GYNECOLOGY

Increased risk of incident chronic medical conditions in infertile women: analysis of US claims data

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BACKGROUND: The risk of common chronic medical conditions among infertile women is not known.

OBJECTIVE: The objective of the study was to study the association between female infertility and the risk of incident chronic disease.

STUDY DESIGN: This was a retrospective cohort analysis using the Optum deidentified Clinformatics Datamart from 2003 through 2016. A total of 64,345 infertile women were identified by infertility diagnosis, testing, or treatment and compared with 3,128,345 noninfertile patients seeking routine gynecologic care. Women with a prior diagnosis of the relevant chronic disease or cancer or with either diagnosis within 6 months of the index event were excluded. The main outcome was a diagnosis of incident chronic disease as identified by *International Classification of Diseases*, ninth revision/*International Classification of Diseases*, 10th revision codes. Results were adjusted for age, index year, nulliparity, race, smoking, obesity, number of visits per year, and highest level of education.

RESULTS: Infertile patients were more likely to develop diabetes (adjusted hazard risk, 1.44, confidence interval, 1.38—1.49), renal disease (adjusted hazard risk, 1.22, confidence interval, 1.12—1.32), liver disease (adjusted hazard risk, 1.25, confidence interval, 1.20—1.30), cerebrovascular disease (adjusted hazard risk, 1.26, confidence interval, 1.15—1.38), ischemic heart disease (adjusted hazard risk, 1.16, confidence interval, 1.09—1.24), other heart disease (adjusted hazard risk, 1.16, confidence interval, 1.12—1.20), and drug abuse (adjusted hazard risk, 1.24, confidence interval, 1.15—1.33) compared with noninfertile patients. Infertile patients were significantly less likely to develop alcohol abuse (adjusted hazard risk, 0.86, confidence interval, 0.79—0.95) compared with noninfertile patients. Risk associations were similar after excluding women with polycystic ovarian syndrome and premature ovarian insufficiency. In subgroup analyses of women who underwent pregnancy and childbirth during enrollment, several previously noted risk associations were attenuated compared with the overall cohort.

CONCLUSION: While the absolute risk of chronic disease is low, infertility is associated with an increased risk of incident chronic disease compared with a group of noninfertile women.

Key words: chronic disease, female infertility, fertility treatment

Approximately 15% of couples in the United States are diagnosed with infertility, with female infertility identified in at least 50% of cases.[1] The association between female infertility and chronic medical conditions is an area of ongoing investigation, and emerging data suggest that infertility may provide a window to overall health.

Increased risk of chronic medical conditions has been noted, for example, in infertile men.[2] In women, obesity, cancer, diabetes, and other medical conditions can lead to infertility and are associated with increased morbidity and early mortality.[3-6] Infertility, premature ovarian insufficiency (POI) and polycystic ovarian syndrome (PCOS) have been associated with an increased risk of cardiovascular disease,[7-16] while a few published studies that have used large population databases have not found significantly increased rates of cardiovascular disease in women who conceived with in bitro fertilization.[17-19]

Infertile patients have also been shown to have a higher risk of anxiety and depression.[20-23] Information on the risk of other mental health disorders and infertility, however, is limited. Overall, large gaps exist in the literature, particularly with respect to the risk associations between noncardiovascular chronic diseases and mental health with infertility.

The physiologic changes that accompany pregnancy and childbirth have been shown to reveal the risk of later development of chronic disease and mental illness.[24-29] There is limited information, however, on the risk associations of chronic diseases in infertile women who undergo pregnancy and childbirth. There is, however, a correlation between age at birth of last child and maternal longevity, suggesting a slower rate of aging in women with late childbearing compared with women who complete childbearing at a younger age.[30,31] Given the association between chronic disease and premature death and disability,[32] one can hypothesize that infertile women who achieve pregnancy and childbirth may have an altered risk of chronic disease.

The goal of our study was to investigate whether infertility was associated with a subsequent risk of developing several common chronic medical conditions. In addition, we sought to investigate whether pregnancy and childbirth modify the association between infertility and chronic disease.

Materials and Methods

Patients

We analyzed subjects in the Optum deidentified Clinformatics Datamart between 2003 and 2016. Optum's Clinformatics Data Mart is derived from a database of administrative health claims for a total of more than 57 million unique lives over a 9-year period (January 2003 through December 2016). These administrative claims submitted

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AJOG at a Glance

Why was this study conducted?

The risk of common chronic medical conditions among infertile women is not known.

Key findings

Using an insurance claims database, we compared development of incident chronic disease among 64,345 infertile women and 3,128,345 noninfertile women from 2003 through 2016. Infertile women were more likely to develop diabetes, renal disease, liver disease, cerebrovascular disease, ischemic heart disease, other heart disease, and drug abuse compared with noninfertile women but were less likely to develop alcohol abuse compared with noninfertile women. Risk associations were similar after excluding women with polycystic ovarian syndrome and premature ovarian insufficiency. In subgroup analyses of women who underwent pregnancy and childbirth during enrollment, several risk associations were attenuated compared ith the overall cohort.

What does this add to what is known?

Through previously unexplored risk associations, we report that infertile women may have a higher risk of developing several incident chronic medical conditions compared with noninfertile women.

for payment by providers and pharmacies are verified, adjudicated, adjusted, and deidentified prior to inclusion. The population is geographically diverse, spanning all 50 states and comprises both commercial and Medicare Advantage health plan data. This study was exempt from approval by the Stanford Institutional Review Board.

Given the variation in infertility coding and reimbursement practices in the United States, we attempted to be as broad as possible. The cohort of infertile women was comprised of women with an infertility diagnosis, women receiving fertility testing, or women receiving fertility treatment. Women with an infertility diagnosis were identified by outpatient claims (*International Classification of Diseases*, ninth revision [ICD-9]/*International Classification of Diseases*, 10th revision [ICD-10]: ICD-9, 628.x, 614.6, V26.89; ICD-10, E23.0, N73.6, N97.x, Z31.81).

Fertility testing was identified through diagnosis codes (V26.21, Z31.41) or the presence of a procedure code (CPT) for hysterosalpingogram (74740). Hysterosalpingogram was chosen to identify infertile women because it is commonly ordered as part of an initial fertility evaluation to assess tubal patency but is not otherwise part of routine gynecologic care.[33]

Patients receiving fertility treatment were identified by the presence of a CPT code for intrauterine artificial insemination (58322), follicular puncture for oocyte retrieval (58970), or intrauterine embryo transfer (58974). The presence of a pharmacy claim for a prescription for clomiphene citrate or a gonadotropin (follicle-stimulating hormone, human menopausal gonadotropin, human chorionic gonadotropin [HCG]) was also used to identify patients receiving fertility treatment.

Clomiphene was chosen because it is routinely used to induce ovulation for women with anovulatory infertility as well as to promote superovulation for women who are ovulatory and is not prescribed for nonfertility indications.[34] Gonadotropins (follicle-stimulating hormone, human menopausal gonadotropin, HCG) have comprised the standard approach for ovulation stimulation and induction for assisted reproductive technology since they were first implemented in 1981, and HCG has consistently been used to trigger final oocyte maturation in assisted reproductive technology cycles.[35]

The comparison group was composed of women receiving routine gynecologic care who did not have an infertility diagnosis or procedure codes for fertility testing or treatment. These patients were identified through the presence of a claim for a well-woman visit (V72.31, Z01.411, Z01.419), encounter for contraceptive management (V25.0, V25.01—V25.04, V25.09, Z30.011, Z30.012, Z30.015, Z30.016, Z30.017, Z30.018, Z30.02, Z30.09), placement or removal of an intrauterine device (V25.11—V25.13, Z30.430, Z30.432, Z30.433), placement of a contraceptive implant (V25.5, Z30.8), bilateral tubal ligation (V25.2, Z30.2), contraceptive surveillance (V25.40—V25.43, V25.49, Z30.40, Z30.41, Z30.42, Z30.431, Z30.436, Z30.44, Z30.45, Z30.49), and Papanicolau smear (V72.32, Z12.4, 88141—88155, 88164-—88167, 88174—5, Q0091, G0101).

In both groups, women who became pregnant and had a delivery were identified by diagnosis and procedure codes indicating the conclusion of a pregnancy. These diagnosis and procedure codes were obtained from a literature search of insurance claims data used to identify various pregnancy outcomes.[36,37]

We recorded the first date of a relevant diagnosis or procedure code as the index date. For patients in the infertile group, the index date was the date of infertility diagnosis, testing, or treatment. For patients in the noninfertile group, the index date was the date of encounter for any of the services listed in the previous text. A woman who received an infertility diagnosis at any time during enrollment was assigned to the infertile cohort. Therefore, women could not contribute person-time as both infertile and noninfertile.

To be included in the study, patients were required to be between 20 and 45 years old on the index date and enrolled in a plan covered by the database for at least 6 months before and after the index date. In all groups, patients with a prior diagnosis of the relevant chronic disease or cancer or with either diagnosis within the 6 months following the index date were excluded from the study. This was identified through the presence of any claim with an ICD-9/10 diagnosis code for cancer or the relevant chronic disease.

For each patient, the number of outpatient visits after the index date was determined based on the presence of claims for CPT codes indicating new and follow-up visits, consultations, or preventive medicine encounters. Diagnosis codes for obesity (278.0, E66.9, E66.01, E66.3, E66.2), smoking (305.1, V15.82, F17.200, Z87.891), and nulliparity (V22.0, V23.81, V23.83, O0.95, O0.96) were used to identify potential confounders.

Outcome ascertainment

The most common chronic nonmalignant diseases in the United States were identified using data from the Centers for Disease Control and Prevention and other state-level departments of health and based on prior analyses our group has performed on infertile men.[2] Chronic disease diagnoses were identified using diagnosis codes on inpatient and outpatient claims.

Specifically, we identified a diagnosis of hypertension (ICD-9: 401−405, ICD-9: I10−16), diabetes of any type (ICD-9: 250, ICD-10: E08−13), hyperlipidemia (ICD-9: 272.0−4, ICD-10: E78.4−5, E78.2, E78.00, E78.1), renal disease (ICD-9: 580−8; ICD-10: N17-19), chronic pulmonary disease (ICD-9: 490−496, ICD-10: J40−47), liver disease (ICD-9: 570−3, ICD-10: K70−77, B18−19), peripheral vascular disease (ICD-9: 440−443, ICD-10: I70−79), cerebrovascular disease (ICD-9: 430−438, ICD-10: I60−69), ischemic heart disease (ICD-9: 410−414, ICD-10: I20−25), other heart disease (ICD-9: 420−429, ICD-10: I30−52), depression (ICD-9: 296.2−3, 298.0, 300.4, 309.1, 311, ICD-10: F32−33), alcohol abuse (ICD-9: 291.0−291.3, 291.5, 291.8, 291.81, 291.89, 291.9, 303.00−303.93, 305.00−305.03, V113, 303.x, ICD-10: F10, Z71.4x), drug abuse (ICD-9: 292.0, 292.82−292.89, 292.9, 304.00−304.93, 305.20−305.93, 648.30−648.34, 304.x, ICD-10: Z71.5x, F11, F12, F13, F14, F15, F16, F18, F19), anxiety disorder (ICD-9: 293.84, 300.0, 313.0, ICD-10: F40, F41, F06.4), and bipolar disorder (ICD-9: 296.0, 296.4−296.8, ICD-10: F31).

A sensitivity analysis was performed in which patients with a diagnosis of PCOS (ICD 9: 256.4, 628.0, ICD-10: E28.2, N 97.0) or POI (ICD-9: 256.31, 256.39, ICD-10: E28.310, E28.319, E28.39) were excluded from both cohorts. In this subgroup of patients, the incidence of chronic disease was compared between infertile and noninfertile groups.

Subset analyses were also performed comparing incidence of chronic disease among women in both infertile and noninfertile cohorts who became pregnant and had a delivery during the enrollment period. Finally, subset analyses limited to women with progressively longer follow-up were performed to determine how short follow-up affected results.

Statistical analysis

Patients accrued at risk time beginning from their index dates until the chronic disease diagnosis or the last enrollment date in a health plan in the Optum insurance claims database. The risk of chronic disease between infertile and noninfertile patients was assessed using a Cox proportional hazards model while adjusting for age, index year, nulliparity, race, smoking, obesity, number of visits per year, and highest level of education. Subgroup analyses were similarly adjusted. A formal statistical test of effect modification by parity was performed for the overall cohort analysis. 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

Patient demographics: infertile patients vs noninfertile patients

Overall, 64,345 patients had a diagnosis of infertility, underwent fertility testing, or underwent fertility treatment. The noninfertile group was comprised of 3,128,345 patients who received routine gynecologic care (Table 1). Patients in the infertile group were older on average at the index date (34.0 ± 5.7 years) compared with the noninfertile group (32.7 ± 7.4 years) (Table 1). Patients were, on average, followed up for 3.8 ± 3.3 years in the infertile group and 3.9 ± 3.3 years in the noninfertile group. Infertile patients were more likely to be nulliparous (17.7%) compared with noninfertile patients (8.5%). In both groups, the majority of patients were white. The geographic distribution was also similar between the infertile and noninfertile subjects.

Comparison of infertile and noninfertile groups

Infertile patients were more likely to develop diabetes (adjusted hazard risk [aHR], 1.44, confidence interval [CI], 1.38−1.49), renal disease (aHR, 1.22, CI, 1.12−1.32), liver disease (aHR, 1.25, CI, 1.20-1.30), cerebrovascular disease (aHR, 1.26, CI, 1.15-1.38), ischemic heart disease (aHR, 1.16, CI, 1.09−1.24), and other heart disease (aHR, 1.16, CI, 1.12−1.20) compared with noninfertile subjects (Table 2).

The incidence of hypertension, hyperlipidemia, chronic pulmonary disease, and peripheral vascular disease was similar for infertile and noninfertile subjects. While infertile patients were more likely to be diagnosed as suffering from drug abuse (aHR, 1.24, CI, 1.15−1.33), rates of depression, anxiety disorders, and bipolar disorders were similar comparing infertile and noninfertile subjects. Infertile women were at a decreased risk of developing alcohol abuse (aHR, 0.86, CI, 0.79−0.94) compared with noninfertile women.

Adjusting for covariates including age, index year, nulliparity, race, smoking, obesity, number of visits per year, and education did not significantly affect any of the results. Analyses were performed including the interaction term between nulliparity and the infertile/noninfertile groups. The only statistically significant interaction was for peripheral vascular disease ($P = .005$).

A sensitivity analysis was performed excluding patients with the diagnoses of PCOS and POI with similar risk estimates and no change in the overall conclusions (Supplemental Table 1). The mean follow-

TABLE 1
Patient demographics of overall infertile cohort and subset of patients within each cohort with pregnancy and subsequent delivery during follow-up period

Variables	Mean (SD)	Full cohort		Delivery cohort	
		Infertile	Control	Infertile	Control
Number of patients		64,345	3,128,345	22,024	626,532
Age, y		34.0 (5.7)	32.7 (7.4)	32.6 (4.9)	29.8 (5.2)
	20–24 (%)	5.3	17.8	4.9	16.6
	25–29 (%)	18.1	20.0	22.5	33.1
	30–34 (%)	29.5	19.3	36.8	31.4
	35–39 (%)	28.1	19.0	27.2	15.2
	40–45 (%)	19.0	24.0	8.6	3.7
Follow-up time, y	Mean (SD)	3.8 (3.3)	3.9 (3.3)	4.5 (3.3)	4.5 (3.4)
	0–1 (%)	16.7	15.9	5.7	11.1
	1–2 (%)	23.9	22.9	22.2	19.6
	2–3 (%)	14.4	14.5	16.6	14.4
	3–4 (%)	9.9	10.2	12.3	11.1
	4+ (%)	35.1	36.5	43.3	43.9
	Total (n)	246,485	12,268,968	98,145	2,791,449
Nulliparity, %		17.7	8.5	42.8	37.0
Obesity, %		18.4	13.6	16.3	13.1
Smoking, %		11.2	9.7	7.1	8.6
Index date, %	2003	9.2	9.9	9.9	10.2
	2004	11.6	10.7	12.0	10.9
	2005	9.6	9.9	9.7	10.0
	2006	8.1	8.9	8.1	9.2
	2007	7.7	8.4	7.9	8.7
	2008	7.3	7.8	7.5	8.3
	2009	6.6	7.0	7.1	7.3
	2010	5.6	5.9	6.0	6.1
	2011	5.8	6.0	6.2	6.1
	2012	5.8	5.8	6.2	5.9
	2013	6.1	5.6	6.2	5.5
	2014	6.2	5.4	6.4	5.2
	2015	6.8	5.8	5.7	4.8
	2016	3.8	3.0	1.4	2.0
Visits per person year	Median (range)	4.1 (0–92.5)	2.7 (0–236.2)	4.5 (0–61.0)	2.6 (0–236.2)
	<1 (%)	12.4	18.6	7.9	17.7
	1–2 (%)	12.8	19.5	11.1	20.6
	2+ (%)	74.9	61.9	81.0	61.7

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TABLE 1
Patient demographics of overall infertile cohort and subset of patients within each cohort with pregnancy and subsequent delivery during follow-up period *(continued)*

Variables	Mean (SD)	Full cohort		Delivery cohort	
		Infertile	Control	Infertile	Control
Race/ethnicity, %	White	61.4	68.4	64.1	65.4
	Asian	10.6	5.3	13.0	7.7
	Black	10.3	10.2	7.1	9.2
	Hispanic	12.4	11.6	10.1	13.0
	Unknown	5.4	4.5	5.7	4.8
Education, %	Less than 12th grade	0.8	0.7	0.4	0.8
	High school diploma	23.2	24.3	17.0	23.3
	Less than Bachelor's degree	50.7	52.8	49.7	53.4
	Bachelor's degree plus	24.7	21.6	32.5	22.0
	Unknown	0.6	0.5	0.5	0.5
Income, %	<$50,000	14.0	15.5	10.2	14.9
	$50,000–100,000	22.1	22.8	22.1	23.8
	$100,000+	26.7	26.2	35.3	26.9
	Unknown	37.2	35.5	32.6	34.5
Region of the country, %	Midwest	24.2	26.1	24.8	26.4
	Northeast	12.9	10.4	15.0	9.8
	South	40.6	45.6	37.0	44.0
	West	22.1	17.8	22.9	19.6
	Unknown	0.3	0.2	0.3	0.2

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up time for both infertile and noninfertile cohorts was 3.9 years. A subset analysis was performed limiting follow-up time to >2, >3, and >4 years in both infertile and noninfertile cohorts. We identified similar point estimates in these analyses.

Patient demographics: subset of patients with a delivery during enrollment

Of the 64,345 patients in the infertile group, 22,024 (34.2%) had a pregnancy and subsequent delivery during the enrollment period (4.5 ± 3.3 years). Of the 3,128,345 patients in the noninfertile group, 626,532 (20.0%) had a pregnancy and subsequent delivery during the enrollment period (4.5 ± 3.4 years). Again, infertile subjects were older (32.6 ± 4.9 years) compared with the noninfertile group (29.8 ± 5.2 years) (Table 1). Infertile patients in the delivery subgroup had a slightly higher prevalence of nulliparity (42.8%) compared with noninfertile patients (37.0%).

Subset analysis of all patients with a delivery during enrollment

An analysis of incident chronic disease in women who became pregnant and had a delivery in both infertile and noninfertile groups was performed (Table 3). The risks of cerebrovascular disease (aHR, 1.18, CI, 0.99–1.4) and ischemic heart disease (aHR, 1.06, CI, 0.92–1.21) were similar between the pregnant/delivery infertile and noninfertile subgroups in contrast to the entire cohort. The risk of diabetes (aHR, 1.51, CI, 1.41–1.61), renal disease (aHR, 1.31, CI, 1.13–1.53), liver disease (aHR, 1.12, CI, 1.04–1.22), and other heart disease (aHR, 1.27, CI, 1.21–1.34) remained significantly elevated in the infertile delivery subgroup compared with the noninfertile subgroup.

The risk of peripheral vascular disease (aHR, 1.14, CI, 1.02–1.27) was significantly increased in the infertile subgroup compared with the noninfertile subgroup but was not significant in the overall comparison between infertile and noninfertile groups. The risks of alcohol or drug abuse, depression, anxiety, and bipolar disorders were similar to the entire cohort. Adjusting for covariates did not significantly affect the results.

Subset analysis of infertile patients with and without a delivery during enrollment

A subset analysis was performed comparing incidence of chronic disease among infertile patients who underwent pregnancy and childbirth during enrollment and infertile patients who

TABLE 2
Absolute incidence, events per person-years, hazard ratios, and 95% CIs for the association between female infertility and incidence of chronic disease

Disease	Total n	Total person-years follow-up	n, %	Events/1000 person-years	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)[a]	Adjusted hazard ratio (95% CI)[b]
Hypertension							
Infertile	58,624	210,267	5,081 (8.67)	24.16	1.19 (1.16–1.23)	1.17 (1.14–1.21)	1.07 (1.04–1.10)
Control	288,1503	10,633,711	216,077 (7.50)	20.32			
Diabetes							
Infertile	61,373	228,225	2,702 (4.40)	11.84	1.63 (1.57–1.69)	1.61 (1.55–1.68)	1.44 (1.38–1.49)
Control	3,030,986	11,647,077	84,950 (2.80)	7.29			
Hyperlipidemia							
Infertile	60,318	216,391	5,444 (9.03)	25.16	1.11 (1.08–1.14)	1.09 (1.06–1.12)	1.02 (1.00–1.05)
Control	2,929,131	10,742,926	244,936 (8.36)	22.80			
Renal disease							
Infertile	63,923	243,515	554 (0.87)	2.28	1.33 (1.22–1.44)	1.32 (1.22–1.44)	1.22 (1.12–1.32)
Control	3,114,393	12,164,496	20,953 (0.67)	1.72			
Chronic pulmonary disease							
Infertile	57,548	205,171	5,339 (9.28)	26.02	1.16 (1.13–1.19)	1.15 (1.12–1.18)	1.07 (1.04–1.10)
Control	2,826,968	10,431,128	234,826 (8.31)	22.51			
Liver disease							
Infertile	62,646	234,458	2128 (3.40)	9.08	1.38 (1.33–1.45)	1.3 (1.32–1.43)	1.25 (1.20–1.30)
Control	3,080,504	11,876,381	78,303 (2.54)	6.59			
Cardiovascular disorders (composite)							
Infertile	60,528	217,973	4775 (7.89)	21.91	1.22 (1.19–1.26)	1.21 (1.17–1.24)	1.14 (1.11– 1.17)
Control	2,974,763	11,074,727	199,150 (6.69)	17.98			
Peripheral vascular disorders							
Infertile	63,837	242,450	983 (1.54)	4.05	1.15 (1.08–1.22)	1.15 (1.08–1.22)	1.08 (1.02–1.15)
Control	3,107,449	12,086,881	42,899 (1.38)	3.55			
Cerebrovascular disease							
Infertile	64,135	244,436	502 (0.78)	2.05	1.32 (1.2–1.44)	1.34 (1.23–1.46)	1.26 (1.15–1.38)
Control	3,120,648	12,190,879	19,135 (0.61)	1.57			

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(continued)

TABLE 2
Absolute incidence, events per person-years, hazard ratios, and 95% CIs for the association between female infertility and incidence of chronic disease
(continued)

Disease	Total n	Total person-years follow-up	n, %	Events/1000 person-years	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)[a]	Adjusted hazard ratio (95% CI)[b]
Ischemic heart disease							
Infertile	63,797	241,540	917 (1.44)	3.8	1.19 (1.12–1.27)	1.23 (1.15–1.31)	1.16 (1.09–1.24)
Control	3,105,239	12,051,069	38,481 (1.24)	3.19			
Other heart disease							
Infertile	61,301	223,374	3766 (6.14)	16.86	1.25 (1.21–.3)	1.24 (1.2–1.28)	1.16 (1.12–1.20)
Control	3,007,786	11,328,132	152,894 (5.08)	13.50			
Mental health disorders (composite)							
Infertile	53,147	182,526	8530 (16.05)	46.73	1.06 (1.04–1.08)	1.06 (1.03–1.08)	1.03 (1.01–1.05)
Control	2,564,788	9,074,562	401,627 (15.66)	44.26			
Alcohol abuse							
Infertile	63,969	244,091	510 (0.80)	2.09	0.88 (0.81–0.96)	0.89 (0.82–0.97)	0.86 (0.79–0.94)
Control	3,103,250	12,116,996	28,711 (0.93)	2.37			
Drug abuse							
Infertile	63,772	242,976	787 (1.23)	3.24	1.33 (1.24–1.43)	1.34 (1.25–1.44)	1.24 (1.15–1.33)
Control	3,104,300	12,131,690	29,663 (0.96)	2.45			
Depression							
Infertile	57,342	203,580	5,997 (10.46)	29.46	1.08 (1.06–1.11)	1.08 (1.05–1.11)	1.04 (1.02–1.07)
Control	2,767,274	10,117,061	275,108 (9.94)	27.19			
Anxiety disorders							
Infertile	57,667	206,073	6,850 (11.88)	33.24	1.05 (1.02–1.08)	1.05 (1.02–1.07)	1.02 (1.00–1.04)
Control	2,810,391	10,304,888	327,499 (11.65)	31.78			
Bipolar disorders							
Infertile	63,484	241,706	673 (1.06)	2.78	1.13 (1.05–1.22)	1.14 (1.06–1.23)	1.08 (1.00–1.17)
Control	3,087,427	12,049,450	29,727 (0.96)	2.47			

CI, confidence interval.

[a] Adjusted for age; [b] Adjusted for age, index year, nulliparity, race, smoking, obesity, number of visits per year, and highest level of education.

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TABLE 3
Absolute incidence, events per person-years, hazard ratios and 95% confidence intervals for the association between female infertility and incidence of chronic disease in the subset of patients with pregnancy and subsequent delivery during follow-up

Disease	Total n	Total person-years follow-up	n, %	Events/1000 person-years	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)[a]	Adjusted hazard ratio (95% CI)[b]
Hypertension							
Infertile subset	21,025	88,386	1838 (8.74)	20.8	1.39 (1.33–1.46)	1.22 (1.16–1.28)	0.98 (0.94–1.03)
Control subset	60,1960	2,574,003	38,556 (6.41)	14.98			
Diabetes							
Infertile subset	21,398	92,441	1013 (4.73)	10.96	1.83 (1.72–1.95)	1.6 (1.5–1.7)	1.51 (1.41–1.61)
Control subset	614,453	2,695,686	16,107 (2.62)	5.98			
Hyperlipidemia							
Infertile subset	21,206	89,487	1704 (8.04)	19.04	1.32 (1.26–1.38)	1.08 (1.03–0.14)	1.02 (0.97–1.07)
Control subset	609,292	2,597,220	37,724 (6.19)	14.52			
Renal disease							
Infertile subset	22,006	97,676	180 (0.82)	1.84	1.51 (1.3–1.76)	1.37 (1.18–1.59)	1.31 (1.13–1.53)
Control subset	626,148	2,784,822	3397 (0.54)	1.22			
Chronic pulmonary disease							
Infertile subset	20,314	84,088	2077 (10.22)	24.7	1.16 (1.11–1.21)	1.13 (1.08–0.18)	1.05 (1.01–1.10)
Control subset	579,302	2,426,182	51,549 (8.90)	21.25			
Liver disease							
Infertile subset	21,736	95,113	650 (2.99)	6.83	1.37 (1.27–0.48)	1.22 (1.12–1.32)	1.12 (1.04–1.22)
Control subset	621,476	2,734,338	13,664 (2.20)	5.00			
Cardiovascular disorders (composite)							
Infertile subset		77,108	3202 (16.36)	41.53	1.4 (1.34–1.47)	1.2 (1.21–1.33)	1.12 (1.08–1.16)
Control subset	560,548	2,267,338	74,932 (13.37)	33.05			
Peripheral vascular disorders							
Infertile subset	22,004	97,515	335 (1.52)	3.44	1.42 (1.28–1.59)	1.22 (1.09–1.36)	1.14 (1.02–1.27)
Control subset	625,732	2,775,737	6782 (1.08)	2.44			
Cerebrovascular disease							
Infertile subset	22,059	98,053	131 (0.59)	1.34	1.44 (1.21–1.71)	1.19 (1–1.42)	1.18 (0.99–1.4)
Control subset	627,200	2,791,505	2625 (0.42)	0.94			

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(continued)

TABLE 3
Absolute incidence, events per person-years, hazard ratios and 95% confidence intervals for the association between female infertility and incidence of chronic disease in the subset of patients with pregnancy and subsequent delivery during follow-up *(continued)*

Disease	Total n	Total person-years follow-up	n, %	Events/1000 person-years	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)[a]	Adjusted hazard ratio (95% CI)[b]
Ischemic heart disease							
Infertile subset	22,016	97,518	226 (1.03)	2.32	1.32 (1.16–1.51)	1.04 (0.91–1.18)	1.06 (0.92–1.21)
Control subset	625,972	2,776,669	4885 (0.78)	1.76			
Other heart disease							
Infertile subset	21,303	89,894	1582 (7.43)	17.6	1.43 (1.36–1.51)	1.32 (1.25–1.39)	1.27 (1.21–1.34)
Control subset	607,549	2,612,094	31,977 (5.26)	12.24			
Mental health disorders (composite)							
Infertile subset	19,368	76,614	3388 (17.49)	44.22	1.08 (1.05–1.12)	1.09 (1.05–1.13)	1.05 (1.01–1.09)
Control subset	548,937	2197968	89,207 (16.25)	40.59			
Alcohol abuse							
Infertile subset	22,040	98,023	125 (0.57)	1.28	0.85 (0.71–1.02)	0.9 (0.75–1.08)	0.87 (0.73–1.05)
Control subset	625,067	2,779,231	4168 (0.67)	1.50			
Drug abuse							
Infertile subset	22,027	97,853	211 (0.96)	2.16	1.06 (0.92–1.21)	1.2 (1.04–1.38)	1.17 (1.02–1.34)
Control subset	623,505	2,774,173	5,652 (0.91)	2.04			
Depression							
Infertile subset	20,517	84,381	2,292 (11.17)	27.16	1.08 (1.04–1.13)	1.09 (1.04–1.13)	1.05 (1.00–1.09)
Control subset	579,263	2,407,454	60,004 (10.36)	24.92			
Anxiety disorders							
Infertile subset	20,477	84,941	2,566 (12.53)	30.21	1.07 (1.03–1.11)	1.07 (1.03–1.12)	1.03 (0.99–1.07)
Control subset	584,682	2,429,511	68,876 (11.78)	28.35			
Bipolar disorders							
Infertile subset	21,954	97,392	189 (0.86)	1.94	1.00 (0.86–1.15)	1.07 (0.92–1.23)	1.03 (0.89–1.19)
Control subset	623,297	2,768,243	5,361 (0.86)	1.94			

CI, confidence interval.

[a] Adjusted for age; [b] Adjusted for age, index year, nulliparity, race, smoking, obesity, number of visits per year, and highest level of education.

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TABLE 4
Absolute incidence, events per person-years, hazard ratios, and 95% CIs for the association between female infertility and incidence of chronic disease in the subset of infertile patients with pregnancy and subsequent delivery during follow-up compared with infertile patients without pregnancy and subsequent delivery during follow-up

Disease	Delivery	Total n	Total person-years follow-up	n, %	Events/1000 person-years	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)[a]	Adjusted hazard ratio (95% CI)[b]
Hypertension	Infertile + Delivery	37,599	121,881	3,243 (8.63)	26.61	0.76 (0.72–081)	0.84 (0.8–0.9)	1.04 (0.97–1.11)
	Infertile - Delivery	21,025	88,386	1,838 (8.74)	20.80			
Diabetes	Infertile + Delivery	39,975	13,5783	1,689 (4.23)	12.44	0.87 (0.8–0.94)	0.9 (0.83–0.97)	1.06 (0.97–1.17)
	Infertile - Delivery	21,398	92,441	1,013 (4.73)	10.96			
Hyperlipidemia	Infertile + Delivery	39,112	126,904	3,740 (9.56)	29.47	0.62 (0.59–0.66)	0.73 (0.68–0.77)	0.84 (0.78–0.90)
	Infertile - Delivery	21,206	89,487	1,704 (8.04)	19.04			
Renal disease	Infertile + Delivery	41,917	145,839	374 (0.89)	2.56	0.7 (0.58–0.83)	0.78 (0.65–0.94)	0.94 (0.76–1.16)
	Infertile - Delivery	22,006	97,676	180 (0.82)	1.84			
Chronic pulmonary disease	Infertile + Delivery	37,234	121,084	3,262 (8.76)	26.94	0.9 (0.85–0.95)	0.92 (0.87–0.98)	0.99 (0.93–1.06)
	Infertile - Delivery	20,314	84,088	2,077 (10.22)	24.70			
Liver disease	Infertile + Delivery	40,910	139,345	1,478 (3.61)	10.61	0.63 (0.57– 0.69)	0.69 (0.62–0.76)	0.79 (0.71–0.88)
	Infertile - Delivery	21,736	95,113	650 (2.99)	6.83			
Cardiovascular disorders (composite)	Infertile + Delivery	35,316	110,296	4564 (2.92)	41.38	0.95 (0.9– 1.01)	1.09 (1.02– 1.16)	1.12 (1.06–1.18)
	Infertile - Delivery	19,573	77,108	3202 (16.36)	41.53			
Peripheral vascular disorders	Infertile + Delivery	41,833	144,935	648 (1.55)	4.47	0.74 (0.65–0.85)	0.92 (0.8–1.06)	0.91 (0.77–1.06)
	Infertile - Delivery	22,004	97,515	335 (1.52)	3.44			
Cerebrovascular disease	Infertile + Delivery	42,076	146,383	371 (0.88)	2.53	0.51 (0.42– 0.62)	0.65 (0.53–0.8)	0.85 (0.67–1.07)
	Infertile - Delivery	22,059	98,053	131 (0.59)	1.34			
Ischemic heart disease	Infertile + Delivery	41,781	144,023	691 (1.65)	4.80	0.47 (0.4–0.54)	0.61 (0.53–0.72)	0.90 (0.76–1.07)
	Infertile - Delivery	22,016	97,518	226 (1.03)	2.32			
Other heart disease	Infertile + Delivery	39,998	133,480	2,184 (5.46)	16.36	1.06 (0.99–1.13)	1.19 (1.11–1.27)	1.36 (1.26–1.46)
	Infertile - Delivery	21,303	89,894	1,582 (7.43)	17.6			
Mental health disorders (composite)	Infertile + Delivery	33,779	105,911	5142 (15.22)	48.55	0.89 (0.85–0.93)	0.89 (0.85–0.93)	0.96 (0.91–1.01)
	Infertile - Delivery	19,368	76,614	3388 (17.49)	44.22			
Alcohol abuse	Infertile + Delivery	41,929	146,068	385 (0.92)	2.64	0.47 (0.39–0.58)	0.47 (0.38–0.58)	0.65 (0.51–0.82)
	Infertile - Delivery	22,040	98,023	125 (0.57)	1.28			

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(continued)

TABLE 4
Absolute incidence, events per person-years, hazard ratios, and 95% CIs for the association between female infertility and incidence of chronic disease in the subset of infertile patients with pregnancy and subsequent delivery during follow-up compared with infertile patients without pregnancy and subsequent delivery during follow-up *(continued)*

Disease	Delivery	Total n	Total person-years follow-up	n, %	Events/1000 person-years	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)[a]	Adjusted hazard ratio (95% CI)[b]
Drug abuse	Infertile + Delivery	41,745	145,124	576 (1.38)	03.97	0.53 (0.46–0.62)	0.52 (0.44–0.61)	0.73 (0.60–0.88)
	Infertile - Delivery	22,027	97,853	211 (0.96)	2.16			
Depression	Infertile + Delivery	36,825	119,200	3,705 (10.06)	31.08	0.85 (0.81–0.9)	0.85 (0.81–0.9)	0.94 (0.88–0.99)
	Infertile - Delivery	20,517	84,381	2,292 (11.17)	27.16			
Anxiety disorders	Infertile + Delivery	37,190	121,132	4,284 (11.52)	35.37	0.83 (0.79–0.88)	0.83 (0.79–0.88)	0.92 (0.87–0.97)
	Infertile - Delivery	20,477	84,941	2,566 (12.53)	30.21			
Bipolar disorders	Infertile + Delivery	41,530	144,313	484 (1.17)	3.35	0.56 (0.48– 0.67)	0.53 (0.45–0.63)	0.76 (0.62–0.92)
	Infertile - Delivery	21,954	97,392	189 (0.86)	1.94			

+, infertile with delivery; –, infertile without delivery; CI, confidence interval.

[a] Adjusted for age; [b] Adjusted for age, index year, nulliparity, race, smoking, obesity, number of visits per year, and highest level of education.

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did not become pregnant and deliver during enrollment (Table 4).

The risks of diabetes (aHR, 1.06, CI, 0.97–1.17), renal disease (aHR, 0.94, CI, 0.76–1.16), cerebrovascular disease (aHR, 0.85, CI, 0.67–1.07), and ischemic heart disease (aHR, 0.90, CI, 0.76–1.07) were similar between the subgroups with and without delivery in contrast to the entire cohort. The risk of hyperlipidemia (aHR, 0.84, CI, 0.78-0.90), bipolar disorder (aHR, 0.76, CI, 0.62–0.92), liver disease (aHR, 0.79, CI, 0.71–0.88), and drug abuse (aHR, 0.73, CI, 0.60–0.88) was significantly lower in the infertile subgroup with delivery compared with the infertile subgroup without delivery. The risks of other heart disease and alcohol abuse were similar to the overall cohort. Adjusting for covariates strengthened the risk associations for all outcomes (Table 4).

Comment

Despite the prevalence of female infertility, there is a paucity of data on the risk association between infertility and development of common chronic nonmalignant diseases. While absolute risks are low, we report that infertile women have an increased risk of several incident chronic diseases compared with noninfertile women. A sensitivity analysis excluding women with PCOS and POI from both cohorts demonstrated similar risk associations.

Our findings are paralleled by previous work demonstrating an increased risk of incident chronic disease in infertile men,[2] suggesting that infertility may provide a window to overall health in both men and women. Our findings are also in concordance with prior studies reporting an association between female infertility and increased risk of cardiovascular disease and diabetes[5,7-13] and present a more comprehensive view by including several additional common chronic diseases with previously unexplored risk associations.

While multiple prior studies report associations between mental illness and infertility,[20-23] we report a significant risk association between infertility and drug abuse but do not find an association with other mental illnesses.

While several studies have examined the association between pregnancy and the risk of chronic diseases,[24-29] we have compared risk of chronic disease between infertile and noninfertile patients who undergo pregnancy and childbirth. In a subgroup analysis comparing the risk of chronic disease among infertile women with and without a delivery, several risk associations were attenuated. Further investigation is warranted to understand the etiology of this protective effect of childbirth. Our findings do corroborate with the body of data demonstrating a correlation between late age at last reproduction and postreproductive longevity.[30,31]

The etiologies of these risk associations are likely multifactorial. By definition, chronic diseases develop over several years and may impair fertility for several years before other clinical manifestations are apparent. Infertile patients were, on average, older than the noninfertile patients; however, the mean age difference of 1.3 years is unlikely to be of clinical significance.

Obesity and smoking, demographic factors that were more prevalent in the infertile group, can impair fertility and increase the risk of chronic disease.[3,38,39] Although we did control for these confounders, it is possible that unmeasured confounding is present. Overall, it is unclear whether infertile patients have a higher frequency of an underlying pathology or whether the emotional or medical impact of infertility is causing these diagnoses to be more frequent after infertility diagnosis.

Limitations

Although the number of women and total years at risk was high, the largest limitations of the study are that average follow-up for each individual and age at final observation were limited and absolute risk of individual chronic diseases was low. We did, however, identify several significant risk associations in a short duration of follow-up. It is not known whether factors related to population turnover in the database are related to chronic disease risk and thus is a source of potential confounding. We did perform a sensitivity analysis limited to women with progressively longer follow-up and identified similar point estimates in these analyses. Furthermore, the limited follow-up time in our study inadvertently selects for the subset of chronic diseases that present at an early age.

The database we utilized includes patients insured commercially and through Medicare but may not represent all US women, and there is selection bias of the population. In addition, details regarding infertility diagnosis and treatment are not fully captured in insurance claims data. For example, patients could have sought fertility treatment outside insurance coverage. This would have not been captured in our database and led to nondifferential misclassification with a regression to a null finding.

Despite this likely underestimate of associations, we still found differences between the overall infertile and noninfertile cohorts. In addition, increased care utilization among patients with infertility diagnoses may increase the likelihood of being diagnosed with a chronic medical condition because of observational bias. While we controlled for several covariates in our data analysis, our ability to capture some was limited because of the lack of granular data in an administrative dataset.

Finally, because of the high number of outcomes investigated, there is a possibility that a small fraction of the results are false positives because of the role of chance. The high number of statistically significant associations we found, however, suggests that our findings are not due to chance alone.

Future studies would incorporate longer-term follow-up and separately examine the incidence of chronic disease in women diagnosed with infertility compared with infertile women who then have fertility treatment. Nevertheless, other studies have validated the use of insurance claims data to investigate incident health outcomes.[2] Future studies would also control for potential confounders including oral and long-acting contraceptive use, age at first birth, and oligomenorrhea, which may affect both fertility and chronic disease risk. ■

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SUPPLEMENTARY TABLE 1

Absolute incidence, events per person-years, hazard ratios, and 95% confidence intervals for the association between female infertility and incidence of chronic disease, excluding patients with a diagnosis of PCOS or POI from both cohorts

Variables	Infertile				Control				Hazard ratio (95% CI)[a]
Disease	Total n	Total person-years follow-up	n (%)	Events/1000 person-years	Total n	Total person-years follow-up	n (%)	Events/1000 person-years	Infertile vs control
Hypertension	39,668	140,851	3197 (8.06)	22.7	2,793,822	10,268,325	203,312 (7.28)	19.8	1.01 (0.98—1.05)
Diabetes	41,921	155,042	1453 (3.47)	9.37	2,938,140	11,241,424	75,966 (2.59)	6.76	1.21 (1.15—1.27)
Hyperlipidemia	40,987	145,521	3557 (8.68)	24.44	2,839,659	10,377,219	229,625 (8.09)	22.13	0.99 (0.95—1.02)
Renal disease	43,271	162,753	374 (0.86)	2.30	3,013,096	11,700,768	19,574 (0.65)	1.67	1.23 (1.11— 1.36)
Chronic pulmonary disease	38,937	137,574	3503 (9.00)	25.46	2,739,104	10,061,569	222,787 (8.13)	22.14	1.07 (1.04— 1.11)
Liver disease	42,434	156,994	1371 (3.23)	8.73	2,982,055	11,438,326	72058 (2.42)	6.30	1.24 (1.17— 1.31)
Peripheral vascular disorders	43,195	161,968	673 (1.56)	4.16	3,006,378	11,626,792	40,515 (1.35)	3.48	1.09 (1.01— 1.17)
Cerebrovascular disease	43,412	163,411	356 (0.82)	2.18	3,018,986	11,725,124	17,949 (0.59)	1.53	1.29 (1.16—1.43)
Ischemic heart disease	43,159	161,360	644 (1.49)	3.99	3,004,370	11,594,009	36,148 (1.2)	3.12	1.17 (1.08— 1.26)
Other heart disease	41,377	149,188	2,466 (5.96)	16.53	2,911,426	10,911,922	144,423 (4.96)	13.24	1.14 (1.09— 1.18)
Alcohol abuse	43,287	163,148	363 (0.84)	2.22	3,001,989	11,652,251	27,530 (0.92)	2.36	0.90 (0.81— 0.995)
Drug abuse	43,123	162,265	554 (1.28)	3.41	3,003,257	11,668,288	27,975 (0.93)	2.40	1.32 (1.22— 1.44)
Depression	38,595	135,888	3,925 (10.17)	28.88	2,682,541	9,768,399	260,855 (9.72)	26.70	1.05 (1.02— 1.09)
Anxiety disorders	38,849	137,110	4,593 (11.82)	33.5	2,722,584	9,941,134	310,948 (11.42)	31.28	1.06 (1.03— 1.09)
Bipolar disorders	42,977	161,635	454 (1.06)	2.81	2,987,673	11,593,256	27,787 (0.93)	2.40	1.14 (1.04— 1.25)

CI, confidence interval.

[a] Adjusted for age, index year, nulliparity, race, smoking, obesity, number of visits per year, and highest level of education.

Murugappan et al. Increased risk of chronic medical conditions in infertile women. Am J Obstet Gynecol 2019.