may be treated with psychotherapy, medication, or a combination of the two. The use of antidepressants has been associated with a wide range of side effects, including sexual symptoms such as loss of libido, erectile dysfunction, and anorgasmia (3, 4). Selective serotonin reuptake inhibitors (SSRIs), the most commonly prescribed class of antidepressants, have been associated with reduced semen quality in several studies

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Reprint requests: Jennifer J. Yland, M.S., Department of Epidemiology, Boston University School of Public Health, 715 Albany Street, Boston, Massachusetts 02118 (E-mail: yland@bu.edu).

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(5–7). Thus, depression and use of antidepressants could play a role in the etiology of infertility (8, 9). However, disentangling the role of depression from the effects of antidepressant medications is challenging.

Approximately 40% to 50% of infertility among couples is attributable to male factors (10). Studies of the associations between stress, depression, or anxiety and semen quality have yielded inconsistent results (11–17). Whereas several studies have reported an association between depression or depressive symptoms and poor semen quality (11, 15, 17), others have found no meaningful association (12, 14). In addition well-being (16) and stress (13) have been associated with some, but not all, semen quality parameters. The heterogeneity of these findings could be because of different research settings, laboratory instruments, or analytic techniques, including confounding control. In addition, not all studies accounted for abstinence time (time since the last ejaculation) before semen sampling, which can substantially affect measurements of semen quality (18). We prospectively evaluated the relationships of depressive symptoms and antidepressant use with semen quality among men participating in a preconception cohort study.

MATERIALS AND METHODS

Study Population

This investigation was conducted within Pregnancy Study Online (PRESTO), a web-based North American prospective cohort study of women planning to become pregnant and their male partners (2013–2020) (19). After completing a baseline questionnaire, female participants were given the option to invite their male partners aged ≥ 21 years to participate. Male partners residing in the United States who were enrolled in PRESTO, who reported ≤ 6 months of pregnancy attempt time at study entry, and whose female partners reported having a regular menstrual cycle were invited to participate in a semen-testing substudy (20). The present analysis was conducted among 329 men who participated in this substudy and who provided results from at least one semen test ($n = 566$ samples). The Boston University Medical Campus Institutional Review Board approved the study protocols for PRESTO and the semen substudy. All participants provided online informed consent.

Ascertainment of Semen Quality Data

Semen testing was performed with the Trak Male Fertility Testing System (Sandstone Diagnostics, Inc., Pleasanton, California), an at-home semen-testing device (20–23). Male participants were mailed a battery-powered mini-centrifuge, two test kits, and an instructional guide for using the system. The test kits included a sample collection cup that additionally measured semen volume and plastic cartridges for measuring sperm concentration and motile sperm concentration (Supplemental Fig. 1, available online). The participants were asked to complete both semen tests at an interval of 7 to 10 days during their partner's luteal phase (to avoid interfering with intercourse during the fertile window) and to aim for a consistent abstinence time before

both tests. After ejaculating into the collection cup, the participants loaded approximately 0.25 mL of semen into the cartridge and spun the sample for 6 minutes in the provided centrifuge.

The Trak system provides a visual measurement of semen volume (mL), sperm concentration (millions/mL), and motile sperm concentration (millions/mL). Using an online platform, the participants were instructed to report their visual assessment of the test results, to upload smartphone images of their concentration and motility results for calibration purposes, and to report their abstinence time in days for each test. Men who uploaded both tests were provided with \$20 compensation for their efforts. However, some men provided results from only one test. We calculated percent motility as motile sperm concentration/sperm concentration, total sperm count in ejaculate (millions) as (sperm concentration $\times$ semen volume), and total motile sperm count (millions) as (motile sperm concentration $\times$ semen volume).

Ascertainment of Exposure and Covariate Data

In the baseline questionnaire, the participants provided information on their sociodemographic characteristics, lifestyle, and medical history. The participants were asked if they had ever been diagnosed with depression. Those who responded “yes” were asked to report the year they were first diagnosed, whether they had ever taken medication for depression, whether they had taken medication for depression within the past 4 weeks, and the name of the medication they took most recently. Analogous questions were asked about anxiety and panic disorders. From these data, we generated variables for recent use (within 4 weeks) of any psychotropic medication, any SSRI, any serotonin-norepinephrine reuptake inhibitor (SNRI), any other antidepressant (atypical, tetracyclic, and tricyclic antidepressants), and any nonantidepressant psychotropic medication (Supplemental Table 1). In addition, each participant completed the Major Depression Inventory (MDI), a 12-item tool that assesses depressive symptoms during the past 2 weeks (range of scores: 0–50), with a higher score indicating more severe symptoms (24). The MDI has been validated previously in other populations and has high sensitivity (0.86) and specificity (0.86) compared with clinician-diagnosed major depressive disorder (25). Suggested MDI threshold values are 21 for mild depression, 26 for moderate depression, and 31 for severe depression. We created an additional dichotomous exposure variable for reporting a history of depression diagnosis or having an MDI score ≥ 21 (the threshold for mild depression).

Statistical Analysis

We performed three sets of analyses: an analysis that dichotomized semen parameters using clinical standards; an analysis that included each semen parameter as a continuous, log-transformed quantitative variable; and an analysis that evaluated the extent to which the association between a history of depression diagnosis and selected semen parameters (if any) was mediated by the use of psychotropic medications.

In the first analysis, we dichotomized semen quality parameters using the World Health Organization (WHO) lower reference limits (26, 27). We estimated risk ratios for the associations between the exposure variables and low semen volume (<1.5 mL), low sperm concentration (<15 million/mL), low motility (<40%), low total sperm count (<39 million), and low total motile sperm count (<16 million). The exposures evaluated were a history of depression diagnosis (ever vs. never), MDI score (change associated with a 5-unit increase in MDI score), any evidence of depression (ever diagnosed or MDI score ≥ 21 vs. neither marker), and recent use of psychotropic medication (any use vs. no use in the past 4 weeks). For these analyses, we fitted log-binomial generalized estimating equation (GEE) models accounting for correlated outcomes within men who contributed results from two semen tests (the unit of observation was semen test).

For the second analysis, we estimated the percent difference in semen volume (mL), sperm concentration (millions/mL), motility (%), total sperm count (millions), and total motile sperm count (millions) associated with the exposure variables. The exposures evaluated were a history of depression diagnosis, MDI score, recent use of psychotropic medication, and recent use of SSRIs (any use vs. no use in the past 4 weeks). We converted continuous measures of semen parameters to their natural logarithms to reduce the influence of extreme values and fitted GEE models with a normal distribution and identity link function. From the regression coefficients (β), we calculated percent differences (%Ds) in mean semen parameter values as $\%D = [100 \times (e^{\beta} - 1)]$. For MDI score, we multiplied %D by five to estimate the change associated with a five-unit increase in MDI score. We calculated 95% CIs for the %Ds by applying the same transformation to the upper and lower 95% confidence interval (CI) boundaries for β . In addition, we fitted restricted cubic splines to allow for a smoothed fit of the relation between MDI score and semen parameters (28) and used the %GLMCURV9 macro (29) to model each spline with knots at the 10th, 50th, and 90th percentiles of the distribution of MDI scores (2, 8, and 19) in our study population.

For the third analysis, we evaluated potential mediation of the association between a history of depression diagnosis and the risk of poor semen quality (WHO reference limits) by recent use of psychotropic medications. Mediation analysis decomposes the relationship between a history of depression diagnosis and poor semen quality into direct and indirect, or mediated, effects. The direct effect represents the effect of a history of depression diagnosis on poor semen quality, independently of psychotropic medication use, whereas the indirect effect represents the effect of the exposure that acts through psychotropic medication use. These methods have been described previously in detail (30–32). We used the %mediation macro to perform these analyses (33).

Potential confounders were selected a priori on the basis of prior knowledge and a directed acyclic graph. The models were adjusted for abstinence time (days), age (years), body mass index (kg/m^2), multivitamin or folate supplement use (yes/no), sleep duration (hours/night), and having ever impregnated a partner (yes/no). In addition, models for

antidepressant use were adjusted for history of depression diagnosis (ever/never). In the mediation analyses, we adjusted only for abstinence time (days) and age (years) because larger models failed to converge. We used multiple imputations by fully conditional specification to impute missing values for covariates and semen parameter variables. The percentage of missing data was <2% for all covariates. There were complete data for semen volume, but sperm concentration and motility were imputed for 0.5% and 38.4% of participants, respectively. The percentage of missing data was higher for motility because we began measuring motility in April 2018. We generated 25 imputed datasets and used PROC MIANALYZE to combine coefficient and standard error estimates. All analyses were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

A total of 329 men contributed results from 566 semen samples. Among these men, 49 (15%) reported having ever been diagnosed with depression (Table 1). Compared with men who had never been diagnosed with depression, these men were less likely to have obtained a college degree, were more likely to report currently smoking and sleeping more than 8 hours per night, and reported less physical activity on average. In addition, participants with a diagnosis of depression had less frequent sexual intercourse, were more likely to report a history of infertility, and were less likely to report that they had been able to have an erection and/or ejaculation when desired in the past few months. Among men who had ever been diagnosed with depression, 29% had recently used an SSRI, 10% had used an SNRI, 10% had used other antidepressants, and 8% had used nonantidepressant psychotropic medications. In total, 53% of men who had ever been diagnosed with depression reported recent use of psychotropic medications. However, 37% of men who reported recent use of psychotropic medications had never been diagnosed with depression. Forty-one men (12%) reported using any psychotropic medication during the 4 weeks before baseline, and 19 men (6%) reported using an SSRI. Among participants who recently used an SSRI, none reported concomitant use of an SNRI or other antidepressant.

The median and interquartile range (IQR) for the time from completion of the baseline questionnaire until semen testing was 2.1 weeks (IQR 1.3, 3.7) for the first semen sample and 5.0 weeks (IQR 3.4, 7.9) for the second semen sample. This corresponds to 6.1 (IQR 5.3, 7.7) and 9.0 (IQR 7.4, 11.9) weeks after the targeted time in the questionnaire asking about medication use (“4 weeks before baseline”). On average, semen volume was 4.0 mL per ejaculate (IQR 3.0, 5.0), sperm concentration was 49 million/mL (IQR 28, 90), sperm motility was 55% (IQR 36%, 81%), total sperm count was 180 million (IQR 99, 321), and total motile sperm count was 95 million (IQR 41, 175) (Table 2). On the basis of the WHO lower reference limits, 2% of participants had low semen volume, 11% had low sperm concentration, 30% had low sperm motility, 10% had low total sperm count, and 10% had low total motile sperm count. We present semen quality characteristics according to history of depression diagnosis in Table 2.

TABLE 1

Baseline characteristics of male PRESTO participants who participated in the semen substudy, according to depression diagnosis and recent psychotropic medication use, 2013–2020 (n = 329 men).

Characteristic	Depression diagnosis		Recent PM use ^a	
	Never diagnosed (n = 280)	Ever diagnosed (n = 49)	No (n = 288)	Yes (n = 41)
Age (y), mean	31.8	32.8	31.7	33.4
BMI (kg/m ²), mean	28.5	30.2	28.6	29.9
≥ College degree, %	75.0	67.4	74.3	70.7
Currently employed, %	94.6	93.9	94.4	95.1
Current regular or occasional smoker, %	11.1	14.3	11.5	12.2
Alcoholic beverages (drinks/wk), mean	5.5	6.7	5.4	8.2
≥ 14/wk, %	9.6	12.2	9.0	17.1
Sugar-sweetened beverages (drinks/wk), mean	3.8	3.7	3.8	3.9
≥ 7/wk, %	19.3	22.5	19.4	22.0
Using multivitamins or folate supplements, %	42.5	38.8	41.3	46.3
Sleep duration (h/d), %				
<7	30.7	30.6	29.2	41.5
7–8	66.1	61.2	67.0	53.7
≥9	3.2	8.2	3.8	4.9
Vigorous physical activity (MET-h/wk), ^b mean	17.1	12.2	17.0	12.3
Intercourse ≤ 1/wk, %	27.5	34.7	27.8	34.2
Ever impregnated a partner, %	38.9	42.9	38.2	48.8
History of infertility, %	6.4	14.3	7.3	9.8
Able to have erection in last few months, %	98.2	89.8	97.9	90.2
Abstinence time before sample collection (d), mean	3.6	3.4	3.6	3.3
Mental health diagnoses				
Ever diagnosed with depression, %	—	—	8.0	63.4
Age at first diagnosis (y), mean	—	25.0	21.9	27.5
Ever diagnosed with anxiety disorder, %	6.4	40.8	6.3	48.8
Age at first diagnosis (y), mean	26.8	22.9	24.9	25.5
MDI score, %				
<20	93.9	71.4	93.4	70.7
20–24	3.2	14.3	3.1	17.1
25–29	1.8	4.1	2.1	2.4
≥30	1.1	10.2	1.4	9.8
Recent use of antidepressant and psychotropic medications ^a				
SSRI, %	1.8	28.6	—	46.3
SNRI, %	0.4	10.2	—	14.6
Other antidepressants, %	1.1	10.2	—	19.5
Nonantidepressant PM, %	2.1	8.2	—	24.4

Note: BMI = body mass index; MET = metabolic equivalent of task; MDI = Major Depression Inventory; PM = psychotropic medication; PRESTO = Pregnancy Study Online; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

^a Recent use is defined as use in the 4 weeks before baseline.

^b Total METs of physical activity were calculated by multiplying the average number of hours per week engaged in various activities by METs estimated from the Compendium of Physical Activities.

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Compared with men who had never been diagnosed with depression, those who had ever been diagnosed with depression had a 4.3-fold increased risk of low semen volume, after adjustment for abstinence time, age, body mass index, use of multivitamins or folate supplements, sleep duration, and having ever impregnated a partner (95% CI 1.16, 16) (Table 3). The adjusted risk ratio (aRR) for low sperm concentration, percent motility, total sperm count, and total motile sperm count was 0.89 (95% CI 0.44, 1.77), 1.13 (95% CI 0.77, 1.65), 0.75 (95%

CI 0.35, 1.61), and 0.68 (95% CI 0.29, 1.60), respectively. A five-unit increase in MDI score was associated with a 1.38-fold increased risk of low semen volume (95% CI 0.92, 2.1) and a 1.12-fold increased risk of low total motile sperm count (95% CI 0.95, 1.33) but was not meaningfully associated with low sperm concentration, percent motility, or total sperm count. For the composite marker of depression (ever diagnosed with depression or MDI score ≥ 21), the aRR was 4.4 (95% CI 1.18, 17) for low semen volume, 0.91 (95% CI 0.47,

TABLE 2

Semen quality parameters of 329 study participants contributing results from 566 semen tests, overall and according to depression diagnosis (2013–2020).

Semen parameter	Overall	Never diagnosed with depression	Ever diagnosed with depression
	(n = 566 samples)	(n = 483 samples)	(n = 83 samples)
	Median (IQR)	Median (IQR)	Median (IQR)
Semen volume (mL)	4.0 (3.0, 5.0)	4.0 (3.0, 5.0)	3.5 (2.8, 5.0)
Sperm concentration (millions/mL)	49 (28, 90)	49 (28, 90)	52 (28, 90)
Sperm motility (%)	55 (36, 81)	56 (37, 84)	50 (32, 75)
Total sperm count (millions)	180 (99, 321)	180 (99, 321)	196 (105, 324)
Total motile sperm count (millions)	95 (41, 175)	96 (42, 175)	84 (36, 175)
2010 WHO lower reference limits	no. (%)	no. (%)	no. (%)
Semen volume <1.5 mL	9 (1.6)	5 (1.0)	4 (4.8)
Sperm concentration <15 million/mL	62 (11.0)	54 (11.2)	8 (9.6)
Sperm motility <40%	172 (30.4)	150 (29.0)	32 (38.6)
Total sperm count <39 million	59 (10.4)	52 (10.8)	7 (8.4)
Total motile sperm count <16 million	55 (9.7)	50 (10.4)	5 (6.0)

Note: IQR = interquartile range; WHO = World Health Organization.

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1.78) for low sperm concentration, 1.26 (95% CI 0.92, 1.72) for low sperm motility, 1.06 (95% CI 0.58, 1.95) for low total sperm count, and 1.16 (95% CI 0.61, 2.2) for low total motile sperm count. Recent use of psychotropic medications was associated with an increased risk of low sperm concentration (aRR 1.32; 95% CI 0.65, 2.7), percent motility (aRR 1.37; 95% CI 0.95, 1.98), total sperm count (aRR 1.14; 95% CI 0.56, 2.3), and total motile sperm count (aRR 1.33; 95% CI 0.64, 2.8) but was not meaningfully associated with the risk of low semen volume. When we additionally adjusted for history of depression diagnosis, the aRR was 0.44 (95% CI 0.03, 6.7) for semen

volume, 1.66 (95% CI 0.70, 4.0) for sperm concentration, 1.44 (95% CI 0.89, 2.3) for percent motility, 1.40 (95% CI 0.61, 3.2) for total sperm count, and 1.84 (95% CI 0.71, 4.8) for total motile sperm count. The corresponding risk differences and their 95% CIs are presented in [Supplemental Table 2](#).

A history of depression diagnosis was associated with a 7.3% decrease in semen volume (95% CI –18%, 5.1%), a 20% increase in sperm concentration (95% CI –7.7%, 57%), a 2% decrease in sperm motility (95% CI –18%, 16%), an 11% increase in total sperm count (95% CI –16%, 47%), and a 10% increase in total motile sperm count (95% CI –23%,

TABLE 3

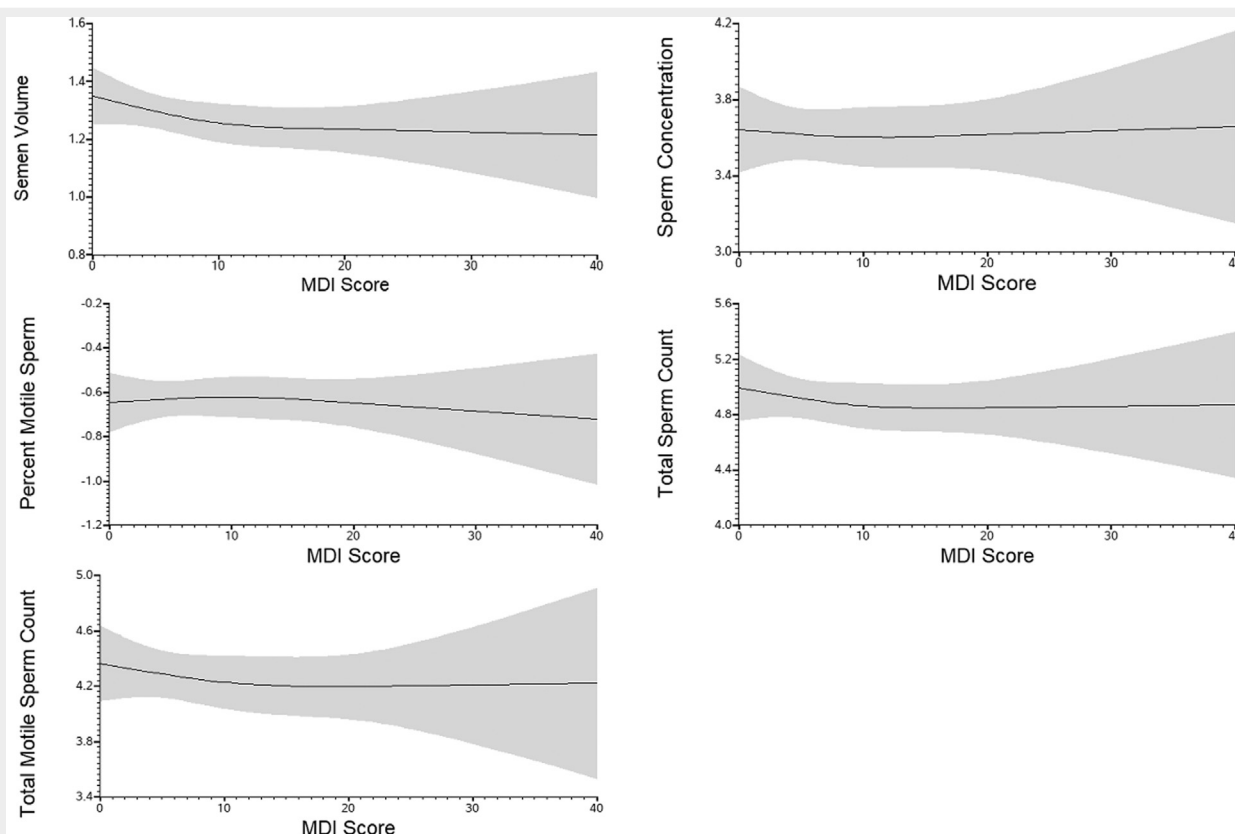
Associations of depression diagnosis, MDI score, and use of psychotropic medication with semen quality parameters, using 2010 WHO lower reference limits. Results from analysis of 329 study participants who contributed results from 566 semen tests (2013–2020).

Exposure	Semen parameter (2010 WHO lower reference limits)				
	Semen volume	Sperm concentration	Sperm motility	Total sperm count	Total motile sperm count
	<1.5 mL RR (95% CI)	<15 million/mL RR (95% CI)	<40% RR (95% CI)	<39 million RR (95% CI)	<16 million RR (95% CI)
Ever diagnosed with depression (referent: never diagnosed)					
Model A	4.3 (1.16, 16)	0.89 (0.44, 1.77)	1.13 (0.77, 1.65)	0.75 (0.35, 1.61)	0.68 (0.29, 1.60)
MDI score (5-unit increase)					
Model A	1.38 (0.92, 2.1)	1.05 (0.89, 1.23)	1.01 (0.90, 1.13)	1.07 (0.91, 1.24)	1.12 (0.95, 1.33)
Depression diagnosis or MDI score ≥21 (referent: no evidence of depression)					
Model A	4.4 (1.18, 17)	0.91 (0.47, 1.78)	1.26 (0.92, 1.72)	1.06 (0.58, 1.95)	1.16 (0.61, 2.2)
Recent PM use (referent: no recent PM use)					
Model A	1.00 (0.14, 7.2)	1.32 (0.65, 2.7)	1.37 (0.95, 1.98)	1.14 (0.56, 2.3)	1.33 (0.64, 2.8)
Model B	0.44 (0.03, 6.7)	1.66 (0.70, 4.0)	1.44 (0.89, 2.3)	1.40 (0.61, 3.2)	1.84 (0.71, 4.8)

Note: Generalized estimating equation models were used to account for correlated outcomes between samples from the same participant. Risk ratios compare the risk of having a test result below the clinical cut-point between men with different MDI scores. Model A was adjusted for abstinence time, age, body mass index, use of multivitamins or folate supplements, sleep duration, and having ever impregnated a partner. Model B was adjusted for all variables in model A and depression diagnosis. Recent medication use refers to any use in the 4 weeks before baseline. CI = confidence interval; MDI = Major Depression Inventory; PM = psychotropic medication; RR = risk ratio; WHO = World Health Organization.

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FIGURE 1



Restricted cubic spline for the association between Major Depression Inventory (MDI) score and mean log-transformed semen parameter values. Semen parameter values were log-transformed, and models were adjusted for abstinence time, age, body mass index, use of multivitamins or folate supplements, sleep duration, and having ever impregnated a partner. Splines were modeled with knots at the 10th, 50th, and 90th percentiles of MDI score (2, 8, and 25).

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58%) after adjustment for potential confounders (Supplemental Table 3). We observed no associations between a five-unit increase in MDI score and semen quality for all semen parameters studied (Supplemental Table 3 and Fig. 1). Recent use of psychotropic medications was not associated with semen volume, sperm concentration, or total sperm count but was associated with small decreases in sperm motility and total motile sperm count (Supplemental Table 3). After further adjustment for a history of depression diagnosis, recent use of psychotropic medications was associated with decreases in all semen quality parameters except semen volume, which was not meaningfully associated with medication use. Recent use of SSRIs was associated with small increases in sperm concentration and total sperm count, a small decrease in sperm motility, and no appreciable change in semen volume or total motile sperm count.

The mediation analysis indicated a positive direct effect of a history of depression diagnosis on the risk of low semen volume (aRR 3.4; 95% CI 0.50, 23) but little indirect effect of recent use of psychotropic medications (aRR 0.89; 95% CI 0.33, 2.4) (Supplemental Table 4). For low sperm

concentration, total sperm count, and total motile sperm count, we observed inverse associations between a history of depression diagnosis and poor semen quality independently of recent use of psychotropic medications and positive associations between a history of depression diagnosis and poor semen quality through recent use of psychotropic medications. We observed no direct effect on percent sperm motility.

DISCUSSION

In this North American preconception cohort study, a history of depression diagnosis and severe current depressive symptoms were associated with a substantially increased risk of low semen volume. This association was consistent when we evaluated a composite marker of depression (ever having received a diagnosis of depression or MDI score suggesting at least mild depression). This relationship did not appear to be mediated by recent use of psychotropic medications, although recent use of psychotropic medications was generally associated with reduced semen quality. We observed no

consistent associations between a history of depression diagnosis or current depressive symptoms and the other semen parameters studied.

Several studies reported that a diagnosis of depression or the presence of depressive symptoms was associated with lower semen volume (15), lower sperm concentration (17), lower sperm count (11, 15, 17), fewer motile sperm (11), and fewer morphologically normal sperm (11). In contrast, two studies reported no association between depression and semen parameters (12, 14). Among 1,076 male members of infertile couples in Slovenia, well-being was positively associated with sperm concentration but not with sperm motility or morphology (16). In a study of 744 fertile men in the United States, experiencing stressful life events (such as job loss) in the 3 months before semen sample collection was associated with lower sperm concentration and total sperm count (13). Although we observed positive associations of depression and severity of symptoms with low semen volume, we did not observe consistent associations with the other semen quality parameters studied.

In this study, recent use of psychotropic medications was associated with a decreased risk of low semen volume but increased risks of low sperm concentration, low sperm motility, low total sperm count, and low total motile sperm count. Most studies of the effects of antidepressant use on semen quality have evaluated SSRIs specifically. In a randomized trial of sertraline (an SSRI) vs. behavioral therapy for premature ejaculation, men who received sertraline had decreased sperm concentration after the intervention compared with baseline but no changes in semen volume or percent sperm motility (6). In a study of men with premature ejaculation, sperm concentration and percent motility were decreased after 3 months of treatment with escitalopram (an SSRI) compared with baseline (7). In contrast, two studies reported little association between SSRI use and semen volume, sperm concentration, or percent motility (34, 35). A study of treatment of depression with clomipramine (a tricyclic antidepressant) found that semen volume, sperm concentration, and percent motility were lower in the treated group ($n = 11$) than in the untreated group ($n = 15$) (36). However, it was impossible to disentangle the effect of depression from the effect of medication use in this study because the comparison group consisted of men without depression. In the present study, we observed substantial confounding by depression diagnosis, which biased the results upward for semen volume but downward for all other parameters.

Ejaculation is an intricate process that can be affected by cognitive disorders or their treatments. The potential mechanisms by which depression and the use of psychotropic medications influence semen volume are complex. Stress, anxiety, and depression may affect semen production through changes in hormonal homeostasis and inflammatory processes (37). In addition, premature ejaculation may play a role, as this condition is associated with depression and is treated with antidepressants (38, 39). The effects of psychotropic medications on semen quality may be because of a combination of dysregulation of circulating sex hormones and local changes in spermatogenesis (37, 40). In addition, the use of antidepressants has been linked to the syndrome of inappropriate

antidiuretic hormone secretion and its sequela hyponatremia (41, 42), which could affect semen volume. Although there is biologic plausibility for the relationships among depression, use of antidepressants, and semen quality, the potential effects of depression and antidepressants on fecundity is unclear. The ejaculate provides protection and nutrition to allow sperm to survive in the female reproductive tract. Therefore, a lower volume of ejaculate could impair the ability of sperm (regardless of their number or motility) to successfully reach the egg. However, the utility of the WHO reference values for evaluating male fertility has been debated (43). A study in Denmark reported that neither semen volume nor sperm motility was predictive of fecundability, but that sperm concentration was strongly associated with the likelihood of pregnancy (44). Another study found that sperm count, motility, and morphology, but not semen volume or sperm concentration, were associated with infertility (45).

There were several potential sources of misclassification in this study. First, we observed some digit preference in reporting of semen volume, which was on the basis of self-report. Misclassification because of digit preference is unlikely for sperm motility and concentration, which were calibrated by trained Trak staff. The analysis of continuous semen parameter values is less sensitive to digit preference than the analysis of dichotomous semen quality outcomes, yet both were consistent in indicating inverse associations between depression and semen volume. Second, it is possible that some spillage may have occurred when the participants collected their samples, which could have caused errors in the measurement of semen volume. We would expect this error to result in nondifferential misclassification of semen volume, which would generally attenuate our results toward the null. However, in a previous evaluation of the Trak system, only 5% of participants reported that collecting their sample into the cup was “difficult” or “very difficult,” and 91% of participants reported that they believed they performed the test correctly (20). Thus, the effect of this potential bias would likely be small. Third, there may have been misclassification of psychotropic medication use. Although there is no established gold standard for measuring medication use, several studies have compared self-reported use of antidepressants with pharmacy claims and reported agreement of at least 85% (46, 47). Although we expect high specificity for this variable, it is possible that some men who took psychotropic medications did not report their use (low sensitivity). We performed a quantitative analysis to consider the potential extent of bias because of misclassification of psychotropic medication use. Because psychotropic medication use was ascertained before semen testing, we would expect any misclassification of exposure to be nondifferential. The RR unadjusted for misclassification of exposure or confounding was 1.66 on the basis of our observed data. Assuming a specificity of 99%, the misclassification-adjusted RR ranged from 1.83 under 60% sensitivity to 1.71 under 99% sensitivity. The potential extent of bias was greater in magnitude, but still toward the null, with a specificity of 95%. We evaluated a wide range of plausible sensitivities because we do not have a suitable reference value in the absence of an established gold standard. The results of this bias analysis suggest that our

findings for the associations between recent use of psychotropic medications and poor semen quality could be biased toward the null.

In addition, selection bias was a possibility, because only 53% of male PRESTO participants who were invited to participate in this semen substudy agreed to participate. The percentage of men who had ever impregnated a partner was slightly lower among those who agreed to participate (42%) than among those who declined to participate (50%), and the prevalence of depression was higher among those who agreed to participate (16%) than among those who did not (10%). However, having ever impregnated a partner was not associated with having received a diagnosis of depression. Further, we adjusted our analyses for having previously impregnated a partner to reduce the potential for confounding or selection bias. Thus, we do not expect appreciable bias because of selection.

Finally, there were two limitations to the scope of this study. First, our ability to evaluate specific classes of antidepressants was limited because of the small number of men who had recently used a psychotropic medication at baseline. Second, the Trak system does not measure all semen parameters. Thus, we were unable to examine the effects of depression or psychotropic medication use on outcomes such as sperm morphology, progressive motility, and DNA fragmentation.

CONCLUSION

In conclusion, this is one of the few prospective studies of men residing throughout the United States who were enrolled irrespective of fertility status and who were not required to visit a centralized laboratory for semen analysis. Overall, we observed an increased risk of low semen volume associated with both a history of depression diagnosis and severe depressive symptoms. This association was not mediated by recent use of psychotropic medications. Use of psychotropic medication was associated with worse semen quality as measured by sperm concentration, sperm motility, total sperm count, and total motile sperm count, although the associations were imprecise. These associations were substantially confounded by a history of depression diagnosis.

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Estudio norteamericano prospectivo de depresión, uso de medicación psicotrópica, y calidad espermática.

Objetivo: Evaluar las asociaciones de los antecedentes de depresión diagnosticada, síntomas actuales de depresión, y uso reciente de medicación psicotrópica con la calidad espermática y considerar la asociación entre depresión y calidad del semen por el uso de medicamentos.

Diseño: Estudio de cohorte prospectivo.

Lugar: Estados Unidos.

Paciente(s): Los pacientes eran 329 hombres ≥ 21 años (566 muestras de semen) que participaron en un subestudio de análisis de semen de Pregnancy Study Online. Pregnancy Study Online es un estudio en curso de cohorte previo a la concepción basado en la web de parejas que intentan concebir. Al inicio del estudio, los participantes informaron sobre el diagnóstico de depresión y los síntomas depresivos utilizando el Major Depression Inventory, el uso de medicamentos en las últimas 4 semanas y covariables seleccionadas.

Intervención: No aplica.

Medida(s) principales: Los hombres utilizaron un equipo de análisis de semen en casa (Trak; Sandstone Diagnostics, Inc., Pleasanton, California) para medir el volumen de semen, la concentración de espermatozoides y la concentración de espermatozoides móviles. Calculamos el porcentaje de motilidad, el recuento total de espermatozoides en el eyaculado, y el recuento total de espermatozoides móviles.

Resultado(s): Cuarenta y nueve hombres (15%) informaron antecedentes de diagnóstico de depresión y 41 (12%) informaron sobre el uso reciente de medicamentos psicotrópicos.

Un historial de diagnóstico de depresión se asoció con un aumento de 4.3 veces en el riesgo de volumen bajo de semen ($<1,5$ ml) (IC del 95% 1.16, 16). Un aumento de 5 unidades en la puntuación del Major Depression Inventory se asoció con un aumento de 1.38 veces en el riesgo de volumen bajo de semen (95% CI 0.92, 2.1). Los resultados para otros parámetros del semen fueron inconsistentes. El uso reciente de medicamentos psicotrópicos fue asociado con una peor calidad del semen, y esta asociación fue confundida por un historial de diagnóstico de depresión. La asociación observada entre la depresión y el volumen de semen mostró una pequeña mediación por el uso de medicamentos psicotrópicos.

Conclusión(es): Un historial de depresión diagnosticada y síntomas depresivos graves en el momento de la inscripción se asociaron con un volumen de semen bajo.