Male Infertility and Future Cardiometabolic Health: Does the Association Vary by Sociodemographic Factors?

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OBJECTIVE To determine whether the association between male infertility and incident cardiometabolic disease is modified by socioeconomics, race, or geographic region.

MATERIALS AND METHOD Retrospective review of data from insurance claims from Optum's de-identified Clinformatics Data Mart Database. Subjects were men, 18-50 years old, with an associated diagnosis of infertility in the United States between 2003 and 2016. Analytical sample were men captured by the Optum's de-identified Clinformatics Data Mart Database with an associated diagnosis of infertility. Men were classified as either infertile, or not, based on diagnosis or procedural codes. Cardiometabolic health outcomes were then assessed using current procedural terminology codes for diabetes, hypertension, hyperlipidemia, and heart disease. Confounding factors were controlled for such as race, education, socioecomonic status, and region. The main outcomes were development of diabetes, hypertension, hyperlipidemia, and heart disease.

RESULTS A total of 76,343 males were diagnosed with male factor infertility, 60,072 males who underwent fertility testing, and 183,742 males that underwent vasectomy (control population). For all men, infertile men had a higher risk of incident hypertension, diabetes, hyperlipidemia, and heart disease when compared to those undergoing vasectomy. Identical associations were found across all education, income, racial, and geographic strata.

CONCLUSION Our study suggests that men with infertility have a higher risk of cardiometabolic disease in the years following a fertility evaluation regardless of race, region, or socioeconomic status. UROLOGY 133: 121–128, 2019. © 2019 Elsevier Inc.

Fifteen percent of couples are unable to conceive after 1 year of trying and are labeled infertile.[1,2] With an estimated 1.9% of all births conceived by IVF resulting in nearly 76,000 live births in the United States in 2016, assisted reproductive techniques (ART) have excellent success.[3,4] While there has been extensive focus on the outcomes of children born to infertile couples via ART since its inception, until recently there has been less focus on the health of their infertile fathers. However, recent data have suggested that infertile men are at higher risk of morbidity and mortality in the years following the infertility evaluation.[5-8]

Several groups have previously demonstrated that men with infertility in are at a higher risk of incident cardiometabolic disease including diabetes and heart disease.[9,10] However, to date most populations studied have been homogenous or with incomplete sociodemographic data by which to identify infertile groups at highest risk and better identify a possible etiology. Investigators have posited genetic, environmental, developmental, and lifestyle related factors to explain the association. By examining the relationship between infertility and future cardiometabolic health among different races, sociodemographic groups, and geographic regions, it may be possible to gain insight into which infertile male populations are most at risk for later morbidity as well as understand possible etiologies. Given varying rates of cardiometabolic disease in different socioeconomic groups, we hypothesized that

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incidence of cardiometabolic disease in infertile men would vary by sociodemographic factors.

MATERIALS AND METHODS

Patients

We utilized the Optum's de-identified Clinformatics Data Mart Database which is a database from a large national insurance provider that stores data from adjudicated and paid insurance claims from 2003 to 2016. Optum is a national database with information from adjudicated and paid insurance claims of privately-insured individuals and included between 6 and 7 million males annually during the study period. Individuals in the database represent a geographically and ethnically diverse population from a variety of age groups. Data include patient demographic characteristics, international classification of diseases (ICD-9 and 10) codes, and current procedural terminology (CPT) codes.

For the purpose of our study, we focused on men with an infertility diagnosis code, those undergoing fertility evaluation based on either diagnosis or procedural code and not associated with a code for infertility, and those with a diagnosis of vasectomy counseling or procedure code for vasectomy. Vasectomized men were used as a control as they have similar sociodemographic factors, health care access, and prior studies have at least 90% to be fertile. Men presenting for evaluation of infertility, but having no infertility diagnosed were used a secondary control population[11,12]. These were identified by the presence in inpatient or outpatient claims of an infertility diagnosis code (International Classification of Diseases, 9th edition, Clinical Modification [ICD-9] 606.x or ICD-10 N46.x). We recorded the first date of a relevant diagnosis as the index date. A comparison group of men who underwent fertility testing was assembled based on diagnosis and procedural coding (CPT) for fertility testing or semen analysis (89300, 89310, 89320, 89321, 89322, 89325, 89329, 89330, 89331, and V26.21). Given the variable infertility coding and reimbursement practices in the United States, we attempted to be as broad with our definition as possible. As with the male factor infertility group, we recorded the first date of a relevant diagnosis or procedure code as the index date. In addition, a comparison group of men with claims containing a diagnosis of vasectomy counseling (V25.09, V25.2, and V26.52) or procedure code for vasectomy (CPT 55250 or 55450) was assembled, as this group should include few or no infertile men. Men in this group were assigned an index date as the earliest date of a claim with a vasectomy diagnosis or procedure code.

In order to be included in the study, patients were required to be between 18 and 50 years old on the index date. Patients were also required to be enrolled in a plan covered by the database for at least 1 year after the index date. In all groups, patients with a prior cancer diagnosis or with a cancer diagnosis within the 1 year following the index date were excluded from the study.

Outcome Ascertainment

Health outcomes were identified using diagnosis codes on inpatient and outpatient claims. We chose common health conditions and identified men with codes indicating the presence of specific diseases: hypertension (ICD-9 401-405, ICD-10 I10-I16), diabetes (ICD-9 250, ICD-10 E08-E13), hyperlipidemia (ICD-9 272.0-272.4, ICD-10 E78.00, E78.1, E78.2, E78.4, E78.5), ischemic heart disease (ICD-9 410-414, ICD-10 I20-I25), and other heart disease (ICD-9 420-429, ICD-10 I30-I52).

Statistical Analysis

Patients accrued at risk time beginning from their index dates until disease diagnosis or censored at the last enrollment date in a health plan in the Optum insurance claims database. The risks of chronic diseases between infertile vs the vasectomy groups, and infertile testing vs vasectomy groups were assessed using a Cox proportional hazards model while adjusting for age at index date, race, smoking (ICD-9: 305.1, V15.82; ICD-10: F17.200, Z87.891), obesity, which was determined using diagnosis codes (ICD-9: 278.0; ICD-10: E66.01, E66.2, E66.3, E66.9), which may be been underreported as granular body mass index (BMI) data were not available, number of visits per year, highest level of education, region, and income. All demographic factors were collected from the Optum data set. Men with prevalent comorbid diagnoses or diagnosis within 1 year of follow-up were excluded from the analysis for that particular diagnosis. Analyses were stratified by race, education, income, and region. All P values were 2-sided with $P<.05$ considered statistically significant. Analyses were performed using SAS (version 9.4, SAS Institute, Inc., Cary, NC).

RESULTS

The study population included 76,343 men diagnosed with male factor infertility, 60,072 males who underwent fertility testing with a semen analysis, and 183,742 males that underwent vasectomy (ie, presumed to be fertile) (Table 1). The majority of individuals were between the ages of 30-39 across all groups. The mean age of infertile men was 35.4 ± 5.8 years whereas those attending for vasectomy had a mean of 37.6 ± 5.6 years; 14.2% of the infertile population and 12.1% of the vasectomized men were obese. A total of 10.9% of infertile men and 12.7% of vasectomized men were smokers. With regard to race, 65.5% of infertile males were white, 7.5% black, 10% Asian, and 11.5% Hispanic with the remaining 5.5% unknown. By comparison, 82.2% of vasectomized men were white, 4.7% black, 2% Asian, 7.5% Hispanic, and 3.6% unknown. The majority of both populations were less than college educated, had annual income over $100,000, and resided in the southern United States. Average follow-up time was 4.5 years for infertile individuals and 4.8 years for vasectomized men.

After adjusting for age, follow-up time, obesity, smoking, and health care utilization, male factor infertility was shown to have a higher risk of developing 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 those undergoing vasectomy. The incidence of each comorbid condition did vary based on race/ethnicity, education, income, and region. However, the hazard ratios for all comorbidities were similar across all strata. Analyses stratified by race showed similar patterns (Table 2): the same association between infertility and incident cardiometabolic disease was present for each racial/ethnicity group examined (ie, white, black, Asian, or Hispanic). However, the incidence of cardiometabolic disease did vary by race/ethnicity (P <.0001). The probability of development of diabetes increased over time for all races, however was less in whites (Supplemental Fig. 1).

In a similar fashion, analyses stratified by education (<HS, HS, less than college, or greater than or equal to college) (Table 3), income (<50K, 50-100K, or >100K dollars per year) (Table 4), and region (Supplemental Table 1) showed positive associations between infertility and incident cardiometabolic disease.

Table 1. Demographics of study population

	Category	Infertile	Infertile Evaluation	Vasectomy
N		76,343	60,072	183,742
Age, mean (SD)	Mean	35.3 (5.8)	35.4 (5.8)	37.6 (5.6)
	18-19	0.1	0.2	0
	20-29	15.6	15.1	7.4
	30-39	60.6	60.2	56.0
	40-50	23.7	24.6	36.7
Follow-up, mean (SD)	Mean	4.5 (3.2)	4.2 (3.0)	4.8 (3.3)
Follow-up, median (range)		3.5 (1-14)	3.2 (1-14)	3.8 (1-14)
Obesity		14.2	12.0	12.1
Smoking		10.9	9.9	12.7
Year of evaluation (%)	2003-2007	45.2	34.1	45.2
	2008-2011	30.1	32.6	30.0
	2012-2016	24.7	33.3	24.8
Average visits per person year, median(range)		2.1 (0-93.6)	1.8 (0-80.2)	1.9 (0-75.5)
Race (%)	White	65.5	70.8	82.2
	Black	7.5	6.1	4.7
	Asian	10	8.7	2.0
	Hispanic	11.5	9.3	7.6
	Unknown	5.5	5.0	3.6
Education (%)	<High school	0.5	0.3	0.2
	High school	19.3	15.7	18.9
	Less than college	50.8	51.6	55.3
	More than college	28.9	32.0	25.2
	Unknown	0.4	0.4	0.4
Income (%)	<$50K	9.1	8.2	7.0
	$50-100K	23.8	24.4	23.1
	>$100K	37.1	41.5	45.2
	Unknown	30	25.9	24.7
Geographic Region (%)	Division			
	East North Central	12.9	16.1	17.7
	East South Central	3.3	1.8	3.7
	Middle Atlantic	13.6	9.6	4.3
	Mountain	7.1	9.9	11.0
	New England	5.7	2.5	2.8
	Pacific	10.4	8.9	7.5
	South Atlantic	24.6	24.3	22.8
	Unknown	0.1	0.1	0.1
	West North Central	9.8	11.7	13.9
	West South Central	12.6	15.1	16.2
	Region			
	Midwest	22.7	27.9	31.7
	Northeast	19.2	12.1	7.1
	South	40.5	41.2	42.7
	Unknown	0.1	0.1	0.1
	West	17.5	18.8	18.5

DISCUSSION

This analysis demonstrates that infertile men are at a higher risk of cardiometabolic disease regardless of race/ethnicity, education, income, or region. While we have previously demonstrated an increased risk of chronic non-oncologic adverse outcomes in infertile men, such as diabetes and heart disease, the prior data have been limited by lack of details such as race and socioeconomic status that could have been cofounding the observed hazard ratios.[9] This study was able to evaluate race, educational level, region, and income to determine if these potential confounding factors changed the risk of development of adverse cardiopulmonary outcomes. The data presented here show when these sociodemographic factors are examined, the observed hazard ratios do not change indicating that infertility status is either a potential risk factor or biomarker for later health across all sociodemographic strata.

The primary focus of health outcomes in fertility research has traditionally been on the offspring born to those either deemed clinically infertile or having undergone fertility treatment. A large Danish cohort of 2.5 million children born to women with fertility problems (with no specification of fertility treatment) were shown to have increased incidence of mental disorders.[13] Additionally, a cohort from Australia of 2876 children born via ART showed similar findings.[14] However, until recently, less attention has focused on the health of the infertile male.

Table 2. Risk of medical comorbidities in infertile males stratified by race.

		Infertile		Infertile evaluation			Vasectomy		
Race	Comorbidity	*N*	Observed (%)	*N*	Observed (%)	HR Infertile Vs Evaluation	*N*	Observed (%)	HR Infertile Vs Vasectomy
All	Hypertension	67,232	10,457 (15.55)	53,735	6992 (13.01)	1.04 (1.01-1.08)	159,646	23,193 (14.53)	1.15 (1.13-1.18)
	Diabetes	73,135	4098 (5.6)	58,071	2291 (3.95)	1.13 (1.08-1.19)	178,424	6290 (3.53)	1.5 (1.44-1.57)
	Hyperlipidemia	66,908	13,767 (20.58)	53,111	9448 (17.79)	1.04 (1.01-1.06)	157,055	29,609 (18.85)	1.18 (1.16-1.21)
	Heart disease	72,281	6588 (9.11)	57,293	4274 (7.46)	1.05 (1.01-1.09)	173,558	14,892 (8.58)	1.14 (1.1-1.17)
White	Hypertension	44,181	6746 (15.27)	38,220	4894 (12.80)	1.05 (1.01-1.09)	131,714	18,834 (14.30)	1.15 (1.12-1.19)
	Diabetes	48,263	2233 (4.63)	41,391	1382 (3.34)	1.15 (1.07-1.23)	147,191	4703 (3.2)	1.49 (1.41-1.57)
	Hyperlipidemia	44,395	8488 (19.12)	38,024	6382 (16.78)	1.03 (0.999-1.07)	129,814	24,026 (18.51)	1.15 (1.12-1.18)
	Heart disease	47,408	4310 (9.09)	40,610	3086 (7.6)	1.04 (0.99-1.09)	14,2811	12,162 (8.52)	1.13 (1.09-1.17)
Black	Hypertension	4721	980 (20.76)	3049	551 (18.07)	1.02 (0.92-1.14)	7051	1386 (19.66)	1.18 (1.08-1.28)
	Diabetes	5354	434 (8.11)	3444	211 (6.13)	1.05 (0.89-1.24)	8200	462 (5.63)	1.48 (1.29-1.69)
	Hyperlipidemia	4984	1046 (20.99)	3202	594 (18.55)	0.99 (0.89-1.09)	7343	1496 (20.37)	1.14 (1.05-1.24)
	Heart disease	5327	581 (10.91)	3421	301 (8.8)	1.01 (0.88-1.16)	8087	802 (9.92)	1.16 (1.04-1.3)
Asian	Hypertension	6927	835 (12.05)	4803	486 (10.12)	1.05 (0.93-1.17)	3170	373 (11.77)	1.16 (1.02-1.32)
	Diabetes	7237	514 (7.1)	4992	277 (5.55)	1.09 (0.94-1.27)	3445	177 (5.14)	1.53 (1.28-1.83)
	Hyperlipidemia	6420	1601 (24.94)	4440	980 (22.07)	1.03 (0.95-1.11)	2930	628 (21.43)	1.41 (1.28-1.56)
	Heart disease	7331	507 (6.92)	5067	251 (4.95)	1.22 (1.05-1.42)	3427	245 (7.15)	1.1 (0.94-1.29)
Hispanic	Hypertension	7654	1310 (17.12)	4936	728 (14.75)	1.01 (0.92-1.10)	11,963	1843 (15.41)	1.16 (1.08-1.25)
	Diabetes	8251	665 (8.06)	5327	301 (5.65)	1.19 (1.04-1.37)	13,195	710 (5.38)	1.53 (1.37-1.71)
	Hyperlipidemia	7470	1842 (24.66)	4784	991 (20.71)	1.08 (1.001-1.17)	11,400	2409 (21.13)	1.3 (1.22-1.39)
	Heart disease	8246	816 (9.9)	5298	415 (7.83)	1.08 (0.96-1.22)	13,028	1124 (8.63)	1.22 (1.11-1.34)

Table 3. Risk of medical comorbidities in infertile males stratified by education

		Infertile		Infertile evaluation			Vasectomy		
Education	Comorbidity	*N*	Observed (%)	*N*	Observed (%)	HR Infertile Vs Evaluation	*N*	Observed (%)	HR Infertile Vs Vasectomy
All	Hypertension	67,232	10,457 (15.55)	53,735	6992 (13.01)	1.04 (1.01-1.08)	159,646	23,193 (14.53)	1.15 (1.13-1.18)
	Diabetes	73,135	4098 (5.6)	58,071	2291 (3.95)	1.13 (1.08-1.19)	178,424	6290 (3.53)	1.5 (1.44-1.57)
	Hyperlipidemia	66,908	13,767 (20.58)	53,111	9448 (17.79)	1.04 (1.01-1.06)	157,055	29,609 (18.85)	1.18 (1.16-1.21)
	Heart disease	72,281	6588 (9.11)	57,293	4274 (7.46)	1.05 (1.01-1.09)	173,558	14,892 (8.58)	1.14 (1.1-1.17)
<High School	Hypertension	330	55 (16.67)	168	17 (10.12)	1.76 (0.996-3.12)	350	52 (14.86)	1.6 (1.07-2.4)
	Diabetes	340	27 (7.94)	176	11 (6.25)	1.31 (0.63-2.73)	377	26 (6.9)	1.69 (0.96-2.99)
	Hyperlipidemia	330	60 (18.18)	165	24 (14.55)	1.32 (0.81-2.18)	333	55 (16.52)	1.63 (1.11-2.41)
	Heart disease	357	29 (8.12)	177	8 (4.52)	1.81 (0.8-4.06)	378	23 (6.08)	1.57 (0.87-2.83)
High School	Hypertension	12,586	2316 (18.4)	8285	1330 (16.05)	1.01 (0.95-1.08)	29,466	4966 (16.85)	1.15 (1.09-1.21)
	Diabetes	13,947	945 (6.78)	9052	471 (5.2)	1.06 (0.95-1.19)	33,537	1479 (4.41)	1.44 (1.32-1.57)
	Hyperlipidemia	12,930	2595 (20.07)	8351	1439 (17.23)	1.04 (0.98-1.11)	30,205	5470 (18.11)	1.2 (1.14-1.26)
	Heart disease	13,961	1282 (9.18)	9047	719 (7.95)	0.97 (0.89-1.07)	33,005	2791 (8.46)	1.14 (1.06-1.22)
Less than college	Hypertension	34,008	5456 (16.04)	27,500	3705 (13.47)	1.06 (1.01-1.1)	87,931	13,042 (14.83)	1.16 (1.13-1.2)
	Diabetes	37,132	2122 (5.71)	29,951	1190 (3.97)	1.19 (1.11-1.28)	98,614	3652 (3.7)	1.49 (1.41-1.58)
	Hyperlipidemia	34,030	6984 (20.52)	27,425	4918 (17.93)	1.02 (0.99-1.06)	86,746	16,386 (18.89)	1.18 (1.15-1.22)
	Heart disease	36,766	3244 (8.82)	29,567	2108 (7.13)	1.07 (1.01-1.13)	96,052	8097 (8.43)	1.12 (1.07-1.17)
More than college	Hypertension	20,012	2590 (12.94)	17,582	1905 (10.83)	1.06 (0.997-1.12)	41,278	5037 (12.2)	1.16 (1.1-1.22)
	Diabetes	21,395	988 (4.62)	18,678	609 (3.26)	1.13 (1.02-1.25)	45,210	1115 (2.47)	1.64 (1.5-1.8)
	Hyperlipidemia	19,318	4066 (21.05)	16,965	3034 (17.88)	1.04 (0.995-1.09)	39,142	7592 (19.4)	1.16 (1.11-1.21)
	Heart disease	20,876	2011 (9.63)	18,294	1422 (7.77)	1.1 (1.02-1.17)	43,450	3932 (9.05)	1.18 (1.12-1.25)

Table 4. Risk of medical comorbidities in infertile males stratified by income

		Infertile		Infertile evaluation			Vasectomy		
Income	Comorbidity	*N*	Observed (%)	*N*	Observed (%)	HR Infertile Vs Evaluation	N	Observed (%)	HR Infertile Vs Vasectomy
All	Hypertension	67,232	10,457 (15.55)	53,735	6992 (13.01)	1.04 (1.01-1.08)	159,646	23,193 (14.53)	1.15 (1.13-1.18)
	Diabetes	73,135	4098 (5.6)	58,071	2291 (3.95)	1.13 (1.08-1.19)	178,424	6290 (3.53)	1.5 (1.44-1.57)
	Hyperlipidemia	66,908	13,767 (20.58)	53,111	9448 (17.79)	1.04 (1.01-1.06)	157,055	29,609 (18.85)	1.18 (1.16-1.21)
	Heart disease	72,281	6588 (9.11)	57,293	4274 (7.46)	1.05 (1.01-1.09)	173,558	14,892 (8.58)	1.14 (1.1-1.17)
<50K	Hypertension	5923	1031 (17.41)	4245	605 (14.25)	1.04 (0.94-1.16)	10,948	1727 (15.77)	1.2 (1.11-1.3)
	Diabetes	6560	455 (6.94)	4669	235 (5.03)	1.08 (0.92-1.27)	12,443	526 (4.23)	1.61 (1.41-1.83)
	Hyperlipidemia	6075	1189 (19.57)	4302	725 (16.85)	0.96 (0.88-1.06)	11,230	1834 (16.33)	1.24 (1.15-1.34)
	Heart disease	6575	564 (8.58)	4690	321 (6.84)	1.02 (0.89-1.17)	12,303	958 (7.79)	1.12 (1-1.25)
50-100K	Hypertension	15,640	2596 (16.6)	12,934	1,750 (13.53)	0.99 (0.93-1.05)	36,097	5610 (15.54)	1.13 (1.08-1.19)
	Diabetes	17,231	1083 (6.29)	14,128	592 (4.19)	1.12 (1.01-1.24)	40,935	1678 (4.1)	1.46 (1.34-1.58)
	Hyperlipidemia	15,739	3300 (20.97)	12,981	2,252 (17.35)	0.99 (0.94-1.05)	36,155	6830 (18.89)	1.18 (1.13-1.23)
	Heart disease	17,120	1522 (8.89)	14,011	940 (6.71)	1.05 (0.96-1.13)	40,035	3401 (8.5)	1.1 (1.03-1.17)
100K	Hypertension	24,998	4170 (16.68)	22,338	3,072 (13.75)	1.05 (1.001-1.1)	72,192	11,024 (15.27)	1.15 (1.11-1.2)
	Diabetes	27,259	1585 (5.81)	24,181	976 (4.04)	1.15 (1.06-1.24)	80,796	2894 (3.58)	1.49 (1.4-1.59)
	Hyperlipidemia	24,418	5,857 (23.99)	21,752	4,424 (20.34)	1.03 (0.99-1.07)	69,419	15,097 (21.75)	1.15 (1.11-1.18)
	Heart disease	26,635	2935 (11.02)	23,592	2,107 (8.93)	1.05 (0.99-1.11)	77,796	7639 (9.82)	1.15 (1.1-1.2)

There is limited data on the later health outcomes of infertile men. Long-term follow-up of these individuals can be difficult in the absence of national health systems. As cancer registries exist in many countries, previous studies have focused on the increased incidence of certain cancers in infertile males. Data from private insurance claims have shown that infertile males have a higher risk of incident cancer.[15] Particular attention has been paid to an increased risk of testicular cancer in infertile individuals.[7,16-19] Most recently, an analysis of 20,433 men who had undergone semen analysis and examined the risk of all cancers. Compared to fertile men, there was an increased risk of testicular cancer with a hazard rate of 3.3 with a particularly increased risk among those men identified as oligozoospermic.[16]

To date, the etiology of the association between infertility and later health remains unknown. Authors have argued that genetic, developmental, or lifestyle factors may play a role. As we attempt to understand the association or even target selected screening for men, it would be helpful to know which groups are at highest risk. Moreover, as genetic and lifestyle factors have been posited to explain the association, it would be helpful to understand if the association between fertility and health varies based on race/ethnicity or socioeconomic status, or region.[20] Indeed, it has been shown that semen quality varies based on race, education, and region in the US.[21,22] A study of 1423 Danish men showed that socioeconomic class was not associated with increased risk of hospitalization in the presence of abnormal semen analysis.[23] In the current analysis, we found similar risk regardless of race/ethnicity, education, and income. The results suggest that the link between infertility and cardiometabolic health transcends socioeconomic status or geographic location. Importantly, while whites have an overall lower incidence of cardiometabolic disease, the relative risk of all cardiometabolic disease was similar across all races/ethnicities.[24]

The underlying mechanism driving our findings of increased cardiometabolic risk in infertile individuals remains unknown and is likely multifactorial. As BMI has been linked to infertility, this may help explain the increased risk of adverse cardiometabolic outcomes as obesity itself demonstrates an increased risk of similar outcomes.[25] Hypogonadism has additionally been shown to increase an individual's risk of cardiovascular disease therefore a similar link may exist between infertility and cardiometabolic disease.[26] As a large proportion of the genome, approximately 10%, participates in reproduction it is reasonable to hypothesize that defects within it may affect other areas.[27]

The association identified by this analysis potentially presents a new opportunity for health counseling as men are evaluated for male infertility. Counseling on improved lifestyle modifications may have the potential to mitigate the risk of future morbidity. However, future research needs to establish the etiology of the association between infertility and cardiometabolic disease before strong clinical recommendations can be made.

The present study is limited in the fact that it relies on insurance claims data, which have limited granular data about the enrollees. In addition, follow-up is limited in a largely employed based health care database. Additionally, the extraction of diagnoses requires correct coding of diagnoses in insurance claims and can be subject to bias of the provider. Furthermore, key data on metabolic risk factors, such as family history, physical activity, were not available within the database we used.

In conclusion, in this large cohort of patients, while the overall risk of incident cardiometabolic disease remains low for infertile men, the work suggests that infertile men are at higher risks of cardiometabolic disease regardless of race/ethnicity or socioeconomic status, or region.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2019.06.041.

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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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