Racial and Sociodemographic Differences of Semen Parameters Among US Men Undergoing a Semen Analysis

Clara Helene Glazer, Shufeng Li, Chiyuan Amy Zhang, Aleksander Giwercman, Jens Peter Bonde, and Michael L. Eisenberg

OBJECTIVE To characterize sociodemographic differences in semen parameters among US men undergoing a semen analysis.

MATERIALS AND METHODS Men who provided a semen sample were identified from insurance claims between 2007 and 2016. Differences in semen parameters were characterized according to age, race, education, and region. Mean semen parameters and proportions of men with suboptimal parameters were compared and risks of oligospermia and azoospermia were assessed by logistic regression.

RESULTS Of the 7263 men included, most men were white (55.1%), Hispanic (20.2%), or Asian (10.2%). Asians had the highest mean semen concentrations (69.2×10^6/mL), whereas blacks had the lowest (51.3×10^6/mL). Men from the Midwest were more likely to have oligospermia (odds ratio [OR] 1.62; 95% confidence interval [CI] 1.34-1.94), whereas men from the West were less likely (OR 0.82; 95% CI 0.82-0.94) when compared with men from South. An association between education and sperm concentration was observed. For example, men with a high school diploma or less were more likely to have oligospermia (OR 1.09; 95% CI 0.95-1.26), whereas men with at least a bachelor degree were less likely (OR 0.87; 95% CI 0.76-1.0) when compared with men with less than a bachelor degree.

CONCLUSION As we observed differences in semen quality based on sociodemographic factors, these findings may have clinical implications as relying on a single reference value when guiding infertile couples may be problematic given these variations. Further work is warranted to understand the etiology of such differences and determine if different normative reference values may apply for different populations. UROLOGY 123: 126–132, 2019. © 2018 Elsevier Inc.

It is estimated that 20%-30% of men have sperm counts low enough to impair fertility and half of these men may need fertility treatment to become fathers.[1] To date, the conventional semen analysis includes sperm concentration, motility, morphology, volume, and total sperm counts. While it remains the first step to assess a man's reproductive potential, defining clear thresholds for normative reference values has proven difficult.

The influence of sociodemographic factors on semen quality has previously been investigated with the main focus so far on the influences of region[2,3] and lifestyle factors such as body mass index[4] and smoking.[5] There are indicators of disparities in semen parameters between countries in Europe where Danish men have been shown to have the lowest sperm counts followed by French and Scottish men.[2] A recent study among Baltic men revealed higher sperm counts when compared with men from other European countries.[6] In the United States, however, the influences of regional differences are less thoroughly explored. However, a report from the Study for Future Families SFF revealed regional differences with the lowest sperm counts among men from Missouri.[7]

Data on racial disparities in semen quality are few. One US study found lower sperm counts among blacks in comparison to whites and Hispanics,[7] and another recent study found lower sperm counts among whites compared

Financial Disclosure: *CHG, SL, CAZ, and JPB declare no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work. ME is an advisor for Sandstone. AG reports personal fees from Merck-Serono, Finox, IBSA Pharmaceuticals, Ferring Pharmaceuticals, and from Novo-Nordisk, outside the submitted work.*

Funding Support: *The ReproUnion collaborative study, co-financed by the European Union, Interreg VÖKS paid a portion of CHG's salary and expenses.*

From the Department of Urology, Stanford University School of Medicine, Stanford, CA; the Department of Occupational and Environmental Medicine, Bispebjerg University Hospital, Copenhagen, Denmark; and the Molecular Reproductive Medicine, Department of Translational Medicine, Lund University, Lund, Sweden

Address correspondence to: Clara Helene Glazer, MD, Department of Occupational and Environmental Medicine, Capital Region of Denmark, Bispebjerg – Frederiksberg Hospital, Bispebjerg Bakke 23F, Building 20C, 1st Floor, Copenhagen DK-2400, Denmark. E-mail: clara.helene.glazer.01@regionh.dk

Submitted: July 10, 2018, accepted (with revisions): September 25, 2018

https://doi.org/10.1016/j.urology.2018.09.029
0090-4295

to Asians.[8] However, it may be difficult to draw conclusions based from these reports as black and Hispanic men were under-represented, which is a common limitation in these types of studies. Moreover, diverse recruitment sites across the United States may also limit generalizability with regards to racial and regional differences in semen quality.

Although it is generally accepted that a higher level of education is associated with a decreased risk of chronic diseases and mortality and improved access to healthcare, the influence of educational attainment on semen quality is not well studied. Furthermore, understanding the impact of sociodemographic factors on semen quality among infertile men may be helpful for clinicians when guiding couples and providing prognostic information as well as opportunities for treatment options.

Given the clinical implications for semen quality on both fertility and health,[9] we sought to characterize semen parameters in a large population of diverse men with commercial insurance identified from all 4 regions in the United States.

MATERIAL AND METHODS

We identified a cross-sectional cohort of men in the Optum© Clinformatics® Data Mart Database that is a de-identified database from a large national insurance provider. The database contains claims submitted for payment from approximately 17-19 million annual covered lives over a 9-year period. The population is geographically diverse, spanning all regions within the United States with information on laboratory results from multiple payers linked to each patient.[10] The database contains enrollees with both commercial and Medicare Advantage health plan data. In the United States, fertility treatment may be covered by insurance or paid for out of pocket.

Our cohort includes men who provided a semen analysis between 2007 and 2016. The semen samples were analyzed for concentration, volume, motility, morphology, and total sperm counts per laboratory practices. Given the variation in morphology definitions at different laboratories, we included only laboratories using WHO strict criteria with normal identified as $>4\%$. Men with a history of vasectomy and a diagnosis of cancer before or within 6 months of the initial semen analysis were excluded. For the men who provided multiple semen analyses, only the first sample was used for this present study. The cohort was linked to socioeconomic data to obtain data on race, region, and educational attainment. Institutional review board approval was obtained.

Statistical Analysis

We characterized differences in semen parameters according to the following sociodemographic characteristics: age, region, race, and education. First, mean values in semen parameters between the different sociodemographic categories were analyzed as continuous variables by analysis of variance to test for differences between means. The distribution of semen samples was skewed but transforming the data showed the same trends. Second, the proportion of men with semen parameters below the current WHO guidelines (sperm concentration $<15\times10^6$/mL, semen volume <1.5 mL, motile sperm $<40\%$, morphology $<4\%$, and total sperm count $<39\times10^6$ mL) were quantified and reported as percentages.[11] Third, prevalence odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were analyzed by logistic regression to estimate the risk of oligospermia (sperm concentration $<15\times10^6$) according to each sociodemographic characteristic. Last, the logistic regression was repeated to test for associations between azoospermia and the different categories. All sociodemographic characteristics were considered as possible confounders and added stepwise to the final model. Adjustment for education in the oligospermia analyses were omitted as it did not significantly change the results across any of the sociodemographic characteristics. CIs were reported instead of *P* values as measure of precision in the logistic regression. All statistical analyses were performed with SAS version 9.4.

RESULTS

The demographic characteristics are presented in Table 1. With a mean age of 36.4, our cohort includes 7263 men with a semen analysis. The majority of the men had less than a bachelor degree (55.9%), while fewer had only completed high school or less (20.6%). White men made up the largest percentage of the cohort (55.1%) followed by Hispanics (20.2%) and Asians (10.2%). Men from the South (52.6%) and West (30.9%) regions were most commonly represented.

The mean semen parameters are presented in Table 2. Overall, the mean sperm concentration was 57.9×10^6/mL. The differences in mean sperm concentrations between men of different ages were minimal, although men over the age of 40 years had lower total sperm counts, morphology, motility, and ejaculate volumes. Racial differences were seen where Asians had the highest mean semen concentrations (69.2×10^6/mL) while blacks had the lowest (51.3×10^6/mL). This trend was also accompanied by a higher percentage of black men with semen parameters below the current WHO guidelines (Table 3). An association between educational attainment and semen concentrations was observed with mean concentrations of 55×10^6/mL among those with a high school diploma or less compared with 63.3×10^6/mL among those with at least a bachelor degree. Men from the Northeast had the highest sperm concentrations (63.3 M/mL), while men from the Midwest had the lowest (49.2 M/mL, Table 2).

The cross-sectional analysis between the sociodemographic categories and sperm concentrations below 15×10^6/mL is presented in Table 3. Overall, men over the age of 40 years were more likely to have oligospermia (OR 1.14; 95% CI 1.01-1.30) when compared with younger men. Asians had the lowest risk of oligospermia (OR 0.64; 95% CI 0.52-0.78), whereas blacks and Hispanics had corresponding risk estimates of OR 1.15, 95% CI 0.96-1.39 and OR 1.11, 95% CI 0.97-1.28, respectively, when compared with white men in the adjusted model. Men from the Midwest had the highest adjusted risk of oligospermia (OR 1.62; 95% CI 1.34-1.94), whereas men from the West had the lowest (OR 0.82; 95% CI 0.72-0.94) when compared with men from the South.

The proportions of men with azoospermia are presented in Table 4. Overall, 8.0% of the men were azoospermic. The prevalence of azoospermia increased with age as 4.6% of men aged 18-29 years presented with azoospermia compared with 12.4% of men over the age of 40 years. Asians had the lowest prevalence of azoospermia (5.6%) and were less likely to be azoospermic

Table 1. Population characteristics of the cohort

	n	%
Age groups		
18-29	1199	16.5
30-39	4053	55.8
40 and older	2011	27.7
Education		
High school diploma or less	1494	20.6
Less than bachelor	4057	55.9
Bachelor or higher	1697	23.4
Unknown	14	0.20
Race		
Asian	742	10.2
Black	673	9.3
Hispanic	1465	20.2
White	4002	55.1
Unknown	381	5.3
Region		
Northeast	475	6.5
Midwest	698	9.6
South	3824	52.6
West	2264	30.9
Unknown	20	0.30

after adjustment of confounders (OR 0.60; 95% CI 0.41-0.86) when compared with white men who had the highest prevalence of azoospermia (8.9%). Regional differences in rates of azoospermia were also identified (Table 4).

DISCUSSION

In this cross-sectional study of 7263 US men who provided a semen sample, we observed differences in semen quality across several sociodemographic characteristics. We found that in the United States, men from the Midwest had the lowest mean sperm concentration, whereas men from the West had the highest. In addition, Asian men had the highest mean sperm concentrations and were less likely to be azoospermic compared with white men. There appeared to be an association between educational attainment and semen quality as men with a high school diploma or less had the lowest mean semen concentrations, and were more likely to be oligo- and azoospermic.

Differences in semen quality according to regions have been studied in Europe,[2,6,12,13] but to our knowledge few studies have looked at geographical variations within the United States.[3,14] The SFF in the United States collected semen samples from a cohort of male partners of 512 pregnant women found the lowest sperm counts among men from Missouri,[7] which compares to our results as men from the Midwest had a 62% increased risk of being subfertile compared with men from the South. We observed the highest sperm counts among men from the Northeast and Western regions, which also compare to the SFF, as they observed the highest sperm counts among men from New York and Los Angeles.[3] An older US study of 1263 men who banked sperm prior to vasectomy similarly revealed the highest sperm concentrations among men from New York.[14] It is interesting to note that while SFF recruited fertile men, our cohort likely enriched for infertility given who would be most likely to receive a semen analysis in the United States. Nevertheless, both groups showed similar regional differences. It has been suggested that environmental factors may explain these differences as a study on urine pesticide metabolites from the same group on revealed higher pesticide levels among men from Missouri.[15] Men from Midwest were not at increased risk of azoospermia who may support the hypothesis of

Table 2. Mean semen parameters according to sociodemographic characteristics

	Mean Age	Concentration ($x10^6$/mL)	Sperm Count ($x10^6$)	Semen Volume (mL)	Morphology (%)	Motility (%)
Mean semen concentration overall 57.9						
Age						
18-29	26.8	57.2	164.4	3.0	39.2	58.0
30-39	34.3	58.8	163.7	2.8	39.0	55.6
40 and older	46.2	56.4	141.8	2.6	34.9	50.2
Race						
Asian	35.6	69.2	178.4	2.6	36.3	55.6
Black	37.0	51.3	129.9	2.6	40.6	54.7
Hispanic	36.0	57.8	153.8	2.7	45.2	55.7
White	36.4	56.5	160.1	2.9	35.6	54.4
Unknown	37.6	62.0	169.7	2.9	34.4	52.2
Education						
High school or less	35.7	55.0	148.9	2.7	40.5	54.4
Less than bachelor	36.2	56.8	156.8	2.8	37.6	54.4
Bachelor or higher	37.4	63.3	170.2	2.8	36.9	55.6
Unknown	37.1	59.8	177.6	3.4	39.8	58.8
Region						
Northeast	36.9	63.3	188.0	2.8	25.6	50.6
Midwest	34.3	49.2	140.9	3.0	19.9	52.8
South	35.9	57.1	152.6	2.7	46.1	56.8
West	37.6	61.2	169.2	2.9	31.5	52.2
Unknown	41.0	49.01	112.8	2.6	13.6	44.8

Table 3. Proportions of men with semen parameters below current WHO fifth edition reference values and risks of oligospermia presented as ORs with corresponding CIs

	Sperm Concentration $<15 \times 10^6$/mL	Semen Volume <1.5 mL	Motile Sperm $<40\%$	Total sperm count $<39 \times 10^6$	Morphology $<4\%$	OR Crude	OR Adjusted
Age							
18-29	321/1135 (28.3)	171/1135 (15.1)	210/1067 (19.7)	330/1105 (29.9)	177/1037 (17.1)	1.01 [0.87-1.17]	0.96 [0.83-1.12]*
30-39	1047/3234 (28.0)	602/3836 (15.7)	822/3473 (23.7)	1102/3629 (30.4)	576/3291 (17.5)	-	-
40 and older	512/1659 (30.9)	424/1824 (23.5)	497/1504 (33.0)	578/1609 (36.0)	346/1465 (23.6)	1.15 [1.0-1.20]	1.14 [1.01-1.30]*
Race							
Asian	143/703 (20.3)	134/721 (18.6)	162/675 (24.0)	159/696 (22.8)	113/640 (17.7)	0.60 [0.50-0.74]	0.64 [0.52-0.78]†
Black	205/632 (32.4)	159/654 (24.3)	168/609 (27.6)	244/628 (38.8)	104/57 2 (18.2)	1.14 [0.94-1.36]	1.15 [0.96-1.39]†
Hispanic	411/1339 (30.7)	271/1382 (19.6)	304/1252 (24.6)	439/1295 (33.9)	157/1175 (13.4)	1.05 [0.91-1.20]	1.11 [0.97-1.28]†
White	1041/3509 (29.7)	566/3675 (15.4)	800/3179 (25.2)	1063/3384 (31.4)	665/3100 (21.4)	-	-
Unknown	80/345 (23.2)	67/363 (18.5)	95/329 (28.9)	105/340 (30.9)	60/306 (19.6)	0.72 [0.55-0.92]	0.73 [0.56-0.95]†
Education							
High school or less	436/1382 (31.5)	288/1412 (20.4)	341/1274 (26.8)	458/1348 (34.0)	201/1186 (16.9)	1.11 [0.97-1.27]	1.09 [0.95-1-26]‡
Less than bachelor	1054/3601 (29.3)	628/3745 (16.8)	856/3320 (25.8)	1123/3483 (32.2)	643/3195 (20.1)	-	-
Bachelor or higher	387/1532 (25.3)	278/1624 (17.1)	330/1439 (22.9)	425/1499 (28.3)	255/1399 (18.2)	0.82 [0.71-0.93]	0.87 [0.76-1.00]‡
Unknown	3/13 (23.1)	3/14 (21.4)	2/11 (18.2)	4/13 (30.8)	0/13 (0)	0.75 [0.16-2.37]	0.76 [0.17-2.57]‡
Region							
Northeast	94/402 (23.4)	80/449 (17.8)	95/353 (26.9)	93/407 (22.8)	88/389 (22.6)	0.75 [0.59-0.95]	0.70 [0.55-0.91]§
Midwest	249/632 (39.4)	82/570 (14.4)	129/540 (23.9)	238/619 (38.4)	240/558 (43.0)	1.60 [1.34-1.91]	1.62 [1.34-1.94]§
South	1015/3514 (28.9)	733/3789 (19.3)	804/3357 (23.9)	1160/3502 (33.1)	329/3206 (10.3)	-	-
West	517/1964 (26.3)	296/1969 (15.0)	494/1777 (27.8)	512/1799 (28.5)	435/1626 (26.7)	0.88 [0.78-1.00]	0.82 [0.72-0.94]§
Unknown	5/16 (31.2)	6/18 (33.3)	7/17 (41.2)	7/16 (43.7)	7/14 (50.0)	1.12 [0.35-3.08]	0.94 [0.32-2.74]§

CI, confidence interval; OR, odds ratio.
The denominators and percentages are based on the number of men across all sociodemographic characteristics, excluding those with missing values for the measured semen parameter.
* Adjusted for region, race, and year at semen analysis.
† Adjusted for region, year of semen analysis, and age at semen analysis.
‡ Adjusted for region, race, year of semen analysis, and age at semen analysis.
§ Adjusted for race, year of semen analysis, and age at semen analysis.

Table 4. Proportion of men with azoospermia and risks of azoospermia presented as ORs with corresponding 95% CIs

	N (%)	OR Crude	OR Adjusted
Age group			
18-29	48/1038 (4.6)	0.65 [0.46-0.88]	0.66 [0.48-0.91]*
30-39	244/3497 (7.0)	-	-
40 and older	194/1559 (12.4)	1.90 [1.55-2.3]	1.84 [1.50-2.25]*
Education			
High school or less	119/1294 (9.2)	1.16 [0.92-1.45]	1.25 [0.97-1.59]†
Less than bachelor	269/3351 (8.0)	-	-
Bachelor or higher	98/1436 (6.8)	0.84 [0.66-1.06]	0.79 [0.62-1.01]†
Unknown	0/13 (0)	-	-
Race			
Asian	37/666 (5.6)	0.60 [0.42-0.85]	0.60 [0.42-0.86]‡
Black	41/563 (7.3)	0.80 [0.57-1.12]	0.75 [0.52-1.06]‡
Hispanic	96/1261 (7.6)	0.84 [0.66-1.07]	0.75 [0.58-0.97]‡
White	291/3275 (8.9)	-	-
Unknown	21/329 (6.4)	0.70 [0.43-1.08]	0.60 [0.37-0.94]‡
Region			
Northeast	41/393 (10.5)	1.77 [1.23-2.50]	1.28 [0.86-1.87]§
Midwest	35/501 (7.0)	1.14 [0.77-1.63]	1.00 [0.68-1.48]§
South	203/3280 (6.2)	-	-
West	206/1906 (10.8)	1.84 [1.50-2.25]	1.39 [1.11-1.73]§
Unknown	1/15 (6.7)	1.08 [0.06-5.42]	0.78 [0.04-4.08]§

* Adjusted for region, race, education, and year of semen analysis.
† Adjusted for race, age at semen analysis, and education.
‡ Adjusted for education, age at semen analysis, and year of semen analysis.
§ Adjusted for race, education, age at semen analysis, and year of semen analysis.

environmental effects as azoospermia may have genetic causes such as y chromosome deletions and aneuploidy.[16]

The influence of race on semen quality is not well studied and data among Hispanic and black men are few. Our reports of higher sperm concentrations among Asian men are consistent with a recent US study that found higher sperm concentrations and total sperm counts among Asian men compared with white men from the same geographic region.[8] These findings are further supported by a cross-sectional study of 792 fertile Japanese men, which found sperm counts comparable to that in the best European regions.[17] However, poor semen quality has previously been reported among Chinese men,[18] so conflicting results do exist especially as Asians are a heterogeneous group. The etiologies of these observed differences are unknown. With many causes of male factor infertility termed idiopathic even after karyotyping, Y-microdeletion analysis, and endocrine profiling, it seems plausible that other genetic factors could explain the possible links.[19] Furthermore, a recent meta-analysis on the impact of CAG repeat length in the androgen receptor revealed association with male factor infertility among white but not Asian men.[20] In addition to biological factors, socioeconomic factors such as access to care may play a role. As fertility treatment is expensive in the United States, it is possible that lower income minority groups, such as blacks and Hispanics, may defer treatment and consequently present with poorer semen quality. Indeed, longer duration of infertility prior to seeking fertility treatment has previously been reported among minorities.[21] However, as our cohort includes men with employer-based medical insurance, this explanation may be less likely.

Men with at least a bachelor degree had the highest semen quality across all parameters (except for morphology). These findings could be linked to behavioral risk factors, such as smoking and poor diet associated with less education, although we acknowledge that the causal pathway is complex as other socioeconomic factors inevitably play a role. Men with at least a bachelor degree had a mean age of 37.4 and were perhaps less likely to defer fertility treatment as they would be ready to start a family right away, which could explain the higher sperm concentrations. Also, navigating health care options and understanding treatment regimens are prerequisites for fertility treatment, which means men with a poorer level of education would be at risk for deferring treatment and present with poorer semen quality. This hypothesis compares to findings from the National Survey of Family Growth, a cross-sectional study of 4105 men seeking fertility treatment in the United States, which found that men who had a college degree were more likely to seek fertility treatment.[22] In our study, adjustment for confounders, including age, attenuated the association between education and semen quality, although a trend remained.

Men above the age of 40 years had lower mean total sperm counts, morphology, motility, and ejaculate volumes in our cohort. The mean sperm concentrations differed minimally according to age, although older men had higher risks of both oligospermia and azoospermia after full adjustments. These findings compare to a meta-analysis of 90 studies, which found an age-dependent decline for all sperm parameters except for concentration.[23] The causality for this age-dependent decrease is uncertain, but it has been suggested that oxidative damage from reactive

oxygen species, leading to DNA damage might be contributory.[23] As the paternal age has increased in the United States[24] and 28% of the men in our cohort were above 40 years of age, these finding may have clinical implications as older paternal age have been linked to childhood comorbidity including increased risks of pediatric cancer[25] and autism.[26]

The prevalence and risks of azoospermia differed across sociodemographic characteristics. Overall, 8% of the men were azoospermic, which compares to a recent Danish study where 5% of men identified from infertile couples were azoospermic.[27] Data on regional and racial disparities in azoospermia rates are few as most semen studies of such types have been conducted in fertile men.[2,3,7] Nonetheless, one study of 16,714 infertile men from 5 different cities in India revealed large regional differences in azoospermia cases and it was hypothesized that high levels of fluoride in drinking water and workers exposure to pesticides may be contributory as a high percentage of men were occupationally involved in agriculture.[28] In our cohort, men from the Western region had the highest risk of azoospermia, which is noteworthy as they on average had higher mean sperm concentrations and were less likely to be oligospermic. The latter findings suggest that azoospermia and oligospermia may have different etiologies and support the well-established link between genetic origins and azoospermia. Whites had the highest prevalence of azoospermia that further supports genetic influences as certain post testicular causes of azoospermia, such as mutations in the CFTR gene, is more common among whites.[29]

A major strength of this study is the overall size and the ability to include men from geographically diverse US populations over a period of 9 years. In addition, as our cohort included about 40% nonwhites, minority groups were well represented, which is less common among reproductive studies. However, our study also has limitations. Due to the cross-sectional design, we cannot exclude the possibility of reverse causation as exposure and outcome variables were collected simultaneously. As with other studies that rely on electronic health data, we lacked information regarding lifestyle factors such as smoking, alcohol, and dietary habits that have been shown to affect semen quality in some studies.[30] We were also unable to adjust for chronic diseases, but as the men were relatively young at study inclusion we expect this to have little influence on the results. However, by adjustment of education (where applicable) we expect to have accounted for some of the possible confounding due to lifestyle factors and chronic disease. In addition, we were not able to adjust for period of sexual abstinence, seasonal factors, change of address, or before semen sampling and within and between laboratory variation in semen analysis is unknown—all factors may have effects on results and comparison mode. However, we expect these limitations to be evenly distributed across the groups. In addition, our geographical results compare to finding from SFF that used a strict protocol with regards to semen analyses.[3] We also relied on results from a single semen analysis, although we acknowledge that intravariability in semen quality among the same men exists. However, a previous study compared results using all semen analyses, which showed the same conclusions.[8] Lastly, our cohort is likely enriched from men evaluated for infertility, which may limit generalizability. However, the mean sperm concentration in our cohort was 57.9×10^6/mL, which is comparable to a US study of fertile men with mean sperm concentrations of 60.0×10^6/mL.[7] Further, recruitment of presumably fertile men for semen studies have previously proven difficult with low participation rates, which may introduce selection bias.

Despite these inherent study limitations, these results provide a comprehensive report of differences in semen parameters according to several sociodemographic characteristics. Our findings may have clinical implications as relying on a single reference value may be problematic given the variations based on regions, race, and education within the United States. Further work is warranted to understand the etiology of such differences and determine if different normative reference values may apply for different populations.

Acknowledgment. Data access for this project was provided by the Stanford Center for Population Health Sciences Data Core. The PHS Data Core is supported by a National Institutes of Health National Center for Advancing Translational Science Clinical and Translational Science Award (UL1 TR001085) and internal Stanford funding. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

References

1. Skakkebaek NE, Rajpert-De Meyts E, Buck Louis GM, et al. Male reproductive disorders and fertility trends: influences of environment and genetic susceptibility. *Physiol Rev*. 2016;96:55–97.
2. Jorgensen N, Andersen AG, Eustache F, et al. Regional differences in semen quality in Europe. *Hum Reprod*. 2001;16:1012–1019.
3. Swan SH, Brazil C, Drobnis EZ, et al. Geographic differences in semen quality of fertile U.S. males. *Environ Health Perspect*. 2003;111:414–420.
4. Macdonald AA, Stewart AW, Farquhar CM. Body mass index in relation to semen quality and reproductive hormones in New Zealand men: a cross-sectional study in fertility clinics. *Hum Reprod*. 2013;28:3178–3187.
5. Sharma R, Harlev A, Agarwal A, Esteves SC. Cigarette smoking and semen quality: a new meta-analysis examining the effect of the 2010 world health organization laboratory methods for the examination of human semen. *Eur Urol*. 2016;70:635–645.
6. Erenpreiss J, Punab M, Zilaitiene B, et al. Semen quality of young men from the general population in Baltic countries. *Hum Reprod*. 2017;32:1334–1340.
7. Redmon JB, Thomas W, Ma W, et al. Semen parameters in fertile US men: the study for future families. *Andrology*. 2013;1:806–814.
8. Khandwala YS, Zhang CA, Li S, Behr B, Guo D, Eisenberg ML. Racial variation in semen quality at fertility evaluation. *Urology*. 2017;106:96–102.
9. Glazer CH, Bonde JP, Eisenberg ML, et al. Male infertility and risk of nonmalignant chronic diseases: a systematic review of the epidemiological evidence. *Semin Reprod Med*. 2017;35:282–290.

10. Wallace PJ, Shah ND, Dennen T, Bleicher PA, Crown WH. Optum labs: building a novel node in the learning health care system. *Health Aff (Millwood)*. 2014;33:1187–1194.
11. Cooper TG, Noonan E, von Eckardstein S, et al. World Health Organization reference values for human semen characteristics. *Hum Reprod Update*. 2010;16:231–245.
12. Jensen TK, Vierula M, Hjollund NH, et al. Semen quality among Danish and Finnish men attempting to conceive. The Danish First Pregnancy Planner Study Team. *Eur J Endocrinol*. 2000;142: 47–52.
13. Jorgensen N, Carlsen E, Nermoen I, et al. East-West gradient in semen quality in the Nordic-Baltic area: a study of men from the general population in Denmark, Norway, Estonia and Finland. *Hum Reprod*. 2002;17:2199–2208.
14. Fisch H, Goluboff ET, Olson JH, Feldshuh J, Broder SJ, Barad DH. Semen analyses in 1,283 men from the United States over a 25-year period: no decline in quality. *Fertil Steril*. 1996;65:1009–1014.
15. Swan SH, Kruse RL, Liu F, et al. Semen quality in relation to biomarkers of pesticide exposure. *Environ Health Perspect*. 2003;111:1478–1484.
16. Lee JY, Dada R, Sabanegh E, Carpi A, Agarwal A. Role of genetics in azoospermia. *Urology*. 2011;77:598–601.
17. Iwamoto T, Nozawa S, Yoshiike M, et al. Semen quality of fertile Japanese men: a cross-sectional population-based study of 792 men. *BMJ Open*. 2013;3.
18. Gao L, Fan T, Chen Y, Qiu S. Reference values for vertebral shape in young Chinese women: implication for assessment of vertebral deformity. *Eur Spine J*. 2010;19:1162–1168.
19. Kovac JR, Pastuszak AW, Lamb DJ. The use of genomics, proteomics, and metabolomics in identifying biomarkers of male infertility. *Fertil Steril*. 2013;99:998–1007.
20. Xiao F, Lan A, Lin Z, et al. Impact of CAG repeat length in the androgen receptor gene on male infertility—a meta-analysis. *Reprod Biomed Online*. 2016;33:39–49.
21. Jain T. Socioeconomic and racial disparities among infertility patients seeking care. *Fertil Steril*. 2006;85:876–881.
22. Anderson JE, Farr SL, Jamieson DJ, Warner L, Macaluso M. Infertility services reported by men in the United States: national survey data. *Fertil Steril*. 2009;91:2466–2470.
23. Johnson SL, Dunleavy J, Gemmell NJ, Nakagawa S. Consistent age-dependent declines in human semen quality: a systematic review and meta-analysis. *Ageing Res Rev*. 2015;19:22–33.
24. Khandwala YS, Zhang CA, Lu Y, Eisenberg ML. The age of fathers in the USA is rising: an analysis of 168 867 480 births from 1972 to 2015. *Hum Reprod*. 2017;32:2110–2116.
25. Wang R, Metayer C, Morimoto L, et al. Parental age and risk of pediatric cancer in the offspring: a population-based record-linkage study in California. *Am J Epidemiol*. 2017;186:843–856.
26. Croen LA, Najjar DV, Fireman B, Grether JK. Maternal and paternal age and risk of autism spectrum disorders. *Arch Pediatr Adolesc Med*. 2007;161:334–340.
27. Glazer CH, Bonde JP, Giwercman A, et al. Risk of diabetes according to male factor infertility: a register-based cohort study. *Hum Reprod*. 2017;32:1–8.
28. Mehta RH, Makwana S, Ranga GM, Srinivasan RJ, Virk SS. Prevalences of oligozoospermia and azoospermia in male partners of infertile couples from different parts of India. *Asian J Androl*. 2006;8:89–93.
29. Cocuzza M, Alvarenga C, Pagani R. The epidemiology and etiology of azoospermia. *Clinics (Sao Paulo)*. 2013;68(suppl 1):15–26.
30. Sharma R, Biedenharn KR, Fedor JM, Agarwal A. Lifestyle factors and reproductive health: taking control of your fertility. *Reprod Biol Endocrinol*. 2013;11:66.