14. Hansen M, Greenop K, Bourke J, Baynam G, Hart R, Leonard H. Intellectual disability in children conceived using assisted reproductive technology. *Pediatrics*. 2018;142:e20181269.
15. Eisenberg ML, Li S, Brooks JD, Cullen MR, Baker LC. Sexual function/infertility increased risk of cancer in infertile men : analysis of U.S. claims data. *J Urol*. 2015;193:1596–1601.
16. Hanson HA, Ph D, Anderson RE, Aston KI, Ph D. Subfertility increases risk of testicular cancer : evidence from population-based semen samples. *Fertil Steril*. 2016;105:322–328. e1.
17. Jacobsen R, Bostofte E, Engholm G, Hansen J, Olsen JH, Skakkebæk NE. Risk of testicular cancer in men with abnormal semen characteristics: cohort study. *BMJ*. 2000;321:789–792.
18. Jørgensen N, Vierula M, Jacobsen R, Pukkala E, Perheentupa A, Virtanen HE. Recent adverse trends in semen quality and testis cancer incidence among Finnish men. *Int J Androl*. 2010;34:e37–e48.
19. Walsh TJ, Croughan MS, Schembri M, Chan JM, Turek PJ. Increased risk of testicular germ cell cancer among infertile men. *Arch Intern Med*. 2009;169:351–356.
20. Choy JT, Eisenberg ML. Male infertility as a window to health. *Fertil Steril*. 2018;110:810–814.
21. 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.
22. Glazer CH, Li S, Zhang CA, Giwercman A, Bonde JP, Eisenberg ML. Racial and sociodemographic differences of semen parameters among US men undergoing a semen analysis. *Urology*. 2018;123:126–132.
23. Latif T, Mehlsen J, Eisenberg ML, et al. Semen quality associated with subsequent hospitalizations—Can the effect be explained by socioeconomic status and lifestyle factors ? *Andrology*. 2018;6:428–435.
24. Menke A, Casagrande S, Geiss L, Cowie C. Prevalence of and trends in diabetes among adults in the United States, 1988-2012. *JAMA*. 2019;20910:1021–1029.
25. Salonia A, Matloob R, Gallina A, et al. Are infertile men less healthy than fertile men? Results of a prospective case-control survey. *Eur Urol*. 2009;56:1025–1032.
26. Khaw K, Dowsett M, Folkerd E, et al. Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men (EPIC-Norfolk) prospective population study. *Circulation*. 2007;116:2694–2701.
27. Matzuk MM, Lamb DJ. The biology of infertility : research advances and clinical challenges. *Nat Med*. 2008;14:1197–1214.

EDITORIAL COMMENT

There is a plethora of population-based studies evaluating the relationship between male infertility and cardiometabolic conditions, including obesity, diabetes, and heart disease. These studies aim to better characterize this association, identify risk factors, and provide more effective patient counseling and subsequent treatments for high-risk infertile men.[1,2] However, many of these studies have been hampered by homogeneity or a lack of sociodemographic data such as race, socioeconomic status, or geographic region.

The harbinger of this recent interest has been the seminal work of Eisenberg and Glazer et al, who elegantly demonstrated an increased risk of chronic nononcologic adverse outcomes, such as diabetes and heart disease, in infertile men.[1,2] The researchers determined the multifactorial etiology of increased cardiometabolic risk in infertile individuals, and noted a plausible link between male infertility and risk factors such as BMI, obesity, and hypogonadism.[3-7]

In this article, the authors report on the incidence of future cardiometabolic disease in infertile men and hypothesize that this risk varies by sociodemographic factors. They analyzed outcomes extracted from a large United States' insurance-based database of 76,343 men (18-50 years) diagnosed with the male infertility diagnosis code, and assessed by the International Classification of Diseases, 9th edition between 2003 and 2016. A total of 183,742 males that underwent vasectomy served as controls for the sole presumption to be fertile. The cardiometabolic health outcomes were assessed by International Classification of Diseases, 9th editiondiagnosis codes for diabetes, hypertension, hyperlipidemia, and heart disease. The main finding of this study (after adjusting for variables such as age, follow-up time, obesity, smoking, and health care utilization) was that male infertility demonstrated a higher risk of hypertension (HR 1.15, CI 1.13-1.18), diabetes (HR 1.5, CI 1.44-1.57), hyperlipidemia (HR 1.18, CI 1.16-1.21), and heart disease (HR 1.34, CI 1.25-1.45) compared to controls (vasectomy cohort). Similar associations were observed across all education, income, racial, and geographic strata. Taken together, this analysis demonstrates that infertile men are at a higher risk of cardiometabolic disease in the years following a fertility evaluation regardless of race, ethnicity, education, income, or geographical region.

These findings further confirm that, while infertile men are at higher risk of cardiometabolic disease, infertility status transcends socioeconomic status or geographic location and formulates the concept that male infertility is either a potential risk factor or biomarker for later health issues across all sociodemographic strata. Hence, this is of special interest when counseling young men with infertility on lifestyle modifications to mitigate the risk of future morbidity.

Nevertheless, the authors acknowledge the inherited biases and limitations of designing and conducting such a study, utilizing insurance claims data with the apparent lack of granular data on metabolic risk factors, such as family history and physical activity, as well as longitudinal follow-up. Additionally, the extraction of diagnoses requires correct coding of diagnoses in insurance claims and can be subject to bias of the provider.

This published study will likely add to the emerging chorus to exploit male infertility as a risk factor not only for underlying genitourinary malignancies[8-12] but also for cardiometabolic disease. As attractive as such finding appears, further data are necessary to confirm these findings and allow for a new horizon in the field of male infertility.

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References

1. Eisenberg ML, Li S, Cullen MR, Baker LC, Ph D. Increased risk of incident chronic medical conditions in infertile men: analysis of United States claims data. *Fertil Steril*. 2015;105:629–636.
2. Glazer CH, Bonde JP, Giwercman A, et al. Risk of diabetes according to male factor infertility: A register-based cohort study. *Hum Reprod*. 2017;32:1474–1481.
3. Salonia A, Matloob R, Gallina A, et al. Are infertile men less healthy than fertile men? results of a prospective case-control survey. *Eur Urol*. 2009;56:1025–1032.
4. Khaw K, Dowsett M, Folkerd E, et al. Endogenous Testosterone and mortality due to all causes, cardiovascular disease, and cancer in men (EPIC-Norfolk) prospective population study. *Circulation*. 2007;116:2694–2701.

5. Hammoud AO, Gibson M, Peterson CM, et al. Impact of male obesity on infertility: a critical review of the current literature. *Fertil Steril*. 2008;90:897–904.
6. Kort HI, Massey JB, Elsner CW, et al. Impact of body mass index values on sperm quantity and quality. *J Androl*. 2006;27:450–452.
7. Sermondade N, Faure C, Fezeu L, et al. BMI in relation to sperm count: an updated systematic review and collaborative meta-analysis. *Hum Reprod Update*. 2013;19:221–231.
8. Eisenberg ML, Betts P, Herder D, Lamb DJ, Lipshultz LI. Increased risk of cancer among azoospermic men. *Fertil Steril*. 2013;100:681–685.
9. Raman JD, Nobert CF, Goldstein M. Increased incidence of testicular cancer in men presenting with infertility and abnormal semen analysis. *J Urol*. 2005;174:1819–1822. discussion 1822.
10. Hanson HA, Anderson RE, Aston KI, Carrell DT, Smith KR, Hotaling JM. Subfertility increases risk of testicular cancer: evidence from population-based semen samples. *Fertil Steril*. 2016;105:322–328. e1.
11. Eisenberg ML, Li S, Brooks JD, Cullen MR, Baker LC. Increased risk of cancer in infertile men: analysis of U.S. claims data. *J Urol*. 2015;193:1596–1601.
12. Walsh TJ, Schembri M, Turek PJ, et al. Increased risk of high-grade prostate cancer among infertile men. *Cancer*. 2010;116:2140–2147.

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