Review Article

Systematic Literature Review of the Epidemiology of Nongenetic Forms of Hypogonadism in Adult Males

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This study summarizes the literature on the prevalence, incidence, and proportion of patients receiving treatment for male hypogonadism and a systematic literature search was performed for articles published in the last 20 years. Of the 97 studies identified, 96 examined the prevalence, 2 examined the incidence, and 4 examined the proportion of males with hypogonadism patients receiving treatment. Based on studies conducted in Europe and USA, the prevalence of hypogonadism in the general population ranged from 2.1% to 12.8% of middle-aged to older men, with an estimated incidence of 12 new cases per 1,000 person-years. Prevalence was higher among patients with comorbid conditions, such as type 2 diabetes mellitus and obesity. Approximately 10–12% of men with hypogonadism were receiving testosterone treatment. This literature review suggests that there is potentially a significant burden of hypogonadism in the general population. Burden seems to increase with age and in the presence of certain disease conditions. Data suggests that many hypogonadal men who may benefit from testosterone replacement are not receiving treatment. This may be the result of underdiagnosis of the disease, lack of awareness by patients or physicians, irregularities surrounding the diagnostic criteria, and deficiency of long-term safety studies.

1. Introduction

Hypogonadism in men has been defined as a clinical syndrome resulting from failure of the testis to produce physiological levels of testosterone (androgen deficiency) and a normal number of spermatozoa, due to disruption of one or more levels of the hypothalamic-pituitary-testicular axis [1]. A diagnosis of hypogonadism is typically based on the signs and symptoms associated with low T, followed by biochemical confirmation of low testosterone (T) [1]. The most

widely accepted parameter used to establish hypogonadism is the measurement of serum total testosterone (TT) [1]; however, cut-off values used to indicate hypogonadism have not been clearly defined and vary across studies. Recent clinical practice guidelines published by the Endocrine Society have reported that the average TT threshold, at which the likelihood of most symptoms associated with hypogonadism increases, corresponds to the lower limit of the normal range for young men, that is, approximately 300 ng/dL (10.4 nmol/liter) [1]. Correspondingly, a common threshold

TABLE 1: Search strategy executed in PubMed/MEDLINE, EMBASE, and The Cochrane Central Register of Controlled Trials August 31, 2012, and incidence, prevalence, and treatment rates.

Search	Search string [field]	Hits
1	Search “hypogonadism/epidemiology” [mesh]	345
2	Search hypogonadism [title] OR testosterone deficiency* [title] OR “testosterone/deficiency” [mesh] OR testoid deficiency* [title] OR androgen deficiency* [title] OR testosterone replacement therapy* [title]	3173
3	Search epidemiology* [title/abstract] OR incidence [title/abstract] OR prevalence [title/abstract] OR rate [title/abstract] OR rates [title/abstract] OR treatment rate [title/abstract] OR treatment rates [title/abstract]	2380843
4	Search (“epidemiology” [mesh]) OR “incidence” [mesh] OR “prevalence” [mesh])	318545
5	Search #3 OR #4	2472821
6	Search #2 AND #5	331
7	Search #1 OR #6	603
8	Search #7 filters: publication date from 1992/01/01 to 2012/8/31; humans; English; male; adult: 19+ years	298
	Non-English articles	21

used in the literature to indicate hypogonadism is serum TT <300 ng/dL (<10.4 nmol/L); however, cut-off values of <200 ng/dL (6.94 nmol/L) to <350 ng/dL (<12 nmol/L) are not uncommon. These thresholds are sometimes combined with requisite signs and symptoms, but not always. The result is a range of operational definitions of hypogonadism used in the literature, varying in degree of stringency and potentially leading to variations in estimates of prevalence of the disease.

The literature on the epidemiology of hypogonadism is confounded by considerable heterogeneity across studies, varying not only by operational definition but also by patient populations, study design, time frame of study, and geography. Estimates of prevalence, incidence, and treatment rates are influenced by all of these factors. The aim of this systematic review of the epidemiology of hypogonadism was to determine the prevalence and incidence of hypogonadism, as well as the proportion of males with hypogonadism receiving treatment of hypogonadism, while accounting for differences in patient and study characteristics and operational definition of hypogonadism used.

2. Methods

2.1. Eligibility Criteria. Eligible studies were defined in this systematic review as original studies that assessed the prevalence, incidence, or treatment rates of adult males (≥ 18 years of age) with hypogonadism, acquired or idiopathic. Studies on genetic forms of hypogonadism (i.e., Klinefelter’s syndrome) and secondary publications of the same results were not included. Observational studies with sample sizes >30 were included in this review; treatment and intervention studies were excluded.

2.2. Search Methods for Identification of Studies. Three pharmacologic and biomedical literature databases were searched for this systematic literature review: PubMed/MEDLINE database, Cochrane Library Database, and EMBASE. Search strings composed of medical subject heading (MeSH) terms, from the controlled vocabulary indexing hierarchy and/or in-text terms in title and/or abstract fields, were used (Table 1).

Citations were limited to English language articles, published during a 20-year period (January 01, 1992, to August 31, 2012). The reference list of included publications was searched for relevant articles.

2.3. Data Extraction. We abstracted key data elements using a standardized abstraction tool, including type of research design, country, study period, sample size, operational definition of hypogonadism used, study population characteristics, and outcomes. One author screened the search results against the predefined inclusion and exclusion criteria. Titles were evaluated, abstracts were reviewed, and potentially relevant full-text articles were evaluated for relevance. A quality check was conducted on 20% of the abstracts by a second reviewer.

We categorized studies based on population of interest: population-based studies were those with large sample sizes (>1 thousand) and minimal age restrictions and conducted in a specific geographical location; community-based studies were those with relatively smaller sample sizes (i.e., hundreds) and more restricted age ranges and conducted in a specific geographical location; primary care-based studies were those that recruited patients from a general primary care or medical clinic seeking medical care; screening-based studies recruited healthy individuals from a general health screening clinic. Primary care-based studies and screening-based studies were classified together as they were conducted in the same setting. Finally, clinical condition-based studies were those that examined prevalence of hypogonadism in patient populations with specific clinical conditions. We also separately summarized prevalence of hypogonadism by age for studies that provided these data.

3. Results

3.1. Literature Search Results. The literature search identified 1,395 articles that were reviewed for inclusion. After review of titles and abstracts, we evaluated 175 full-text articles and identified 97 articles that met our eligibility criteria: 96 reported on the prevalence of hypogonadism, 2 on the incidence, and 4 on treatment proportions (not mutually

FIGURE 1: Flow diagram.

exclusive). The PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow chart can be found in Figure 1.

3.2. Prevalence of Hypogonadism. Among the 96 identified prevalence studies, 7 were population- ($n = 4$) [2–5] or community- ($n = 3$) [6–8] based studies and 7 were primary care or health screening studies [9–15]. Ten examined age-related changes for hypogonadism [2, 3, 8, 9, 12, 13, 16–19] and seventy-eight were clinical condition-based studies [20–97]. Studies varied considerably in geographic location, patient characteristics, sample sizes, and operational definition for hypogonadism. These studies are described in Tables 2 and 3.

3.2.1. Population-Based Studies. The prevalence of hypogonadism in the 4 population-based studies ranged from 2.1% to 12.8% [2–5] (Table 2). Sample sizes in these studies ranged from 1,490 to 2,966 participants and the mean (SD) ages of the study participants ranged from 47.3 (12.5) to 59.15 (10.8) years. Mean age was not reported in one of the studies [3]; however, the sample was equally divided among men in their 40s, 50s, and 60s [3]. The studies were conducted in Europe (Belgium, Estonia, Hungary, Italy, Poland, Spain, Sweden, and UK) and USA.

The operational definition of hypogonadism used across studies varied considerably: the Study of Health in Pomerania (SHIP, 1997–2001) (Germany) [5] used the most liberal definition of hypogonadism (TT < 300 ng/dL, no symptom criteria) and reported the highest prevalence at 12.8%; the European Male Aging Study (EMAS, 2003–2005) [4] used the most stringent definition of symptomatic hypogonadism

(TT < 317 ng/dL plus 3 specific symptoms of decreased frequency of morning erections, sexual thoughts, and erectile dysfunction) and reported the lowest prevalence at 2.1%. The Boston Area Community Health Survey (BACH, 2002–2005) [3] and the Massachusetts Male Aging Study (MMAS, 1987–1989) [2], both USA based, used similar operational definitions of symptomatic hypogonadism (TT cut-offs of <300 ng/dL plus ≥ 1 specific symptom or ≥ 2 nonspecific symptoms (BACH) and either TT <200 ng/dL plus ≥ 3 symptoms or TT 200–400 ng/dL plus FT <8.91 ng/dL plus ≥ 3 symptoms (see Table 2)) with reported prevalence of 5.6% (BACH) and 6.0% (MMAS), respectively.

3.2.2. Community-Based Studies. The prevalence of hypogonadism among the 3 community-based studies ranged from 9.5% to 31.2% (Table 2) [6–8]. All studies were cross-sectional and were conducted in Austria, China (Hong Kong), and Malaysia. The sample sizes ranged from 247 to 351 men, and the mean (SD) ages of men varied from 54 (NR) to 75.8 (0.4) years. The operational definition of hypogonadism varied considerably, with TT cut-offs ranging from <200 to <400, with and without low FT, and with and without symptoms. The highest prevalence (31.2%) was reported in a study of men with a mean age of 75.8 years [6].

3.2.3. Primary Care/Screening-Based Studies. Seven cross-sectional studies, conducted in Brazil, Chile, India, Italy, Taiwan, and USA, examined the prevalence of hypogonadism in a primary care or screening-based settings [9–15] (Table 2). Prevalence was higher than that observed in the general population surveys, ranging from 12% [10, 12] to 38.7% [13], with the majority around 20% [11, 12, 14, 15]. The sample sizes

TABLE 2: Prevalence of hypogonadism in population-, community-, and primary care or screening-based populations.

Author, year, and study name	Country and years of data collected	Study design	N	Age, mean (SD), and range	Definition of hypogonadism used	Reported prevalence (%)
Population-based studies						
Haring et al., 2010 [5] (SHIP)	Germany, 1997–2001	Population-based	1490	50.65 (15.41), NR	TT < 300 ng/dL	12.8
Araujo et al., 2007 [3] (BACH)	USA, 2002–2005	Population-based	1475	47.3 (12.5), NR	TT < 300 ng/dL + FT < 5 ng/dL + ≥ 1 specific symptom or ≥ 2 nonspecific symptoms [†]	5.6
Araujo et al., 2004 [2] (MMAS)	USA, 1987–1997	Population-based	1691	NR (NR), 40–70**	TT < 200 ng/dL + ≥ 3 symptoms ^{††} ; OR: TT 200–400 ng/dL + FT < 8.91 ng/dL + ≥ 3 symptoms ^{††}	6
Tajar et al., 2012 [4] (EMAS)	8 European countries, 2003–2005	Population-based ^{†††}	2966	59.15 (10.82), 40–79	TT < 317 ng/dL + 3 specific symptoms*	2.1
Community-based studies						
Ponholzer et al., 2010 [6]	Austria, 2000–2002	Community-based	247	75.8 (0.4), 75–78	TT < 350 ng/dL	31.2
Khoo et al., 2008 [7]	Malaysia, NR	Community-based	351	58 (7), 50–93	TT < 317 ng/dL TT < 317 ng/dL + positive symptoms on ADAM	19.1 6
Wong et al., 2006 [8]	China (Hong Kong), 2003–2004	Community-based	252	54 (NR), 45–64	TT < 200 ng/dL + ≥ 3 of 7 symptoms OR: TT 200–400 ng/dL + FT < 0.3093 nmol/L + ≥ 3 of 7 symptoms	9.52
Primary care and screening studies						
Mulligan et al., 2006 [13] (HIM)	USA, 2003–2004	Primary care patients	2162	60.5 (10.33), 45–96	TT < 300 ng/dL	38.7
Schneider et al., 2009 (DETECT) [15]	Germany, 2003	Primary care patients	2719	58.7 (13.4), NR	TT < 300 ng/dL	19.3
Nardoza et al., 2011 [14]	Brazil, 2009	Health screening	1623	57 (NR), 24–87	TT < 300 ng/dL	19.8
Goel et al., 2009 [11]	India, 2006	Health Screening ^{††††}	157	53.1 (NR), 40–60;	TT < 300 ng/dL TT < 300 ng/dL + Symptoms	24.2 20.4
Liu et al., 2009 [12]	Taiwan, 2007–2008	Health screening	734	57.4 (6.7), 43–87	TT < 300 ng/dL TT < 300 ng/dL + FT < 5 ng/dL + symptoms	24.1 12
Blümel et al., 2009 [9]	Chile, NR	Primary care patients	96	55.1 (12.0), 40–85	BT < 198.4 ng/dL + symptoms***	28.1
Di Luigi et al., 2010 [10]	Italy	Health screening	183	61.9 (7.5), 50–75	TT < 230 ng/dL	12

TT: 200 ng/dL = 6.94 nmol/L; 230 ng/dL = 8 nmol/L; 300 ng/dL = 10.4 nmol/L; 317 ng/dL = 11 nmol/L; 350 ng/dL = 12 nmol/L; FT: 5 ng/dL = 0.17 nmol/L; 8.9 ng/dL = 0.3092 nmol/L.

ADAM: androgen deficiency in the aging male; BACH: Boston Area Community Health; BT: bioavailable testosterone; cFT: calculated free testosterone; DETECT: diabetes cardiovascular risk-evaluation: targets and essential data for commitment of treatment; EMAS: European Male Aging Study; HIM: hypogonadism in males; MMAS: Massachusetts Male Aging Study; NR = not reported; SHIP = Study of Health in Pomerania; TT = total testosterone.

*Decreased frequency of morning erections, sexual thoughts, and erectile dysfunction.

**Participants were equally divided between men in their 40s, 50s, and 60s with a similar mean age to the BACH data.

***Positive answer to items 1 or 7, or any 3 other questions on the ADAM questionnaire.

[†]Specific symptoms include low libido, erectile dysfunction, or osteoporosis; the nonspecific symptoms include sleep disturbance, depressed mood, lethargy, or low physical performance.

^{††}Symptoms include loss of libido, erectile dysfunction, depression, lethargy, inability to concentrate, sleep disturbance, irritability, and depressed mood.

^{†††}4.4% of original population were excluded which included men already receiving testosterone replacement therapy.

^{††††}Study subjects were healthy hospital employees volunteered for a health check-up.

ranged from 96 to 2,719 men and the mean (SD) age of the participants in the studies ranged from 53.1 (NR) to 61.9 (7.5) years. Six of the studies used low TT to define hypogonadism [10–15] and one study used low bioavailable T and symptoms [9]. Using TT <300 ng/dL as a marker, prevalence was 19.3% [15], 19.8% [14], 24.1% [12], 24.2% [11], and 38.7% [13]. One study used a stricter TT threshold (TT < 230 ng/dL) with a lower resulting prevalence of 12% [10]. Adding symptoms as a criterion, the prevalence decreased from 24.1% to 12% [12] and from 24.2% to 20.4% [11].

3.2.4. Clinical Condition-Based Studies. A total of 78 studies were identified and assessed prevalence of hypogonadism among patients with specific medical conditions (Table 3). The prevalence varied considerably by medical condition. Hypogonadism occurred commonly among patients with type 2 diabetes mellitus (T2DM). Thirteen studies conducted in the UK, Australia, India, Italy, and USA showed the prevalence of hypogonadism in patients with T2DM ranging from 4.4% to above 45% [23, 25, 29, 36, 40, 45, 47, 48, 50, 56, 61, 71, 87] varying based on the definition of hypogonadism used: prevalence ranged from 4.4% to 36% using TT <8 mmol [23, 29, 45, 50, 56, 61, 71], from 24.5 to 43% using TT <10.4 mmol [36, 40, 47, 48], and from 34.7% to 45% using TT <12 mmol [25, 87]. Hypogonadism was also common among obese patients with prevalence ranging from 15% to 78.8% [22, 54, 74] and among patients with MetS, ranging from 30 to 35% [27, 62, 83]. When combined with obesity or metabolic syndrome (MetS), prevalence estimates among patients with T2DM were higher (51% [39] and 43% [70] for patients with T2DM and obesity and MetS, resp.).

Prevalence of hypogonadism in patients with cardiac disease [44, 55, 65, 67, 84, 94, 95], erectile dysfunction [24, 26, 32–35, 37, 49, 52, 59, 66, 85, 88], HIV [31, 38, 58, 78, 92, 93, 96], respiratory disease [51, 57, 64], depression [53, 68], cancer [43, 46, 63, 75, 76, 79, 80, 82, 91], rheumatoid arthritis [89], osteoporosis [30, 42], chronic kidney disease [21, 28, 60, 97], sickle cell disease [86], myopathies [20, 41, 52, 73, 90], urological diseases [77, 81], Peyronie's disease [69], and Alzheimer's and Parkinson's disease [72] is detailed in Table 3.

3.2.5. Prevalence of Hypogonadism by Age. A total of 10 studies, conducted in Chile, China, Europe, Italy, and USA, examined changes in prevalence of hypogonadism with age (Table 4) [2, 3, 8, 9, 12, 13, 16–19]. Sample sizes ranged from 96 to 2,162 and mean (SD) ages ranged from 47.3 (12.5) to 61.9 (7.5) years. Five of the studies were population-based [2, 3, 17–19], one was community-based [8], and 4 were primary care-/screening-based [9, 12, 13, 16]; one was longitudinal [17] and 9 were cross-sectional [2, 3, 8, 9, 12, 13, 16, 18, 19].

The prevalence of hypogonadism increased with each increasing age category [2, 3, 8, 9, 12, 13, 16–19], with the rare exception within certain age categories [3, 8] (Table 4). Three of the studies reported significant *P* values for trend [2, 9, 12], 3 reported significant differences between older and younger age categories [3, 9, 18], 2 studies did not conduct statistical analysis for differences in prevalence by age [17, 19], and one study was nonsignificant [8]. One cross-sectional study [13]

reported a 17% (95% CI, 1.08–1.27) increase in risk of hypogonadism, for every 10-year increase in age. Prevalence ranged from approximately 0.1% to 16.5% among men aged 40–49, from 0.6% to 31.8% among men aged 50–59, from 3.2% to 30.1% among men aged 60–69, up to 66.7% among men of age ≥70 years [2, 3, 12, 17–19], and 49% in the study that assessed the 80+ age category [17] (not all studies used the same age cut-offs).

3.3. Incidence of Hypogonadism. In two population-based studies (SHIP [5] and BACH [2]), in which incidence was examined, the reported incidence was 12.3 cases per 1,000 person-years in the US and 11.7 cases per 1000 person-years in Germany.

3.4. Treatment Rates for Hypogonadism. The proportion of patients receiving treatment was defined as the percentage of men with hypogonadism who were receiving testosterone therapy. Only 4 studies were identified and reported treatment proportions: one population-based [98], one primary care-based [13], and 2 clinical condition-based studies [38, 79]. The population-based (BACH) and clinical-based studies (HIM) reported that 10% [98] and 12% [13] of patients were receiving treatment for hypogonadism, respectively. Among the clinical condition-based studies, 12.1% of 144 childhood cancer survivors [79] and 38% of 296 men with HIV were on treatment for hypogonadism [38].

4. Discussion

In this systematic review, we identified 97 studies that met our inclusion/exclusion criteria for assessing the epidemiology of hypogonadism. The prevalence of hypogonadism was high and varied according to the operational definition of hypogonadism used and the population studied. The prevalence of hypogonadism in the population-based, community-based, and primary care- or screening-based studies ranged from 2.1 to 12.8% [9–15], from 9.5 to 31.2% [9–18], and from 12 to 38.7% [9–15], respectively. The prevalence was higher among clinical-based populations with specific conditions. For example, among patients with T2DM, obesity, and MetS, the prevalence ranged from 4.4 to >50% [23, 25, 29, 36, 40, 45, 47, 48, 50, 56, 61, 71, 87], from 15 to 78.8% [22, 54, 74], and from 30 to 35% [27, 62, 83], respectively.

In most instances, studies showed a linear relationship between prevalence and the degree of liberalness in the operational definition of hypogonadism [4, 5, 7, 12]. For instance, Haring et al. [5] reported prevalence estimates below TT levels of 8.0, 8.7, 10.4, and 12.0 nmol/L, which were 3.4%, 4.5%, 12.8%, and 21.6%. The added criteria of symptoms typically ensued a lower prevalence due to increased stringency of diagnosis. Among the population- and community-based studies, those that used a more stringent definition of hypogonadism, which included symptoms and low T, reported the lowest prevalence, ranging from 2.1% to 9.52% [2–4, 7, 8], while those using a more liberal definition of hypogonadism (low T only) reported higher prevalence, ranging from 19.1% to 31.2% [5–7]. The association between definition of

TABLE 3: Prevalence of hypogonadism among patients with specific conditions.

Author, year, and study name	Country and years of data collected	Study population	<i>N</i>	Definition of hypogonadism used	Prevalence (%) among patients with disease of interest
Type 2 diabetes mellitus (T2DM)					
Kapoor et al., 2007 [56]	UK/not specified	Primary care retinopathy Screening service and medical clinic	355 men with T2DM	TT < 8 nmol/L TT 8–12 nmol/L	17 25
Biswas et al., 2012 [25]	UK/not specified	Medical clinic	329 T2DM (<i>n</i> = 115) T1DM (<i>n</i> = 93) controls (<i>n</i> = 12)	TT < 11.9 nM	45
Chen et al., 2006 [29]	Australia/NZ/1992 to 2000	Population-based	195 T2DM (<i>n</i> = 35) Non-T2DM (<i>n</i> = 160)	TT < 8.0 nmol/L	14.3
Corona et al., 2006 [36]	Italy/not specified	Medical clinic	1246 T2DM (<i>n</i> = 199)	TT < 10.4 nmol/L	24.5
Anderson et al., 2012 [23]	UK/January 2008–June 2009	Medical clinic	387 T2DM (<i>n</i> = 353) T1DM (<i>n</i> = 23)	TT < 8.0 nmol/L TT 8–11.99 nmol/L	4.4 32.1
Talukder et al., 2010 [87]	India/May 2008–April 2009	Medical clinic	420 T2DM (<i>n</i> = 170) non-T2DM (<i>n</i> = 40)	Symptoms/signs of hypogonadism and TT ≤ 12 nmol/L	34.7
Dhindsa et al., 2004 [40]	US/not specified	Medical clinic	103 men with T2DM	TT < 300 ng/dL	33
Grossmann et al., 2008 [48]	Australia/not specified	Medical clinic	649 T2DM (<i>n</i> = 574) T1DM (<i>n</i> = 69)	TT < 10 nmol/L	43
Grossmann et al., 2009 [47]	Australia/2005	Medical clinic	464 men with T2DM	TT < 10 nmol/L	43
La Vignera et al., 2009 [61]	Italy/not specified	Medical clinic	110 men with T2DM	TT < 231 ng/mL	10
Ogbera et al., 2011 [71]	Nigeria/December 2009 to May 2010	Medical clinic	203 men with T2DM	TT < 8 nmol/L	36
Hackett et al., 2009 [50]	UK/September 2007 and May 2008	Medical clinic	488 men with T2DM	TT < 8 nmol/LTT 8–12 nmol/L	15.5 33.8
Ganesh et al., 2009 [45]	India/not specified	Medical clinic	100 men with T2DM	cFT < 64.8 pg/mL (0.225 nmol/L)	15
T2DM + obesity or metabolic syndrome (MetS)					
Ogbera 2011 [70]	Nigeria/December 2009 to May 2010	Medical clinic	203 men with T2DM + MetS (<i>n</i> = 90)	T2DM + TT < 12 nmol/L	36
				T2DM + MetS	43
				T2DM + MetS + low TT	47
Dhindsa et al., 2010 [39]	US/not specified	Medical clinic	1849	FT < 300 ng/dL or 10.4 nmol/L:	
			Obesity + T2DM (<i>n</i> = 398)	Obesity and T2DM	51
			Obesity (<i>n</i> = 398)	Obese	31
Obesity					
Hofstra et al., 2008 [54]	The Netherlands/not specified	Medical clinic	160 obese males	TT < 11 nmol/L	57.7

TABLE 3: Continued.

Author, year, and study name	Country and years of data collected	Study population	N	Definition of hypogonadism used	Prevalence (%) among patients with disease of interest
Pellitero et al., 2012 [74]	Spain/not specified	Clinical research center	33 obese males	TT < 300 ng/dL TT < 200 ng/dL + FT < 65 pg/mL TT < 300 but > 200 ng/dL FT low and TT > 300 ng/dL	78.8 100 23.1 3.85
Allan et al., 2006 [22]	Australia/May 2001–February 2003	Community-based	223 Obese (<i>n</i> = 99) Nonobese (<i>n</i> = 124)	TT < 8 nmol/L plus symptoms Obese Nonobese	15 3
MetS					
Laaksonen et al., 2005 [62]	Finland/1987–2001	Population-based	854 men with MetS	TT < 11 nmol/L	10.7
Singh et al., 2011 [83]	India/not specified	Medical clinic	95 men with MetS	FT < 0.225 nmol/L	30.2
Caldas et al., 2009 [27]	Brazil/January 2003 to March 2007	Medical clinic	80 men with MetS	TT < 300 ng/dL	30.0
Cardiac disease					
Jankowska et al., 2006 [55]	Poland/October 2001 to November 2002	Medical clinic	574 CHF (<i>n</i> = 208) health controls (<i>n</i> = 366)	Serum TT and FT levels at or below the 10th percentile of healthy peers	13–39 (by age)
Wang et al., 2010 [94]	China/March 1, 2005, to May 31, 2007	Medical clinic	175 men with CHF	Serum levels at or below the 10th percentile of healthy peers	21.7
Serra et al., 2012 [84]	Italy/not specified	Medical clinic	52 male heart transplantation recipients	TT < 10.4 nmol/L	34.6
Florvaag et al., 2012 [44]	Germany/not specified	Medical clinic	137 male heart failure patients	Free testosterone (age-related cut-off values)	39
Malkin et al., 2010 [67]	UK/June 2000 and June 2002	Medical clinic	930 men with coronary disease	TT < 8.1 nmol/L	16.9
Wehr et al., 2010 [95]	Germany/1997 to 2000	Medical clinic	2299 men who were routinely referred for coronary angiography	T < 11.3 nmol/L	18
Lerchbaum et al., 2012 [65]	Germany/1997–2000	Medical clinic	2069 men with coronary disease	TT < 11.3 nM	18.4
Erectile dysfunction (ED)					
Köhler et al., 2008 [59]	US/1987 to 2002	Chart review	2794 men presenting for ED evaluation	TT < 300 ng/dL	23
Bunch et al., 2002 [26]	US/1996 to 1999	Chart review	501 men with ED	TT < 300 ng/dL	44
Corona et al., 2009 [33]	Italy/not specified	Chart review	2302 men with ED	TT < 12 nmol/L + symptoms	28.1
Arafa et al., 2012 [24]	Egypt/not specified	Medical clinic	212 men T2DM + ED	TT < 300 ng/dL + symptoms	41
Guay et al., 2010 [49]	US/July 1995 to July 1997	Chart review	990 with men ED	10.4 nmol/L + symptoms	36.3

TABLE 3: Continued.

Author, year, and study name	Country and years of data collected	Study population	N	Definition of hypogonadism used	Prevalence (%) among patients with disease of interest
Makhlouf et al., 2008 [66]	US/July 2001 to June 2003	Medical clinic	157 men with ED	TT < 300 mg/dL	36
Corona et al., 2007 [35]	Italy/not specified	Medical clinic	1134 men with ED	TT < 10.4 nmol/L	16.9
Corona et al., 2010 [37]	Italy/2000 to 2007	Medical clinic	1687 men with ED	TT 230–300 ng/dL no symptoms	13.3
Corona et al., 2009 [34]	Italy/January 2001 to April 2008	Medical clinic	1093 men with ED		
Somani et al., 2010 [85]	UK/March 2007–August 2008	Medical clinic	124 men with ED	Low TT (not further defined)	23.4
Corona et al., 2010 [32]	Italy/January 2001–April 2009	Medical chart review	3712 men with sexual dysfunction	TT < 8 nmol/L + symptoms	7.5
Tan et al., 2011 [88]	Multiethnic Asia/Pacific/2003	Medical chart review	1046 ED (<i>n</i> = 194)	TT < 10.4 nmol/L	20.4
Hamidi et al., 2012 [52]	Iran/November 2009 to August 2010	Medical clinic	241 men with ED	FT < 5 ng/dL	36.5
HIV					
Klein et al., 2005 [58]	US/not specified	Community-based	502 (had or at risk of HIV)	TT < 300 ng/dL	45.6
Crum-Cianflone et al., 2007 [38]	US/September 2004 to May 2005	HIV medical clinic	300 HIV+	TT < 300 ng/dL	17
Wahlstrom et al., 2000 [93]	US/not specified	Observational study	20 HIV+	T ≤ 410 ng/dL	25
Collazos et al., 2009 [31]	Spain/not specified	Medical chart review	188 HIV+	T < 2.6 ng/mL	3.7
Wunder et al., 2007 [96]	Switzerland/not specified	Cohort study	139 HIV+	FT below the age-adjusted normal limits	70
Wagner et al., 1995 [92]	US/not specified	Study setting (baseline data)	234 HIV+	TT ≤ 400 ng/dL	38
Rietschel et al., 2000 [78]	US/November 1997–April 1999	Cohort study	90 HIV+	Low TT/FT	19
Respiratory disease					
Laghi et al., 2005 [64]	US/not specified	Cohort study	101 men with COPD	FT < 50 pg/mL	37.6
Kirbas et al., 2007 [57]	Turkey/November 2004 to July 2006	Medical clinic	96 men with obstructive sleep apnea	TT < 2.62 ng/mL	19.8
Halabi et al., 2011 [51]	US/not specified	Medical clinic	104 men with COPD	FT < 35 pg/mL for patients < 70 years; FT < 30 pg/mL for patients ≥ 70 years	33.6
Depression					
Hintikka et al., 2009 [53]	Finland/1998, 1999, 2001, and 2005	Population-based	116 with and without psychological symptoms	FT < 160 pmol/L plus BDI scores: +depressive symptoms	28.8
				–depressive symptoms	10.5
McIntyre et al., 2006 [68]	Canada/not specified	Medical clinic	94 men with and without depression	TT < 12.14 nmol/L: Men with depression	34
				Men without depression	6

TABLE 3: Continued.

Author, year, and study name	Country and years of data collected	Study population	N	Definition of hypogonadism used	Prevalence (%) among patients with disease of interest
Cancer					
Tromp et al., 2011 [91]	The Netherlands/2008	Medical clinics	565 male 5-year survivors of childhood cancer	T < 11.0 nmol/L	12.4
Lackner et al., 2007 [63]	Austria/not specified	Medical clinic	68 men with testicular cancer	T < 3.0 ng/mL + symptoms	33.8
Pühse et al., 2011 [75]	Germany/2004	Medical clinic	376 men with testicular germ-cell cancer (TGCC)	TT 2.84 ng/mL or 9.85 nmol/L	~25
Fleishman et al., 2010 [43]	US/July 2007 through July 2009	Medical clinic	428 male patients with nontestosterone-related cancer	TT < 300 ng/dL	48
Salonia et al., 2011 [80]	Italy/June 2006 and June 2008	Medical clinic	673 prostate cancer patients	TT < 3 ng/mL	21.4%
Greenfield et al., 2007 [46]	US/not specified	Medical clinic	389 cancer survivors	TT < 10 nmol/L	13.6
Rajagopal et al., 2004 [76]	US/not specified	Chart review	40 cancer survivors	<345 ng/dL	
				All	65
				On opioids	90
				Not on opioids	40
Schatzl et al., 2001 [82]	Austria/January 1999–April 2000	Medical clinic	156 men with prostate cancer	TT < 3.0 ng/mL	33.3
Romerius et al., 2009 [79]	Sweden/2004–2006	Medical clinic	292 men with history of childhood treatment of cancer or brain tumor	T < 10 nmol/L	23
Rheumatoid arthritis (RA)					
Tengstrand et al., 2002 [89]	Sweden/not specified	Medical clinic	104 patients with RA	<6.5 nmol/L–8.1 nmol/L (age dependent)	31.7
Osteoporosis					
Fink et al., 2006 [42]	US/March 2000 to April 2002	Medical clinics	3674 men with osteoporosis	TT < 200 ng/dL	6.9
Clapauch et al., 2008 [30]	Brazil/January 2005	Medical clinic	216 men with osteoporosis	cFT < 6.5 ng/dL + symptoms	25
Chronic kidney disease (CKD)					
Yilmaz et al., 2011 [97]	Turkey/March 2006 to June 2010	Medical clinic	239 men with CKD	TT 10 nmol/L	33
Carrero et al., 2011 [28]	Sweden/June 1999 and October 2007	Medical clinics	260 men with ESRD	TT < 10 nmol/L	44
Kyriazis et al., 2011 [60]	Greece/October 2005 and December 2006	Medical clinic	111 male hemodialysis patients	TT < 8 nmol/L	49
Albaaj et al., 2006 [21]	UK/not specified	Medical clinic	214 male patients with CKD or ESRD	TT < 10 nmol/L	26.2
Myopathies					
Travison et al., 2008 [90]	Canada/3-year study	Medical clinic	59 men with myopathies	10–30 nmol/L	54
Durga et al., 2011 [41]	US/July 2006 to April 2007	Medical clinic	60 men with spinal cord injuries	TT < 325 ng/dL	43.3

TABLE 3: Continued.

Author, year, and study name	Country and years of data collected	Study population	N	Definition of hypogonadism used	Prevalence (%) among patients with disease of interest
Okun et al., 2002 [73]	US/not specified	Medical clinic	68 men with PD	FT < 70 pg/mL	35
Abbasi et al., 1994 [20]	US/not specified	Medical clinic	102 men with poststroke hemiplegia	TT < 2.5 percentile of the healthy old men	17
Miscellaneous diseases					
Schatzl et al., 2000 [81]	Austria/October 1998 to May 1999	Medical clinic	312 men with lower urinary tract symptoms	T < 3 ng/mL	22.1
Rhoden et al., 2005 [77]	Brazil/January 2000 to December 2001	Medical clinic	746 urological patients	TT < 13.87 nmol/L	24.5
Taddesse et al., 2012 [86]	US/September 21 to December 21, 2010	Medical clinic	34 men with sickle cell	T ≤ 250 ng/dL	24
Okun et al., 2004 [72]	US/not specified	Chart review	118 men with PD + AD	PD + T < 325 ng/mL AD + T < 325 ng/mL	35 38
Moreno et al., 2009 [69]	US/January 2006 to January 2008	Medical chart review	121 men with Peyronie's disease	TT < 300 ng/dL	29.5

CHD: chronic heart failure; CKD: chronic kidney disease; ED: erectile dysfunction; ESRD: end stage renal disease; MetS: metabolic syndrome; RA: rheumatoid arthritis; T2DM: type 2 diabetes mellitus; PD: Parkinson's disease; AD: Alzheimer's disease.

hypogonadism and prevalence was also apparent among the primary care-/health screening-based studies (12–39%).

Prevalence also varied by age. Hypogonadism was consistently found to increase with age for studies reporting data by age (REF), with one study citing an increase of 17% (95% CI, 1.08–1.27) in risk of hypogonadism, for every 10-year increase in age [13]. One study that had a considerably older cohort (mean age of 75.8 years) [6] reported the highest prevalence (31.2%) among community-based studies. It was estimated in a 2007 publication that there were 4.7 million American men aging 30–79 years with symptomatic androgen deficiency [3]. It was projected that there will be as many as 6.5 million American men aging 30–79 years with symptomatic hypogonadism by 2025, an increase of 38% from the year 2000 population estimates, due to an aging population [3].

Despite the significant prevalence of hypogonadism, data suggest that the vast majority of hypogonadal men are not receiving treatment for this condition [13, 98]. Reasons for this low treatment proportion have not been definitively determined; however, contributing factors may include inadequate knowledge base among physicians regarding hypogonadism and uncertainty regarding diagnostic criteria. The main indication for testosterone replacement therapy is sexual dysfunction with symptoms of reduced libido and/or erectile dysfunction. This may not be an issue to some men and therefore they are not treated or subjects may decline therapy. Also, individuals may not be able to afford therapy in countries where people have to pay for their prescriptions and healthcare. Furthermore, with the lack of long-term placebo-controlled safety studies, some clinicians may have concerns especially in the older man in regard to risks of prostate cancer and cardiovascular disease, even though there is limited evidence from current published studies or

meta-analyses. The only study which did show a possible relationship between testosterone replacement therapy and cardiovascular events was the TOM trial [99]. However, this study involved the administration of larger testosterone doses than those used in normal clinical practice and was not sufficiently powered to detect an increase in cardiovascular events. A similar trial where routine doses of testosterone were used did not detect any increase in cardiovascular events [100].

Results of this review highlight the fact that there is no standardized definition used in the hypogonadism epidemiologic research. The hypogonadism literature reports wide-ranging prevalence based not only on the different populations or subpopulations studied, but also on the use of diverse biochemical cut points or varied choices of symptoms. The actual prevalence of disease that a clinician will treat in his or her office may in fact be higher than what we found in this review, as clinicians may use a more liberal definition of hypogonadism to base their treatment decisions on.

The studies in this review represented a wide geographic distribution with samples from USA, Europe, Asia, and South America. The prevalence of hypogonadism may vary by geographical location, as recently demonstrated in a large ($n = 5003$) international cohort of older men (>65 years of age) showing important geographical differences in concentrations of T [101]. However, differences in patient populations and operational definitions used across studies made it difficult to interpret the findings based on geography in the current review.

We can expect approximately 12 new cases of hypogonadism per 1,000 person-years [2, 5] and approximately 481,000 new cases of hypogonadism per year in US men aged 40–69 years [2]. It has been projected that there will be as

TABLE 4: Prevalence of hypogonadism by age.

Author and year (study name)	Country and years of data collected	Study design	N	Age, mean (SD), and range	Definition of hypogonadism used	Prevalence, per age group, years (%)	
Harman et al., 2001 (BLSA) [17]	USA, 40-year period	Population-based	890	53.8 (16.0), NR	TT < 325 ng/dL OR FT < 0.153 nmol/L	20–29	<5
						30–39	<5
						40–49	<10
						50–59	12
						60–69	19
						70–79	28
						>80	49 ^a
Wu et al., 2010 [19] (EMAS)	8 European countries, 2003–2005	Population-based	2966	59.15 (10.82), 40–79	TT < 317 ng/dL + FT < 220 pmol/L + ≥3 sexual symptoms [#]	40–49	0.1
						50–59	0.6
						60–69	3.2
						70–79	5.1 ^b
Araujo et al., 2007 [3] (BACH)	USA, 2002–2005	Population-based	1475	47.3 (12.5)	TT < 300 ng/dL + FT < 5 ng/dL + ≥1 specific symptom or ≥2 nonspecific symptoms [†]	30–39	1.1
						40–49	4.1
						50–59	8.1
						60–69	9.1
						70–79	22.1 ^c
Araujo et al., 2004 [2] (MMAS)	USA, 1987–1997	Population-based	1691	NR (NR), 40–70	TT < 200 ng/dL + ≥3 symptoms ^{††} ; OR: TT 200–400 ng/dL + FT < 8.91 ng/dL + ≥3 symptoms ^{††}	40–49	4.1
						50–59	4.5
						60–70	9.4 ^d
Li et al., 2005 [18]	China, 2002–2003	Population-based study	1080	NR (NR), 20–>70	cFT < 0.3 nmol/L	40–49	13.0
						50–59	31.8
						60–69	30.1
						>70	46.7 ^e
Wong et al., 2006 [8]	China, 2003–2004	Community- based	252	54 (NR), 45–64	TT < 200 ng/dL + ≥3 of 7 symptoms OR: TT 200–400 ng/dL + FT < 0.3093 nmol/L + ≥3 of 7 symptoms	45–49	8.2
						50–54	6.3
						55–59	10
						60–65	16.7 ^f
Mulligan et al., 2006 [13] (HIM)	USA, 2003–2004	Primary care patients	2162	60.5 (10.33), 45–96	TT < 300 ng/dL	45–54	34
						55–64	40.2
						65–74	39.9
						75–84	45.5
						85+	50
						50–54	6.33
						55–59	10
						60–64	16.67 ^g
Liu et al., 2009 [12]	Taiwan, 2007–2008	Health screening clinic in a medical center	734	57.4 (6.7), 43–87	TT < 300 ng/dL	40–49	16.5
						50–59	23
						60–69	28.9
						≥70	37.2 ^h

TABLE 4: Continued.

Author and year (study name)	Country and years of data collected	Study design	N	Age, mean (SD), and range	Definition of hypogonadism used	Prevalence, per age group, years (%)	
Di Luigi et al., 2010 [16]	Italy, NR	Health screening clinic*	183	61.9 ± 7.5 years (range 50–75).	TT < 230 ng/dL	50–59	5.4
						60–69	10
						70–79	27.5 ⁱ
Blümel et al., 2009 [9]	Chile, NR	Primary care-based (health services center)	96	55.1 ± 12.0 years (range 40–85 years)	BT < 198.4 ng/dL + symptoms**	40–54	17.9
						55–69	29.2
						≥70	66.7 ^j

TT: 200 ng/dL = 6.94 nmol/L; 230 ng/dL = 8 nmol/L; 300 ng/dL = 10.4 nmol/L; 317 ng/dL = 11 nmol/L; 325 ng/dL = 11.3 nmol/L; 350 ng/dL = 12 nmol/L; FT: 5 ng/dL = 0.17 nmol/L; 8.9 ng/dL = 0.3092 nmol/L.

ADAM: androgen deficiency in the aging male; BACH: Boston Area Community Health; BT: bioavailable testosterone; cFT: calculated free testosterone; EMAS: European Male Aging Study; HIM: hypogonadism in males; MMAS: Massachusetts Male Aging Study; NR: not reported; SHIP: Study of Health in Pomerania; TT = total testosterone.

^aNo statistical test done; ^bno statistical test done; ^call pairwise comparisons, $P < 0.05$ over 70 versus all other age groups; ^d P values for trend <0.001 ; ^echi square $P < 0.000$; ^fnot significant; ^gno statistical test done; ^h $P < 0.019$ for trend; ⁱ $P < 0.01$ versus age 50–59 and age 60–69; ^j P value for trend $P < 0.0004$.

[†]Specific symptoms include low libido, erectile dysfunction, or osteoporosis; the nonspecific symptoms include sleep disturbance, depressed mood, lethargy, or low physical performance.

^{††}Symptoms include loss of libido, erectile dysfunction, depression, lethargy, inability to concentrate, sleep disturbance, irritability, and depressed mood.

[#]Specific signs/symptoms are low libido, erectile dysfunction, or osteoporosis.

*To evaluate risks associated with participation in sports in a group of healthy athletic men.

**Positive answer to items 1 or 7, or any 3 other questions on the ADAM questionnaire.

many as 6.5 million US men aging 30–79 years with symptomatic AD by 2025 [3], an increase of 38% from the year 2000 population estimates, due to an aging population. While there is no conclusive evidence from this review that the prevalence of hypogonadism in the general population is increasing over time, there is evidence that the prevalence of hypogonadism does increase with age and with certain comorbidities such as T2DM and obesity, all of which are increasing in the general population. It follows that there may well be an increasing proportion of older men who will benefit from treatment for hypogonadism. As the proportion of the world's population in the older ages continues to increase, the importance of studying, diagnosing, and treating male hypogonadism will also rise.

The mainstay treatment of low testosterone is testosterone replacement therapy (TRT), although there is indication that modification of diet and exercise regimes have the ability to improve testosterone levels [99]. Despite the significant prevalence of hypogonadism, self-reported data suggest that the vast majority of hypogonadal men are not receiving TRT treatment for this condition [13, 98]. Reasons for this low treatment proportion have not been definitively determined; however, contributing factors may include inadequate knowledge base among physicians regarding hypogonadism and uncertainty regarding diagnostic criteria. The main indication for TRT is sexual dysfunction, which, for some men, may not affect their daily lives, and therefore they choose not to be treated. Also, individuals may not be able to afford therapy in countries where people have to pay for their prescriptions and healthcare.

Another impeding factor for prescribing TRT may be a concern over the potential risk of cardiovascular disease and prostate cancer. The safety of TRT lacks examination in large, prospective, and adequately powered controlled trials [100].

Smaller studies have been published, some suggesting an association between testosterone replacement therapy and cardiovascular adverse events [100]. The TOM trial was terminated early due to an increased frequency of cardiovascular events in the men treated with testosterone [102]. However, this study involved the administration of larger testosterone doses than those used in normal clinical practice and was not sufficiently powered to detect an increase in cardiovascular events. A similar trial, which used routine doses of testosterone, did not detect any increase in cardiovascular events [103]. To address the question of safety and in lieu of long term, prospective safety data, the Endocrine Society Task Force on Testosterone Use in Adult Men commissioned a meta-analysis of randomized and observational studies with long-term follow-up in testosterone therapy in 2010. The analyses of 51 studies found no significant effect of TRT on mortality, prostate, or cardiovascular outcomes [100]. More recently, a retrospective database study of 8709 male veterans who underwent coronary angiography between 2005 and 2011 reported an increased risk (absolute risk increase: 5.8% (95% CI: –1.4% to 13.1%)) of experiencing an adverse cardiovascular event (all-cause mortality, MI, or ischemic stroke) among TRT versus nontreated men at 3 years after coronary angiography [104]. Although this study garnered media attention, it is limited by serious methodological concerns which put the results in question.

4.1. Limitations. A general limitation in hypogonadism research is the lack of a standardized operational definition of hypogonadism. Recently, professional societies have proposed operational definitions which include criteria of specific signs and symptoms plus biochemical low TT, typically defined as TT < 300 ng/dL (< 10.4 nmol/L) [1]. However, the literature is confounded by numerous studies using

a variety of different definitions: some include sign and symptom criteria and others do not; biochemical TT thresholds used range from <8 nmol/L to <12 nmol/L, others use an FT criterion and no TT (as men with normal TT may be quite symptomatic in clinical due to low FT), and others use a TT and FT criterion. The varying definitions used make comparisons between studies difficult.

The proportions of patients receiving T therapy in the population were obtained from one population-based study and one primary care-based study, both of which reported on the number of participants who were receiving T therapy. Medication use, including use of T therapy, was assessed by patient self-report in the studies. Self-report of medication use is subjective and is at risk of both reporting bias and measurement bias. A more accurate measurement of treatment proportions could be obtained from chart review or commercial claims database study and may be an interesting objective for a future study.

As with all systematic reviews, publication bias, which can lead to bias if only positive studies or studies with a statistically significant difference are published, is an issue in this review. Another limitation of this review is that a quality appraisal of the individual studies was not conducted. Although methodological aspects of the individual studies, which may have influenced outcomes or comparisons between studies, were considered and commented on during the assessment of the evidence, a systematic quality assessment of the studies was not carried out.

5. Conclusions

This literature review suggests that there is potentially a significant burden of hypogonadism in the general population. The burden of hypogonadism increases with age and in the presence of certain clinical conditions, such as T2DM and obesity. Data suggested that the vast majority of hypogonadal men in the general population are not receiving treatment. This may be the result of underdiagnosis of the disease, due to lack of awareness by patients and/or physicians and the irregularities surrounding the diagnostic criteria.

Disclosure

The authors met criteria for authorship as recommended by the International Committee of Medical Journal Editors and are fully responsible for all content and editorial decisions and were involved in all stages of paper development. This original paper has not been previously presented in whole by the authors. A portion of the information has been presented as a poster entitled "The prevalence, incidence and treatment rates of hypogonadism in men across geographies: a systematic review of the literature" at the ISPOR, May 18–22, 2013, New Orleans, LA.

Conflict of Interests

Victoria Zarotsky and Wendy Carman are employees of Optum and were contracted by Merck & Co., Inc., to conduct

this study. Donna Coffin is employee of Boolean Research Consulting Services who was contracted by Optum. Ming-Yi Huang is a Postdoctoral Fellow funded by Merck & Co., Inc. Puneet K. Singhal is employed by Merck & Co., Inc. T. Hugh Jones has received research grants from BayerHealthcare, UK, and honoraria for educational lectures and/or advisory boards from BayerHealthcare, Clarus, Lilly, Merck, and Prostrakan. T. Hugh Jones and Abraham Morgentaler have served as Consultants to Merck & Co., Inc., for this study.

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