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Clinical correlation among male infertility and overall male health: A systematic review of the literature

Francesco Del Giudice[1,2,*], Alex M. Kasman[2,*], Matteo Ferro[3], Alessandro Sciarra[1], Ettore De Berardinis[1], Federico Belladelli[2,4], Andrea Salonia[4], Michael L. Eisenberg[2,5]

[1]Department of Maternal-Infant and Urological Sciences, "Sapienza" Rome University, Policlinico Umberto I Hospital, Rome, Italy, [2]Department of Urology, Stanford University School of Medicine, Stanford, CA, USA, [3]Division of Urology, European Institute of Oncology (IEO), Milan, [4]Unit of Urology/Division of Oncology, IRCCS Ospedale San Rafaele, URI, Milan, Italy, [5]Department of Obstetrics and Gynecology, Stanford University School of Medicine, Stanford, CA, USA

Purpose: Ongoing evidence has suggested the role of male factor infertility as a potential predictor of mortality and general health status. The aim of the present review is to update the current knowledge base regarding the association between male factor infertility and general health through a critical review of the literature.

Materials and Methods: A systematic review of the literature was carried out from inception to November 2019 in order to evaluate significant associations between male infertility and adverse health outcomes such as cardiovascular, oncologic, metabolic and autoimmune diseases as well as overall mortality.

Results: In all, 27 studies met inclusion criteria and were critically examined. Five studies examined male infertility and cardiovascular disease risk, 11 examined oncologic risk (e.g., overall cancer risk, testis and prostate cancer), 8 examined aggregate chronic medical diseases and 5 infertility related to incidence of mortality, for a total of 599,807 men diagnosed with any male factor infertility covering a period from 1916 to 2016.

Conclusions: A man's fertility and overall health appear to be interconnected. Therefore, a diagnosis of male infertility may allow a window into future comorbidity and/or mortality which may help guide clinical decisions and counseling. Several possible etiologies such as genetic, epigenetic, developmental, and lifestyle-based factors need to be further evaluated in order to establish the underlying mechanisms between male infertility and health.

Keywords: Androgens; Health; Hypogonadism; Infertility, male; Mortality

INTRODUCTION

About 15% of couples do not achieve pregnancy within 1 year of attempting to conceive and thus are labeled as infertile [1,2]. Of those couples, male factor infertility is the underlying cause in 30% to 50% of cases [3]. Primary or secondary hypogonadism is a well-established predictor of male infertility as it can lead to alterations in all sperm parameters, with oligo-azoospermic men found to be hypogonadal in approximately 43% to 45% of cases which itself is associated

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Corresponding Author: Michael L. Eisenberg https://orcid.org/0000-0001-5482-0141
Department of Urology, Stanford University School of Medicine, 300 Pasteur Drive, Stanford, CA 94305-5118, USA
TEL: +1-650-723-5700, FAX: +1-650-724-9609, E-mail: eisenberg@stanford.edu
*These authors contributed equally to this study and should be considered co-first authors.

with impaired health (e.g., cardiovascular disease [CVD]) [4]. Recent literature has also identified lower sperm counts as an independent predictor of comorbidity and mortality [5-9].

As such male infertility has been proposed as an independent risk factor for poor health status and early mortality, while the etiology of this relationship remains unclear [10]. However, existing studies examining the prevalence of co-morbidities, morbidity, and mortality among infertile men are heterogeneous and contain often low level of evidence (LE). Given the increasing number of reports in this context, there is a need for synthesis of the data in order to better translate the conclusions into clinical practice and effective counseling.

As worldwide sperm counts continue to fall there may be an increase in the prevalence of male factor infertility [9,10]. As such, male infertility as a biomarker for future health and mortality will become more relevant. In the current study, we aim to systematically review the literature and present the findings regarding male infertility and co-morbidities/mortality.

MATERIALS AND METHODS

1. Evidence acquisition

We performed a systematic review of the literature in PubMed, Embase, and Cochrane from inception to November 18th, 2019, without language restriction, to identify studies that examined male factor infertility and overall health, morbidity, and mortality. The reference lists of the included studies were also screened for relevant articles. Only original articles were included and critically evaluated. Case reports, abstracts and meeting reports were excluded from the analysis. Search terms included but were not limited to: male infertility, AND semen quality AND general health AND male comorbidities or male general dysfunction, AND male overall survival; secondary fields: male mortality; male hypogonadism; infertility and cardiovascular diseases; infertility and cancer development; infertility and chronic diseases; infertility and genetic associations; infertility and development associations. For all studies, we evaluated the LE according to the European Association of Urology (EAU) guidelines [11].

2. Selection of the studies and criteria of inclusion

Entry into the analysis was restricted to data collected from original studies and those that examined subfertile/infertile males by semen analysis or those subjects with known male factor infertility. The reviewers utilized the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to develop the review [12]. Three authors (FDG, FB, EDB, and AMK) independently screened the titles and abstracts of all articles using predefined inclusion criteria. The full-text articles were examined independently by four authors (MLE, FDG, MF, and AS) to determine whether or not they met the inclusion criteria. Final inclusion was determined by consensus of all investigators. Selected articles meeting the inclusion criteria were then critically analyzed and data synthesized. The diagnosis of subfertile/infertility was based on failure to conceive for at least 12 months and/or on impaired semen analyses below the normal references values according to the World Health Organization (WHO) classification [13]) presence of other known male-related infertility factors (i.e., presence of varicocele; men seeking for fertility testing/treatments).

The definition of CVD included a variety of different cardiovascular disorders, including ischemic coronary disease, cardiac failure and hypertension. All possible oncological associations with male infertility were examined. Analyses regarding chronic comorbidities and male infertility included metabolic syndrome and associated conditions such as obesity, insulin resistance, and dyslipidemia. All autoimmune disorder associations were included, such as multiple sclerosis (MS) and other rheumatological conditions (i.e., rheumatoid arthritis, psoriasis, Graves' disease, and autoimmune thyroiditis). Mortality including death from any causes retrieved.

3. Assessment of quality for studies included

The quality of the identified studies was assessed independently by two reviewers (FDG, FB) using the "Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies," provided by the National Institute of Health (NIH) [14], by assessing the potential risk for selection bias, information bias, measurement bias, or confounding (confounding includes cointerventions, differences at baseline in patient characteristics, and other issues as shown in Supplementary Table 1) [15-41]. Studies were rated as good, fair, and poor quality, where high risk of bias translated to a rating of poor quality ("−") and low risk of bias translated to a rating of good quality ("+").

RESULTS

1. Search results

The initial search yielded 334 articles (PubMed, 238; Cochrane, 62; and Embase, 34). One-hundred-ninety-six were excluded as they contained overlapping data or were duplicates appearing in multiple databases. Of the remaining 138,

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72 were further excluded since they did not examine male infertility (42), contained animal experiments (9), or were review papers or editorials (21). Full-text articles were then reevaluated and critically analyzed for the remaining 46 journal references. Within this in-depth review, a further 19 did not meet the inclusion criteria. The remaining 27 studies were included in our review (Fig. 1). No study was considered to be seriously flawed as per the "Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies" [14]. Studies' risk to performance bias was moderately low across all the 27 studies. The risk of attrition bias due to incomplete outcome data was absent across all the studies (Supplementary Table 1) [15-41].

2. Study locations and types

Regarding infertility and CVD, 5 studies examined this association [15-19]. Four [15-17,19] were conducted in the United States (US), and 1 [18] in Europe (Italy). All of these were single-center retrospective surveys (Table 1). Eleven studies [20-30] examined infertility and its association with oncological malignancies. Of these, 7 [21,24-29] of these were conducted in the US, while 4 [20,22,23,30] were from Europe (Denmark and Sweden). Eight of eleven [23-30] were single-center retrospective population-based reviews while the remaining 3 [20-22] were case–control cohort studies (Table 1). For chronic disease association with male factor infertility, a total of 8 studies [16,18,31-36] were included. Of these, 3 [16,33,36] were conducted in the US, 3 [18,32,34] in Italy, 1 [35] in Denmark, and 1 [31] in Qatar. Four [16,18,35,36] of 8 studies were single-center retrospective reviews while 3 [31-33] of them were single-center population-based cross-sectional studies and 1 [34] was a prospective case-control study (Table 1). Five [37-41] articles examined infertility and the risk of death. All 5 references were retrospective cohort studies. There was one [39] multicentered experience from the USA and the remaining four [37,38,40,41] from Europe (Denmark×2, Germany, Sweden) (Table 1). Of note, two studies (Eisenberg et al. [16] and Ferlin et al. [18]) analyzed multiple outcomes and therefore appear in multiple subsections.

3. Study sample sizes, participant ages, and follow-up

Given the lower LE, cross sectional and case-control studies included in the present review were separately considered with regard to available cumulative demographics characteristics. In total, nearly 600,000 men were included from 27 studies (Table 1) [15-41]. Within the 27 studies, there was a heterogenous population of men with regard to fertility—diagnosis of infertility, semen parameters qualifying them as infertile, presenting for fertility evaluation, or were childless.

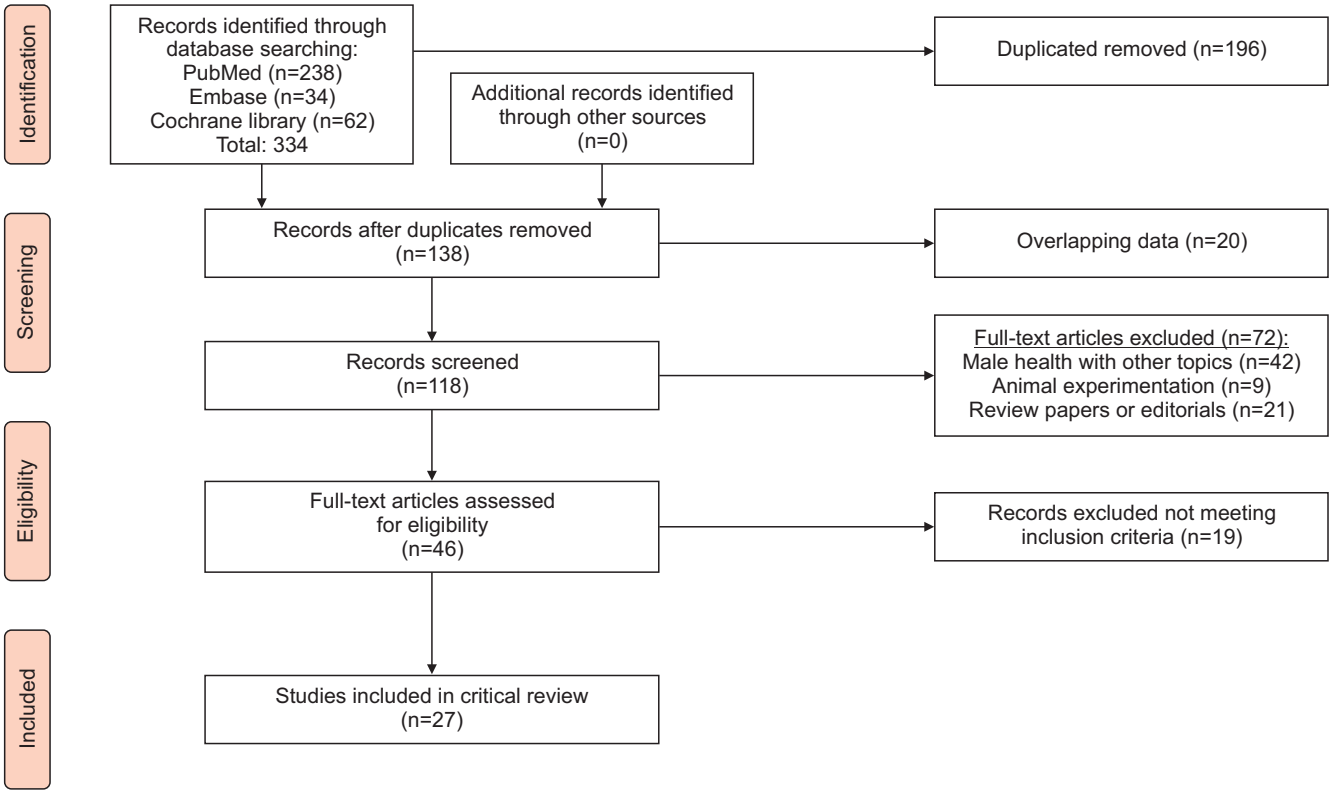

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Table 1. Characteristics of the studies included assessing associations

Author	Year	Country	Study design	Period	Sample size (n)	Mean/median age (y)	Subject description	Main findings	Level of evidence
Association between infertility and CVD									
Eisenberg et al. [15]	2011	USA	Retrospective cohort study	1996–2005	11,258 childless men 125,645 (1 to 5 children) father Total: 136,903	61.9 63 62.7	Association between offspring number and CVD death from the National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study	• Childless men and CVD death: HR, 1.17 (95% CI, 1.03–1.32) • Four children: HR, 1.06 (95% CI, 0.92–1.22) • Three children: HR, 1.02 (95% CI, 0.90–1.16) • Two children: HR, 1.02 (95% CI, 0.90–1.16) • One child: HR, 1.11 (95% CI, 0.95–1.30)	III-2
Eisenberg et al. [16]	2016	USA	Retrospective cohort study	2001–2009	13,027 with male factor infertility 23,860 receiving fertility testing 79,099 vasectomy Total: 115,986	33.08±6.02 32.79±5.86 34.97±5.89	Infertile/subfertile men from the Truven Health Market Scan® database	• Infertile men compared to fertility testing for ischemic heart disease: HR, 1.48 (95% CI, 1.19–1.84) • Infertile men compared to vasectomy group for ischemic heart disease: HR, 1.20 (95% CI, 1.09–1.32) • Infertile men compared to vasectomy for hypertension: HR, 1.09 (95% CI, 1.02–1.17)	III-2
Wang et al. [17]	2018	USA	Retrospective cohort study	2001–2009	4,459 with varicocele 21,840 infertility testing 78,226 vasectomy Total: 104,525	32.2±5.9 32.9±5.8 35.0±5.9	Association between varicoceles and CVD from the Truven Health Market Scan® database	• Men with varicocele compared to fertility testing for overall heart disease: HR, 1.22 (95% CI, 1.03–1.45) • Men with varicocele compared to vasectomy for overall heart disease: HR, 1.32 (95% CI, 1.13–1.54) - For ischemic heart disease: HR, 1.36 (95% CI, 1.02–1.82) - Other heart diseases: HR, 1.27 (95% CI, 1.07–1.51)	III-2
Ferlin et al. [18]	2019	Italy	Retrospective cohort study	2013–2016	5,177 infertile men	31.7±7.9	Prospectively collected database of 11,516 males of infertile couples who had semen analysis in tertiary university center form the north-east of Italy.	• Men with a low sperm count (<39 million/ejaculate) compared to normospermic males: - Hypogonadism: OR, 12.2; 95% CI, 10.2–14.6 - High BP: 132 vs.128 mmHg; p<0.001 - Metabolic syndrome: OR, 1.246; 95% CI, 1.005–1.545	III-2
Kasman et al. [19]	2019	USA	Retrospective cohort study	2003–2016	76,343 male factor infertility 60,072 fertility testing 183,742 vasectomy Total: 320,157	35.3±5.8 35.4±5.8 37.6±5.6	Men with male factor infertility and men undergone infertility testing form the Optum's de-identified Clinformatics Data Mart Database	• Men with male factor infertility compared to vasectomy for hypertension: HR, 1.15 (95% CI, 1.13–1.18) • Men with male factor infertility compared to vasectomy for heart disease: HR, 1.34 (95% CI, 1.25–1.45)	III-2

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Table 1. Continued

Author	Year	Country	Study design	Period	Sample size (n)	Mean/median age (y)	Subject description	Main findings	Level of evidence
Association between infertility and oncological malignancies									
Møller and Skakkebaek [20]	1999	Denmark	Case–control cohort study	1916–1970	514 testis Ca (n=282 infertile) 720 controls Total: 1,234	NR	Men with testis cancer from the Danish Cancer Registry; controls selected from the Danish population with the Danish Central Population Register	• Testis Ca among men with children: RR, 0.63 (95% CI, 0.47–0.85) • Testis Ca for men with lower offspring than expected on the basis of their age: RR, 1.98 (95% CI, 1.43–2.75)	III-3
Doria-Rose et al. [21]	2005	USA	Case–control cohort study	1977–1983	329 testis Ca (n=173 infertile) 672 controls Total: 1,001	49 (29–69) NR	Men with testis cancer from 13 counties of western Washington State within the Cancer Surveillance System, a part of the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) Program	• Testis Ca among men with children compared to infertile men: OR, 0.76 (95% CI, 0.54–1.06) • Testis Ca among infertile men compared to fertile controls: OR, 2.40 (95% CI, 1.00–5.77)	III-3
Ruhayel et al. [22]	2010	Sweden	Case–control cohort study	1996–2005	445 PCa (n=50 infertile) 446 controls Total: 891	74.3±5.7 74.3±5.7	Men with PCa within "the Malmo Diet and Cancer Study" cohort in Sweden	• PCa among infertile men compared to fertile controls: OR, 0.45 (95% CI, 0.25–0.83)	III-3
Jacobsen et al. [23]	2000	Denmark	Retrospective cohort study	1963–1995	32,442 subfertile men: 89 testis Ca 6 peritoneal Ca 386 other malignancies	NR	Men undergoing fertility testing at the Sperm Analysis Laboratory in Copenhagen screened for testis and other malignancies incidence	• Testis Ca among subfertile men: SIR, 1.6 (95% CI, 1.3–1.9) • Digestive organs Ca among subfertile men: SIR, 3.7 (95% CI, 1.3–8.0) • Any malignancies: SIR, 1.1 (95% CI, 1.0–1.2)	III-2
Raman et al. [24]	2005	USA	Retrospective cohort study	1990–2000	3,847 infertile men: 10 testis Ca	32.6	Infertile men and abnormal semen analysis from a single urologist from the New York metropolitan area. The National Cancer Institute (SEER) database as control population.	• Testis Ca among azoospermic (n=2) and severe oligospermic (n=8): SIR, 22.9 (95% CI, 22.4–23.5)	III-2

Table 1. Continued

Author	Year	Country	Study design	Period	Sample size (n)	Mean/median age (y)	Subject description	Main findings	Level of evidence
Walsh et al. [25]	2009	USA	Retrospective cohort study	1967–1998	22,562 infertile men: 34 testis Ca	38.1±7.4	Men with male infertility factor (clinical presentation with abnormal semen parameters according 1999-WHO criteria) from 15 California infertility centers linked to California Cancer Registry.	• Testis Ca (n=34) among men seeking infertility treatment: SIR, 1.3 (95% CI, 0.9–1.9) • Testis Ca (n=13) among known male factor infertility: SIR, 2.8 (95% CI, 1.3–6.0)	III-2
Walsh et al. [26]	2010	USA	Retrospective cohort study	1967–1998	22,562 infertile men: 168 PCa	36.7	Men with infertility factors (clinical presentation with abnormal semen parameters according 1999-WHO criteria) from 15 California infertility centers linked to California Cancer Registry.	• PCa among men evaluated for infertility: SIR, 0.9 (95% CI, 0.8–1.1) • csPCa among men with known infertility factor: - SIR, 2.0 (95% CI,1.2–3.0) - HR, 2.6 (95% CI, 1.4–4.8)	III-2
Eisenberg et al. [27]	2013	USA	Retrospective cohort study	1989–2009	451 azoospermic men 1,787 non-azoospermic Total: 2,238	35.5±8.3 35.8±6.9	Infertile men from andrology database at the Baylor College of Medicine Special Procedures Laboratory linked to Texas Cancer Registry (TCR)	• Any malignancies among all infertile subjects: SIR, 1.7 (95% CI, 1.2–2.5) • Any malignancies among azoospermic men: SIR, 2.9 (95% CI, 1.4–5.4) • Any malignancies among non-azoospermic men: SIR, 1.4 (95% CI, 0.9–2.2)	III-2
Eisenberg et al. [28]	2015	USA	Retrospective cohort study	2001–2009	76,083 infertile men 112,655 vasectomy 760,830 fertile control Total: 949,568	35.08±5.89	Infertile men matched for development of any cancer diagnosis among the Truven Health Market Scan® database	• Testis Ca among infertile men: SIR, 1.71 (95% CI, 1.28–1.75); HR (vs. control), 1.99 (1.47–2.70); HR (vs. vasectomy),1.50 (1.01–2.229) • Testis Ca among men with male factor infertility: SIR, 1.79 (95% CI, 1.24–2.50) • PCa among infertile men: SIR, 2.83 (95% CI, 2.26–3.49); HR (vs. control), 1.78 (1.41–2.25); HR (vs. vasectomy), 1.22 (0.93–1.59) • PCa among men with male factor infertility: SIR, 3.5 (95% CI, 2.72–4.44) • NHL among infertile men: SIR, 3.18 (95% CI, 2.53–2.93); HR (vs. control), 1.76 (1.39–2.23); HR (vs. vasectomy), 1.71 (1.25–2.32) • NHL among men with male factor infertility: SIR, 3.42 (95% CI, 2.58–4.42) • Any malignancies among infertile men: SIR, 1.8 (95% CI, 1.66–1.95); HR (vs. control), 1.49 (1.37–1.63); HR (vs. vasectomy) 1.19 (1.07–1.32) • Any malignancies among men with male factor infertility: SIR, 1.99 (95% CI, 1.80–2.19)	III-2

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Table 1. Continued

Author	Year	Country	Study design	Period	Sample size (n)	Mean/median age (y)	Subject description	Main findings	Level of evidence
Hanson et al. [29]	2016	USA	Retrospective cohort study	1996–2011	20,433 subfertile men 20,433 fertile men Total: 40,866	32±6.4	Subfertile men from the Subfertility Health and Assisted Reproduction (SHARE) study combining the University of Utah and Intermountain Health Care's database with Utah Population Database (UPDB) and the Utah Cancer Registry	• Testis Ca among infertile men compared to controls: HR (azoospermic), 3.67 (0.45–30.25); HR (oligospermic), 1.89 (4.91–2.82) • PCa among infertile men compared to controls: no significant association • Any malignancies among infertile men compared to controls: HR (azoospermic), 1.00 (0.49–2.06); HR (oligospermic), 1.66 (1.13–2.41)	III-2
Al-Jebari et al. [30]	2019	Sweden	Retrospective cohort study	1994–2014	1,145,990 fertile men 20,618 infertile (IVF) 14,882 (ICSI) Total: 1,181,490	32.5±6.2 36.6±5.3 36.9±6.0	Men from the Swedish Medical Birth Register, Swedish National Quality Register for Assisted Reproduction and Swedish Cancer Registry, the Swedish Register of Education, and the Swedish Cause of Death Register	• PCa among men using ART compared to fertile controls: - ICSI: HR, 1.64; 95% CI, 1.25–2.15 - IVF: HR, 1.33; 95% CI, 1.06–1.66	III-2
Association between infertility and chronic medical conditions									
Bener et al. [31]	2009	Qatar	Population-based cross-sectional	2008	225 diabetic men 632 non-diabetic	45.4±8.8 42.3±8.6	Qatari infertile men from Primary health care centers and out-patient clinics of the Hamad General Hospital	Primary infertile men (16%) and secondary infertile men (19.1%) significantly higher in DM prevalence (p=0.003) compared to non-diabetic men	
Ventimiglia et al. [32]	2015	Italy	Population-based cross-sectional	2005–2014	2,100 infertile men	42 (18–56)	Men assessed at a single academic center in Italy for couple's infertility (non-interracial infertile couples only)	Increased number of oligozoospermic and azoospermic men among patients with CCI>1 (p<0.05)	
Eisenberg et al. [33]	2015	USA	Population-based cross-sectional	1994–2011	9,387 infertile men	37.8±6.33	Men who underwent semen analysis from the Stanford Reproductive Endocrinology and Infertility semen database	Men with a higher CCI had lower semen volume, concentration, motility, total sperm count, and morphology scores.	

Table 1. Continued

Author	Year	Country	Study design	Period	Sample size (n)	Mean/median age (y)	Subject description	Main findings	Level of evidence
Salonia et al. [34]	2009	Italy	Prospective Case-Control study	2006–2007	344 infertile men 293 fertile controls	36.9±6.4 37±5.2	Men with male factor infertility from outpatient male reproductive clinic at a tertiary academic center in northern Italy.	• Comorbidity among infertile men compared with fertile controls: CCI: 0.33±0.8 vs 0.14±0.5, p<0.001 (95% CI, 0.08–0.29)	III-3
Eisenberg et al. [16]	2016	USA	Retrospective cohort study	2001–2009	13,027 with male factor infertility 23,860 receiving fertility testing 79,099 vasectomy Total: 115,986	33.08±6.02 32.79±5.86 34.97±5.89	Infertile/subfertile men from Truven Health Market Scan®4 database	• Hypertension among infertile men compared to fertility testing for: - HR, 1.09 (95% CI, 1.02–1.17) • Infertile men with male factor infertility compared to vasectomy for: - (diabetes) HR, 1.30 (95% CI, 1.10–1.53) - (alcohol abuse) HR, 1.48 (95% CI, 1.07–2.05) - (drug abuse) HR, 1.67 (95% CI, 1.06–2.63)	III-2
Glazer et al. [35]	2017	Denmark	Retrospective cohort study	1994–2015	24,011 with male factor infertility 27,052 fertile controls Total: 51,063	33.9 (26.2–46) 33.8 (26.2–45.3)	Men diagnosed with male factor infertility from Danish National *in vitro* fertilization (IVF) registry linked to The Danish Multiple Sclerosis Registry	• MS among men with male factor infertility compared to reference group: - OR, 1.61 (95% CI, 1.04–2.51) - HR, 1.28 (95% CI, 0.76–2.17)	III-2
Brubaker et al. [36]	2018	USA	Retrospective cohort study	2001–2008	33,077 infertile men 77,693 vasectomy 330,770 fertile controls Total: 441,540	33±5.92 34.97±5.89 32.98±5.73	Infertile men from Truven Health Market Scan® claims database	• Infertile men compared to age-matched controls for: - Rheumatoid arthritis: HR, 1.29 (95% CI, 1.02–1.62) - Systemic lupus erythematosus: HR, 2.12 (95% CI, 1.52–2.96) - Psoriasis: HR, 1.20 (95% CI, 1.04–1.37) - Thyroiditis: HR, 1.60 (95% CI, 1.02–2.52) • Infertile men compared to vasectomy controls for: - MS: HR, 1.91; 95% CI, 1.10–3.31 - Grave's disease: HR, 1.4 (95% CI, 1.10–1.92)	III-2
Ferlin et al. [18]	2019	Italy	Retrospective cohort study	2013–2016	5,177 infertile men	31.7±7.9	Prospectively collected database of 11,516 males of infertile couples who had semen analysis in tertiary university center form the north-east of Italy.	• Infertile men with a low sperm count (<39 million/ejaculate) compared to normospermic males for: - Hypogonadism: OR, 12.2 (95% CI, 10.2–14.6) - Metabolic syndrome: OR, 1.246 (95% CI, 1.005–1.545)	III-2

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Table 1. Continued

Author	Year	Country	Study design	Period	Sample size (n)	Mean/median age (y)	Subject description	Main findings	Level of evidence
Association between infertility and overall mortality									
Groos et al. [37]	2006	Germany	Retrospective cohort study	1949–1985	391 normozoospermic 117 oligozoospermic 84 azoospermic Total: 592	NR	Infertile men from andrological service at the Marburg University Hospital between and vital data gathered from public registration offices and a statutory health insurance	• Mortality among oligozoospermic males born within 1892–1931 (n=220) compared to fertile controls: OR, 2.19 (95% CI, 1.307–3.666)	III-2
Jensen et al. [38]	2009	Denmark	Retrospective cohort study	1963–2001	43,277 infertile men 4,425 azoospermic	NR	Men referred to the clinic by general practitioners and urologists within the Copenhagen Sperm Analysis Laboratory from patients living in the Copenhagen area.	• Mortality among men with sperm concentration 40–79.99 10×6/mL: SIR, 0.64 (95% CI, 0.54–0.76) • Mortality among men with sperm concentration 10–19.99 10×6/mL: SIR, 0.79 (95% CI, 0.63–0.99)	III-2
Eisenberg et al. [39]	2014	USA	Retrospective cohort study	1994–2011 (California) 1989–2009 (Texas)	9,006 2,929 Total: 11,935	37.05±5.1 35.03±5.8	Men evaluated for infertility from California, Stanford Reproductive Endocrinology and Infertility semen database and Texas, in the andrology database at the Baylor College of Medicine Special Procedures Laboratory	• Mortality among men evaluated for infertility (California): SIR, 0.37 (95% CI, 0.27–0.49) • Mortality among men evaluated for infertility (Texas): SIR, 0.45 (95% CI, 0.28–0.68) • Mortality among men evaluated for infertility (combined): SIR, 0.39 (95% CI, 0.30–0.49) • Mortality among men with sperm concentration 15 vs. ≥15×10^6/mL (California): HR, 1.89 (95% CI, 0.91–3.94) • Mortality among men with sperm concentration 15 vs. ≥15×10^6/mL (Texas): HR, 8.06 (95% CI, 1.88–34.58) • Mortality among men with sperm concentration 15 vs. ≥15×10^6/mL (combined): HR, 2.20 (95% CI, 1.34–3.62)	III-2
Lundberg et al. [40]	2019	Sweden	Retrospective cohort study	1944–1992	43,598 infertile men 57,733 male factor infertility 2,762,254 fertile controls	NR	Infertile men of patients with related diagnosis of infertility from the Swedish Patient Register linked with the Swedish Total Population Register serving for controls group of fertile subjects	• Mortality among men with diagnosis of infertility compared to control group: HR, 0.98 (95% CI, 0.89–1.08) • Mortality among men with infertility-related diagnosis compared to control group: HR, 1.23 (1.17–1.30)	III-2

Table 1. Continued

Author	Year	Country	Study design	Period	Sample size (n)	Mean/median age (y)	Subject description	Main findings	Level of evidence
Glazer et al. [41]	2019	Denmark	Retrospective cohort study	1994–2015	64,377 infertile ART 320,042 fertile controls: 24,062 male factors 1,906 azoospermic Total: 410,387	33.8 33.3 33.9 34.4	Infertile men who had undergone ART from the Danish IVF register including data on whether infertility was due to male factor linked to the Danish causes of death register and sociodemographic registers.	• Mortality among men undergone ART compared to non-ART controls: HR, 1.12 (95% CI, 1.03–1.21) • Mortality among men with male factor infertility cohort compared to non-ART controls: HR, 1.35 (95% CI, 1.19–1.54) • Mortality among azoospermic men compared to non-ART controls: HR, 3.66 (95% CI, 2.18–6.16) • Mortality among oligospermic men compared to non-ART controls: HR, 1.26 (95% CI, 0.95–1.66)	III-2

CVD, cardiovascular disease; HR, hazard ratio; CI, confidence interval; OR, odds ratio; BP, blood pressure; NR, not reported; RR, relative risk; PCa, prostate cancer; SIR, standardised incidence ratio; WHO, World Health Organization; NHL, non-hodgkins lymphoma; IVF, *in vitro* fertilization; ICSI, intra-cytoplasmic sperm injection; DM, diabetes mellitus; CCI, Charlson comorbidity index; MS, multiple sclerosis.

The sample sizes of each study varied from 857 to 9,387 men among case-control and cross-sectional analyses while the sample sizes for the retrospective cohort population studies ranged from 592 to 2,863,585 men. The mean age of infertile population across the studies varied from 37.8 to 74.3 years for cross sectional and case-control surveys versus 31.7 to 61.9 years for retrospective analyses.

4. Male factor infertility and cardiovascular disorders

Serum testosterone levels decline gradually with age in most men and several epidemiological/observational studies have demonstrated that low testosterone and male factor infertility are associated with an increased in CVD risk [4,42]. Moreover, previous meta-analysis studies have shown that even subclinical hypogonadism may affect the incidence of CVD and overall mortality related to CV events [43-45]. Therefore, authors have postulated that male infertility may be a marker for future cardiovascular risk (via hormonal pathways) or possibly exist as an independent risk factor.

A large retrospective study based on the National Institutes of Health–American Association of Retired Persons (NIH-AARP) Diet and Health registry on 136,903 men highlighted how compared with fathers, childless men had a 17% (hazard ratio [HR], 1.17; 95% confidence interval [CI], 1.03–1.32) increased risk of death from CVD, and this elevated risk appeared to also extend to men with only one child [15]. However, the study lacked semen data and pregnancy intention of the fathers and therefore we cannot say that this association was due to fertility status or other confounding factors.

However, a large retrospective series of more than 13,000 men using the IBM MarketScan database demonstrated that male infertility was an independent predictor of increased risk of chronic medical conditions and, in particular, CVD [16]. Compared to the control group, infertile men had an increased incidence of hypertension, peripheral vascular disease and heart disease (HR, 1.09; 95% CI, 1.02–1.17; HR, 1.52; 95% CI, 1.12–2.07 and HR, 1.20; 95% CI, 1.09–1.32, respectively). Furthermore, using the IBM MarketScan database, Wang et al. [17] demonstrated an association between the presence of varicocele and vascular disorders in a large retrospective cohort of 4,459 men. This is notable as varicocele represents a risk factor for infertility and occurs in about 15% of healthy men and is associated with primary infertility in up to 35% of men presenting for fertility evaluation. In this study, the authors found a higher incidence of heart disease in men with varicoceles compared to men who underwent infertility testing alone (HR, 1.22; 95% CI, 1.03–1.45), and men who underwent vasectomy who served as a fertile control group

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(HR, 1.32; 95% CI, 1.13–1.54). Interestingly, a sub-analysis of these patients stratified for symptomatic vs. asymptomatic varicoceles showed that only symptomatic varicoceles were associated with later health.

Two other studies demonstrated an association between infertility and CVD. In a study of 5,177 subjects, Ferlin et al. [18] showed that men with low sperm count (<39 million/ejaculate) were at a significantly higher risk of hypogonadism (odds ratio [OR], 12.2; 95% CI, 10.2–14.6) and were overall at higher risk for chronic metabolic and cardiovascular disorders. Moreover, the authors concluded that low sperm count, independent of low serum T, was associated with poorer metabolic, cardiovascular, and bone health status. However, the clinical significance of the differences was uncertain. For example, the differences in systolic blood pressure (128 vs. 132 mmHg), homeostatic model assessment (HOMA) index (1.8 vs. 1.9), and hemoglobin A1c (4.6% vs. 4.4%) between men with low and normal total sperm count were only modestly different. Finally, Kasman et al. [19] examined 136,416 males with infertility from the Optum Clinformatics Data Mart Database and found that male factor infertility was associated with the risk for cardiometabolic disease when compared to controls (vasectomized men) regardless of socioeconomic status, race, or geographic region. Men with male factor infertility had a higher risk of developing hypertension (HR, 1.15; 95% CI, 1.13–1.18), and heart disease (HR, 1.34; 95% CI, 1.25–1.45) compared to fertile controls.

5. Male infertility and cancer risk

While the treatment for many cancers are known to have a negative impact on male fertility, male infertility may also be associated with the future risk of cancer [46,47]. The underlying mechanism behind this potential link is unknown however genetic alterations may play a role. For example, one potential cause for male infertility is represented by disruptions in *MLH1* genes, and mutations in these genes can also lead to Lynch syndrome. Using *ERCC1* (excision repair cross-complementing gene 1) or *MSH2* (MutS homolog 2) knockouts, animal models have demonstrated that changes in these genes can lead to azoospermia in mice as well as increased early incidence of all malignant carcinomas [48-50]. However, the underlying etiology behind future cancer risk in infertile men remains unclear.

Among the 11 articles identified evaluating cancer risk in infertile men, the primary intent of the investigators was generally focused on establishing incidence of GU cancers (testicular, prostate cancer [PCa]) among infertile/subfertile subjects. One study which examined the impact of infertility and the overall risk of all cancers was the study of Eisenberg et al. (2013) [27]. In the retrospective cohort study from the Texas Cancer Registry, infertile men were found to be at higher risk of overall cancer (standardized incidence ratio [SIR], 1.7; 95% CI, 1.2–2.5). Of relevance, azoospermic men had the highest risk of cancer (SIR, 2.9; 95% CI, 1.4–5.4). A similar trend for overall cancer risk was confirmed in a 2015 analysis within the IBM MarketScan database which showed an overall HR of 1.49 (95% CI, 1.37–1.63) compared to national U.S. estimate cancer incidence [28]. Moreover, this study confirmed previously observed relationships (i.e., male infertility with testis and PCa: HR, 1.99; 95% CI, 1.47–2.70 and 1.78; 95% CI, 1.41–2.25, respectively) and identified a higher risk of non-Hodgkin lymphoma (HR, 1.76; 95% CI, 1.39–2.23). While these data suggest that infertile men are at an increased risk of all cancers in the years after infertility evaluation, granular details about the men and their evaluation was not available to help elucidate the etiology of the association.

The association between semen quality and cancer remains uncertain due to heterogeneity in the literature. Hanson et al. [29] found that only oligozoospermia was associated with increased risk of all types of cancers, by an HR_{Count} 1.8 (95% CI, 1.2–2.6), while those men with azoospermia did not have a significantly higher risk of cancer development (HR, 1.0; 95% CI, 0.5–2.1). Finally, Jacobsen et al. [23] found that men with abnormal semen characteristics had a small increase (SIR, 1.1; 95% CI, 1.0–1.2) in the incidence of any type of cancer (36 cases per 32,442 men) using linkage with the Danish Cancer Registry.

While some studies examined overall cancer risk, there has been relatively more focus on the future development of genitourinary malignancies in men diagnosed with infertility. Testicular cancer in relation to infertility has been well studied (n=7 studies [20,21,23-25,28,29]) while PCa has had less focus (n=5 studies [22,26,28-30]). Overall, the literature demonstrated a significant increase in the risk of developing testis cancers if a man was diagnosed with infertility or has low semen parameters. The analysis of Raman et al. [24] revealed a 22-fold increased risk (SIR, 22.9; 95% CI, 22.4–23.5) after examining 3,847 men evaluated from a single urologist in the New York metropolitan area during a 10-year period (1990 to 2000), and using the National Cancer Institute (NCI)-Surveillance, Epidemiology, and End Results Program to identify a control population. Of note, Raman's cohort were a highly selected group of subjects with significant alterations (i.e., low sperm concentrations [$<20\times10^6$/mL] and concomitant defects in motility [<50%] or morphology [<50%]) in semen parameters, leading to a diagnosis of infertility with the timing of cancer diagnosis uncertain. In contrast, other studies of male infertility have showed that infertile men may

have a 2- to 3-fold higher risk of testis cancer. For example, Walsh et al. [25] examined 4,459 men diagnosed with male factor infertility (i.e., clinical presentation with abnormal semen parameter–1999 WHO criteria) compared to 14,557 men with normal semen quality and reported a threefold higher risk of testis cancer (SIR, 2.8; 95% CI, 1.3–6.0). Hanson et al. [29] also examined the association between male infertility and testis cancer. In this study, the authors demonstrated that infertile men had a higher incidence of testis cancer when compared to fertile controls. Of note, after stratifying within the infertile group, the investigators found that oligospermic subjects were at higher risk as compared with men with normal semen quality ($HR_{Count,}$ 10.3; 95% CI, 4.1–26.2 vs. HR, 2.9; 95% CI, 1.2–6.7).

With regard of infertility and risk of PCa, our review revealed several publications with conflicting results. In the Swedish study, Al-Jebari et al. [30] examined the risk of developing PCa among infertile men, retrieved from the Swedish Medical Birth Register and the Swedish Multi-generation Register who had achieved fatherhood through assisted reproductive technologies (ART). When the authors examined 35,500 men having undergone *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI), compared to those who fathered children via natural conception, men having undergone ART had a significantly increased risk of development of PCa (HR, 1.64; 95% CI, 1.25–2.15, for ICSI and HR, 1.33; 1.06–1.66, for IVF; respectively). Similar to the Swedish study, Eisenberg et al. [28] found an increased risk of PCa development (HR, 1.78; 95% CI, 1.41–2.25) in men diagnosed with infertility when they examined the IBM MarketScan database from 2001 to 2009 which contains 76,083 number of men with infertility. However, the significance varied based on the control group examined. While the risk of PCa was higher with infertile men compared to an age-matched control, the risk was not significantly different compared to vasectomy men (i.e., arbitrarily considered fertile by definition). In contrast to other studies, Ruhayel et al. [22] utilized a nested case control design within the Malmo Diet and Health Study and observed that infertility status was associated with a lower risk of PCa (OR, 0.45; 95% CI, 0.25–0.83). However, the study design may bias case ascertainment to men with less severe forms of PCa. Next, Hanson et al. [29] found no association with risk of development of PCa using a US cohort. With all studies, it should note that the majority of the men evaluated had not reached the average age of PCa diagnosis (66 years old in the US according to NCI), which may affect the correlation. Walsh et al. [26] revealed that men with male factor infertility had an increased risk of subsequent development of high grade PCa (SIR, 2.0; 95% CI, 1.2–3.0; HR, 2.6; 95% CI; 1.4–4.8) but not overall PCa (SIR, 0.9; 95% CI, 0.8–1.1), thus suggesting that biology rather than screening bias may explain the etiology. Overall, these findings suggest that infertility status per se may be a risk factor for the development of PCa; however due to the heterogeneity in the literature, further studies are necessary.

6. Male infertility and chronic medical conditions

Factors such as smoking, increased body mass index (BMI), alcohol and/or drugs abuse, psychological stress have been associated with increased incidence of chronic diseases such as metabolic syndrome, erectile dysfunction, obesity, hematologic disorders, chronic kidney failure, liver disfunctions and in general with impaired HOMA indices [51-53]. Moreover, these identical factors have been implicated in the development of male infertility and decreased semen parameters [54-56]. However, as up to 10% of the genome is involved in male reproduction and there are only 25,000 genes, it is reasonable to postulate that genes involved in reproduction may also be expressed in other cell types [46]. Thus, defects in male reproduction may also signal an increased risk of the development of chronic disease (i.e., act as a biomarker).

Two large retrospective cohort studies focused on the relationship between male infertility and the risk of incident endocrine-metabolic syndromes, such as diabetes and metabolic syndrome. Wang et al. [17] utilized the IBM MarketScan database to examine more than 13,000 infertile men and found a significant association between the presence of a male factor infertility and the development of diabetes mellitus type 2, alcohol abuse, and drug abuse (HR, 1.30; 95% CI, 1.10–1.53; HR, 1.48; 95% CI, 1.07–2.05; HR, 1.67; 95% CI, 1.06–2.63; respectively) compared to men who had only undergone fertility testing. A second analysis focused on the prevalence of infertility diagnosis from Italy was performed by Ferlin et al. [18]. The authors examined semen quality and reproductive function as a marker of general male health in infertile subjects who had semen analysis in tertiary university center in Italy from a prospectively collected database of 11,516 males. The authors found that men with lower sperm counts were at a higher risk of hypogonadism (OR, 12.2; 95% CI, 10.2–14.6) and a variety constellation of conditions commonly associated with impaired general health, such as higher BMI, waist circumference, systolic pressure, low-density lipoprotein cholesterol, triglycerides, HOMA index and finally lower high-density lipoprotein cholesterol thus leading to a higher prevalence of metabolic syndrome (OR, 1.246; 95% CI, 1.005–1.545) which was independent of their hypogonadism status. Overall, these two studies suggest that male factor infertility may be an independent predictor of future health.

We identified one prospective case-control study and

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two cross-sectional studies that examined the association between comorbidities, identified via the Charlson comorbidity index (CCI), and semen/hormonal parameters. Salonia et al. [34] evaluated 344 consecutive European Caucasian men with male factor infertility and demonstrated a higher prevalence of comorbidities as compared with fertile controls (CCI: 0.33 [0.8] vs. 0.14 [0.5], p<0.001; 95% CI: 0.08–0.29). While 88.4% of the fertile controls had a CCI=0, only 77.3% of the infertile men did (p<0.001). Moreover, at multivariable linear regression model, age, BMI and fertility status were all three found to independently predict CCI scores (β: 0.196, 0.161 and -0.199 respectively; p<0.001). This suggests that infertile patients have more comorbidities (e.g., cardiovascular disorders, pulmonary diseases, connective tissue disorders, liver diseases, DM and different malignant neoplasms) than fertile men. Similarly, the studies of Ventimiglia et al. [32] and Eisenberg et al. [33] confirmed an association among male factor infertility and increased prevalence chronic medical disorders. Different from the article from Salonia et al. [34], where the classic clinical WHO definition of infertility (i.e., >12-month failure with unprotected intercourses) was assumed, in these two studies patients were enrolled according to semen quality alterations. When viewed together, these studies concluded that male infertility or impaired semen parameters is associated with prevalent poor health.

As female factor infertility (e.g., endometriosis) has been associated with incident autoimmune disorders, investigators have also examined autoimmune dysfunction in male infertility patients [56]. While the etiology remains unknown, scientists have argued there may be an immune mediated mechanism to some forms of infertility [57,58]. A Danish group reviewed data from 24,011 infertile men from the Danish National IVF Registry and showed an increased prevalence (OR, 1.61; 95% CI, 1.04–2.51) and incidence (HR, 1.28; 95% CI, 0.76–2.17) of MS within men with known male factor infertility [35]. Brubaker et al. [36] examined IBM Market Scan claims database from 2001 to 2008 with 33,077 infertile men and found an association between autoimmune disorders, such as systemic lupus erythematosus, psoriasis, thyroiditis, MS and Grave's disease, and prior diagnosis of male infertility.

7. Male factory infertility and mortality

Finally, five studies [37-41] have suggested that male infertility is associated with mortality. Initially, a German cohort of 601 men over the span of 35 years who provided a semen sample as part of an andrological evaluation were found to have a higher rate of mortality if they were born between 1892 and 1931 [37]. For men born in other years, no association was identified. While the authors failed to establish a clear relationship between semen quality and mortality, the cohort included men raised in post World War II Germany. Thus, the results may not be generalizable.

More recently, other studies have explored contemporary cohorts to examine the association between male infertility and mortality. Jensen et al. [38] evaluated large cohort of Danish men who had semen analyses performed as part of an infertility evaluation and observed that mortality decreased as sperm concentration increased up to a threshold of 40 million/mL. Subsequently, a study from the US [39] observed that men with two or more semen abnormalities had more than two-fold increased risk (HR, 2.57; 95% CI, 1.26–5.23) of death. A Swedish study from Lundberg et al. [40] examined more than 40,000 men with infertility or infertility-related diagnosis and found no significant association among fertility status and overall death risk (HR, 0.98; 95% CI, 0.89–1.08). While overall there was no association between infertility and death, after stratifying for confounders, the authors noted a 4.58-fold higher risk of death in men with a diagnosis of infertility before the age of 30 years, largely explained by cancer diagnosed before infertility. Here the authors suggested that prevalent disease likely led to the association of male infertility and mortality. Finally, a cohort study from the Danish IVF register reported the results from 64,563 men who had undergone medically assisted reproduction (MAR) between 1994 and 2015 [41]. When looking at the mortality ratios between men who conceived with MAR (all men regardless infertility) vs. those age-matched controls who naturally achieved pregnancy, no significant increased risk was detected (HR, 1.07; 95% CI, 0.98–1.15). Of note, when stratifying by type of male factor infertility, azoospermic males had the highest risk of death (HR, 3.32; 95% CI, 2.02–5.40) while the same association was not proved for oligospermic patients (HR, 1.14; 95% CI, 0.87–1.50) or for those categorized as with "other male factor infertility" (HR, 1.10; 95% CI, 0.75–1.61). As with all registry data, there is limited granular information about the infertile men thus other ailments or non-measured confounders may influence the results. However, the association with infertility and the dose response (as it relates to severity of male infertility diagnosis or level of semen impairment) does suggest a biological explanation.

DISCUSSION

Our review of the existing literature suggests and association between male factor infertility and somatic health. The literature is consistent in findings that demonstrate

higher risk of CVD. Similarly, infertile males appear to be at higher risk of chronic disease regardless of sociodemographic factors. However, the association with cancers varies based on the specific cancer examined and conflicting results exist. Nevertheless, the etiology and clinical implications of the association require further elucidation especially to be able in future to balance the relative influence of the different infertility-related diagnosis (such as idiopathic, immunologic, varicocele, obstructive, cryptorchidism etc.) on the specific comorbidity development.

Overall, the literature suggests that semen parameters and overall testicular function may represent markers of general health [59,60]. As infertile men are evaluated early in life, there is an opportunity for health assessment, counseling, and disease prevention. This latest issue is of critical importance as typically infertile men represent a population of young subjects in which an early finding of hypogonadism, metabolic derangements, and overall risk of mortality may allow for more adequate prevention, management, follow-up, treatment, and lifestyle modifications.

The overall quality of the studies included in the present analysis was good, including six cross-sectional/case-control studies and twenty-one retrospective cohort-based analyses. The LE achieved varied from IV to III-2, which is considered overall good among epidemiological etiology-based studies but in general low. Although this systematic review has several strengths including the rigorous/standardized literature search and the quality assessment performed by three expert researchers in this field, several limitations of our analysis have to be acknowledged. First, the surveys within this research field are mainly directed by two infertility research poles in the US (n=14 studies) and in Europe (n=12 studies) and may not be generalizable to other parts of the world. Therefore, we have to consider that the majority of the outcomes synthetized might be influenced by only selected investigators thus impacting on the overall risk of bias of the studies included. Second, the high level of heterogeneity among the different study designs, the presence of multiple variables which influence fertility outcomes as well as the differences of inclusion criteria for male infertility among the articles makes comparisons between studies challenging.

CONCLUSIONS

Current literature suggests an association between male infertility and risk of chronic disease, comorbidity, CVD, and cancer development. However, the literature remains small, with heterogenous study populations, many of which are retrospective in nature. There is a lack of prospective trials and the studies with the highest LE (i.e., III-2) have an insufficient adjustment of confounders that may preclude them from stating a definitive conclusion about male infertility as precursor of these outcomes. The exact biological mechanisms leading to such conclusions remains uncertain, but likely involves some combination of developmental, hormonal, lifestyle and genetic factors. Future studies will likely provide insight into this important topic.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

AUTHORS' CONTRIBUTIONS

Research conception and design: Francesco Del Giudice and Michael L. Eisenberg. Data acquisition: Francesco Del Giudice, Federico Belladelli, Matteo Ferro, and Alessandro Sciarra. Statistical analysis: not applicable. Data analysis and interpretation: Francesco Del Giudice, Ettore De Berardinis, and Michael L. Eisenberg. Drafting of the manuscript: Francesco Del Giudice, Alex M. Kasman, and Michael L. Eisenberg. Critical revision of the manuscript: Andrea Salonia and Michael L. Eisenberg. Obtaining funding: not applicable. Administrative, technical, or material support: not applicable. Supervision: Michael L. Eisenberg, and Andrea Salonia. Approval of the final manuscript: all authors.

SUPPLEMENTARY MATERIAL

Scan this QR code to see the supplementary material, or visit https://www.icurology.org/src/sm/icurology-61-355-s001.pdf.

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