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The Disappearing Sperms: Analysis of Reports Published Between 1980 and 2015

Pallav Sengupta, MSc, PhD.[1], Sulagna Dutta, MSc[2], and Elzbieta Krajewska-Kulak, MD, PhD[3]

Abstract

Reports regarding the changes in sperm concentration in different counties of the world are inconsistent. Furthermore, the reports that sprung up from specific epidemiological and experimental examinations did not include data of prior studies or geographical variations. The current study, following a previous report of massive fall in semen volume over the past 33 years, attempts to delineate the trend of altering sperm concentrations and factors responsible for this by reviewing article published from 1980 to July 2015 with geographic differences. The current study identified an overall 57% diminution in mean sperm concentration over the past 35 years ($r = -.313$, $p = .0002$), which, when analyzed for each geographical region, identified a significant decline in North America, Europe, Asia, and Africa. An increasing trend of sperm concentration was identified only in Australia. The association of male age with such a trend ($R^2 = .979$) is reported. The authors also correlated male fertility with sperm concentration. Thus, this comprehensive, evidence-based literature review aims to concisely and systematically present the available data on sperm concentration from 1980 to 2015, as well as to statistically analyze the same and correlate male health with the declining pattern of sperm count in a single scientific review to serve the scientific research zone related to reproductive health. It points to the threat of male infertility in times ahead.

Keywords

semen quality, sperm concentration, sperm count

Introduction

There has been recent controversy regarding changes in sperm counts during the past 60 years worldwide (Sengupta, 2014a). It has been reported widely in last two decades that sperm count is declining (Table 1). Subsequently, Rolland, Le Moal, Wagner, Royère, and De Mouzon (2013) reported a 32% decline in sperm count from 1989 to 2005. The deterioration of semen qualities was first reported in 1974 by Nelson and Bunge. Since then, reports published regarding the changes in human semen parameters have been inconsistent. Nieschlag, Lammers, Freischem, Langer, and Wickings (1982) reported no changes, while Ng et al. (2004) revealed significantly different seminal volumes in different age groups. In 1992, Carlsen, Giwercman, Keiding, and Skakkebaek reported a worldwide decline in sperm counts in a meta-analysis of 61 studies between 1938 and 1990 evaluating the semen analyses of 14,947 presumably fertile men from 23 countries. Swan, Elkin, and Fenster (1997) published a reanalysis of the studies included by Carlsen et al. (1992). In that investigation, they reported significant declines in sperm count in the United States, Europe, and Australia, but no such decline in non-Western countries. Similar declines were also proclaimed by numerous other studies, but a clear cause was unable to be established (Auger, Kunstmann, Czyglik, & Jouannet, 1995; Swan et al., 1997). A recent article reported a decline in semen volume in aging males over the past 33 years (Sengupta, 2015). Because of reduced semen volumes, sperm concentrations were increased in older men. Moreover, significantly increased serum follicle-stimulating hormone levels sometime reflect in testicular spermatogenic function (Luetjens, Rolf, Gassner, Werny, & Nieschlag, 2002). Inhibin B as a possible marker for spermatogenesis identifies a moderate but sig-

[1]Lincoln University College, Petaling Jaya, Malaysia
[2]Ex-guest Teacher, Serampore College, University of Calcutta, Kolkata, West Bengal, India
[3]Medical University of Bialystok, Bialystok, Poland

Corresponding Author:
Pallav Sengupta, Faculty of Medicine, Lincoln University College, Petaling Jaya, Malaysia.
Email: pallav@lincoln.edu.my

Table 1. Studies on Changes of Sperm Concentrations in Different Age Groups (1980 to July 2015).

Country	Population	Sample size (*n*)	Male age definition (range/mean/group, in years)	Direction of effect with increasing age	Study
Nigeria	Cohort study	53	20-45	↓ ($p < .01$)	Lapido (1980)
United States	Cohort study	63	No age data	↓ ($p < .001$)	Venable, McClimans, Flake, and Dimick (1980)
United States	Cohort study	90	No age data	↓ ($p < .001$)	Milby and Whorton (1980)
Hong Kong	Andrology laboratory	15	20-40	↓ ($p < .001$)	Wang and Yeung (1980)
United States	Andrology laboratory	89	19-53	↓ ($p < .05$)	Meyer (1981)
Norway	Andrology laboratory	51	20-45	↓ ($p < .01$)	Aabyholm (1981)
United States	Andrology laboratory	132	No age data	↓ ($p < .01$)	Dougherty et al. (1981)
United States	Andrology laboratory	112	>35	↓ ($p < .05$)	Fariss et al. (1981)
Finland	Andrology laboratory	13	A. 25-53; B. 31-47	↓ ($p < .01$)	Frick, Danner, Joos, Kunit, and Luukkainen (1981)
United States	Andrology laboratory	34	No age data	↓ ($p < .005$)	Wyrobek, Brodsky, et al. (1981)
United States	Andrology laboratory	26	No age data	↓ ($p < .01$)	Wyrobek, Watchmaker, et al. (1981)
United Kingdom	Andrology laboratory	35	>25	↓ ($p < .01$)	Aitken, Best, Richardson, Djahanbakhch, and Lees (1982)
United States	Cohort study	90	21-45	↓ ($p < .05$)	Hamill et al. (1982)
United States	Infertility clinic	570	A. 22-30; B. 31-40; C. 41-50; D. >50	↔ (NS)	Benzi, Pastoris, and Dossena (1982)
United States	Independent sampling	4,435	21-45	↔	Tjoa, *Smolensky, His*, Steinberger, Smith (1982)
Israel	Infertility clinic	555	A. 31 (0.2); B. 54 (4.2)	↓ ($p < .05$)	Homonnai, Fainman, David, and Paz (1982)
Germany	Volunteers responding to advertisement	43	A. 29 (3.2); B. 67 (7.8)	↑ ($p < .05$)	Nieschlag et al. (1982)
Egypt	Andrology laboratory	45	19-53	↓ ($p < .01$)	Shaarawy and Mahmoud (1982)
France	Semen donors	809	A. 21-25; B. 26-30; C. 31-35; D. 36-40; E. 41-45; F. 46-50	↔ (NS)	Schwartz et al. (1983)
United States	Andrology laboratory	22	>40	↔	Borghi and Asch (1983)
United Kingdom	Andrology laboratory	38	20-45	↓ ($p < .01$)	Stanwell-Smith et al. (1983)
Sweden	Cohort study	63	21-50	↓ ($p < .01$)	Osser, Gennser, Liedholm, and Ranstam (1983)
Libya	Infertility clinic	1,500	20-45	↓ ($p < .01$)	Sheriff (1983)
Germany	Andrology laboratory	25	25-36	↓ ($p < .005$)	Wickings, Freischem, Langer, and Nieschlag (1983)
Brazil	Andrology laboratory	501	A. 24-29; B. 30-34; C. 35-39; D. 40-44; E. >45	↓ ($p < .05$)	de Castro and Mastrorocco (1984)
United States	Andrology laboratory	36	21-45	↔	Swanson, Mayer, Jones, Lanzendorf, and McDowell (1984)
United Kingdom	Andrology laboratory	47	23-50	↓ ($p < .001$)	Richardson, Aitken, and Loudon (1984)
Australia	Sperm donors	119	20-40	↔	Handelsman, Conway, Boylan, and Turtle (1984)
Israel	Andrology laboratory	12	20-45	↓ ($p < .05$)	Laufer, Margalioth, Navot, Shemesh, and Schenker (1985)

(continued)

Table 1. (continued)

Country	Population	Sample size (*n*)	Male age definition (range/mean/group, in years)	Direction of effect with increasing age	Study
United States	Andrology lab	9	No age data	↓ ($p < .05$)	Lewis, Brazil, and Overstreet (1984)
Greece	Cohort study	114	31.9	↓ ($p < .01$)	Panidis, Asseo, and Papaloucas (1984)
France	Andrology laboratory	52	No age data	↓ ($p < .05$)	Spira (1984)
United States	Cohort study	11	No age data	↓ ($p < .05$)	Ward et al. (1984)
United States	Cohort study	71	A. 31.6; B. 34.9	↓ ($p < .001$)	Rosenberg et al. (1985)
United States	Andrology laboratory	50	No age data	↓	Heussner, Ward, and Legator (1985)
Hong Kong	Family planning clinic	1,239	19-53	↔ (NS)	Wang et al. (1985)
Thailand	Andrology laboratory	307	19-50	↓ ($p < .05$)	Aribarg, Kenkeerati, Vorapaiboonsak, Leepipatpaiboon, and Farley (1986)
United States	Andrology laboratory	12	20-45	↓ ($p < .01$)	Levin, Latimore, Wein, and Van Arsdalen (1986)
United States	Andrology laboratory	42	A. 20-25; B. 50-55	↓	Rui, Thomassen, Oldereid, and Purvis (1986)
Nigeria	Cohort study	100	20-45	↓ ($p < .01$)	Osegbe, Amaku, and Nnatu (1986)
Germany	Cohort study	239	19-40	↔ (NS)	Vogt, Heller, and Borelli (1986)
Italy	Andrology laboratory	18	20-45	↓ ($p < .025$)	Assennato et al. (1987)
Hong Kong	Andrology laboratory	36	No age data	↓ ($p < .05$)	Chan and Wang (1987)
United States	Andrology laboratory	190	No age data	↔	Saaranen, Suonio, Kauhanen, and Saarikoski (1987)
United States	Andrology laboratory	43	No age data	↓ ($p < .05$)	Ratcliffe et al. (1987)
Libya	Cohort study	10	No age data	↓ ($p < .01$)	Sheriff (1987)
Tanzania	Andrology laboratory	120	19-55	↓ ($p < .01$)	Kirei (1987)
United Kingdom	Andrology laboratory	49	No age data	↓ ($p < .05$)	Barratt, Dunphy, Thomas, and Cooke (1988)
United States	Andrology laboratory	28	19-53	↔	Giblin, Poland, Moghissi, Ager, and Olson (1988)
Kuwait	Andrology laboratory	20	20-45	↓ ($p < .0001$)	Ibrahim, Moussa, and Pedersen (1988)
Denmark	Andrology laboratory	14	A. 20-62; B. 29-42	↔ (NS)	Rasmussen et al. (1988)
Denmark	Cohort study	68	No age data	↓ ($p < .05$)	Jelnes (1988)
United States	Andrology laboratory	40	19-53	↓ ($p < .01$)	Welch, Schrader, Turner, and Cullen (1988)
Brazil	Cohort study	12	20-50	↓ ($p < .01$)	Coutinho and Melo (1988)
United States	Cohort study	45	20-45	↓ ($p < .01$)	Schrader, Turner, Breitenstein, and Simon (1988)
United Kingdom	Cohort study	104	21-45	↓ ($p < .01$)	Badenoch, Evans, and McCloskey (1989)
Nigeria	Cohort study	20	19-53	↓ ($p < .001$)	Sobowale and Akiwumi (1989)
France	Andrology laboratory	1222	No age data	↓ ($p < .05$)	Pol, Beuscart, Leroy-Martin, Hermand, and Jablonski (1989)
United Kingdom	Andrology laboratory	15	21-39	↓ ($p < .01$)	Shrivastav et al. (1989)
Denmark	Cross-sectional study	54	A. 33.7; B. 30.6; B. 34.5	↓ ($p < .05$)	Bonde (1990)
Brazil	Andrology laboratory	1890	No age data	↓ ($p < .05$)	de Castro, Jeyendran, and Zaneveld (1990)
Israel	Sperm donors	1,283	34.3 (0.2)	↑ (NS)	Singer, Sagiv, Levinsky, and Allalouf (1990)

(continued)

Table 1. (continued)

Country	Population	Sample size (*n*)	Male age definition (range/mean/group, in years)	Direction of effect with increasing age	Study
China	Andrology laboratory	19	20-45	↓ ($p < .01$)	Zhong et al. (1990)
Germany	Andrology laboratory	25	Mean age 31.0	↔	Cooper, Jockenhövel, and Nieschlag (1991)
United States	Andrology laboratory	48	20-45	↓ ($p < .01$)	Eskenazi et al. (1991)
Nigeria	Andrology laboratory	21	19-24	↓ ($p < .05$)	Nnatu, Giwa-Osagie, and Essien (1991)
Canada	Andrology laboratory	20	No age data	↓ ($p < .05$)	Sugkraroek, Kates, Leader, and Tanphaichitr (1991)
France	Andrology laboratory	20	24-40	↓ ($p < .05$)	Vignon et al. (1991)
Germany	Andrology laboratory	42	20-40	↓ ($p < .01$)	Weidner, Jantos, Schiefer, Haidl, and Friedrich (1991)
United States	Andrology laboratory	10	No age data	↓ ($p < .01$)	Kolon, Philips, and Buch (1992)
United States	Andrology laboratory	142	No age data	↓ ($p < .05$)	Levine et al. (1992)
Libya	Cohort study	1,250	19-53	↓ ($p < .01$)	Sheriff and Legnain (1992)
Germany	Andrology laboratory	22	20-45	↓ ($p < .001$)	Noack-Fuller, De Beer, and Seibert (1993)
United Kingdom	Andrology laboratory	28	23-40	↓ ($p < .001$)	Wallace, Gow, and Hu (1993)
Denmark	Andrology laboratory	42	No age data	↓ ($p < .05$)	Fedder, Askjaer, and Hjort (1993)
Ireland	Andrology laboratory	10	No age data	↓ ($p < .05$)	Cottell and Harrison (1995)
Saudi Arabia	Andrology laboratory	50	No age data	↓ ($p < .05$)	el Shoura et al. (1995)
Germany	Older men planning further children	64	A. 32.2; B. 50.3	↓ ($p < .01$)	Haidl, Jung, and Schill (1996)
Spain	Assisted conception	345	A. ≤30; B. 31-40; C. 41-50; D. 51-64	↑ (NS)	Gallardo et al. (1996)
Germany	Infertility clinic	78	A. <30 (matched by year of attendance); B. <30 (matched by wives' ages); C. >50	↑ (NS)	Rolf, Behre, and Nieschlag (1996)
Finland	Sperm donors	5,719	28-40	↓ ($p < .05$)	Vierula et al. (1996)
Italy	Cohort study	50	20-45	↓ ($p < .001$)	Figa-Talamanca et al. (1996)
Denmark	Andrology laboratory	141	No age data	↓ ($p < .001$)	Jensen, Giwercman, Carlsen, Scheike, and Skakkebaek (1996)
United States	Cohort study	31	No age data	↓ ($p < .05$)	Weyandt, Schrader, Turner, and Simon (1996)
Israel	Sperm donors	188	18-53	↓ ($p < .0001$)	Benshushan, Shoshani, Paltiel, Schenker, and Lewin (1997)
Australia	Volunteers responding to advertisement	689	21-54	↓ ($p < .05$)	Handelsman (1997)
Denmark	Cohort study	1,055	20-30	↔ (NS)	Rasmussen, Erb, Westergaard, and Laursen (1997)
East cape province	Cohort study	400	>37	↓ ($p < .001$)	Robins et al. (1997)
United States	Assisted conception	821	A. ≤39; B. 40-49; C. ≥50	↔ (NS)	Spandorfer, Avrech, Colombero, Palermo, and Rosenwaks (1998)
Spain	Infertility clinic	20,411	31.9 (5.4); 15-74	↑ ($p < .004$)	Andolz, Bielsa, and Vila (1999)

(continued)

Table 1. (continued)

Country	Population	Sample size (*n*)	Male age definition (range/mean/group, in years)	Direction of effect with increasing age	Study
United States	Andrology laboratory	2,065	33.6 (5.8); 19-67	↓ ($p < .02$)	Centola and Eberly (1999)
Slovenia	Infertility clinic	2,343	21-45	↔	Zorn, Virant-Klun, Verdenik, and Meden-Vrtovec (1999)
Denmark	Sperm donors	1,273	A. ≤35; B. >35	↓ ($p < .0001$)	Gyllenborg, Skakkebæk, Nielsen, Keiding, and Giwercman (1999)
Denmark and Finland	Comparative clinical study	632	A. 20-35 (Danish); B. 22-47 (Finnish)	↓ ($p < .0001$)	Jensen et al. (2000)
Slovenia	Cohort study	444	A. ≤35; B. >35	↔ (NS)	Acacio, Gottfried, Israel, and Sokol (2000)
Australia	Sperm donors	448	18-40	↔ (NS)	Costello, Sjoblom, Haddad, Steigrad, and Bosch (2002)
Germany	Infertility laboratory	200	A. 21-25; B. >50	↓ ($p < .05$)	Jung, Schuppe, and Schill (2002)
Brazil	Cohort study	127	14-20	↓ ($p < .001$)	Mori, Cedenho, Koifman, and Srougi (2002)
United States	Fertility clinic	1,176	31.2	↓ ($p < .05$)	Eskenazi et al. (2003)
India	Cohort study	97	22-80	↓ ($p < .005$)	Marimuthu, Kapilashrami, Misro, and Singh (2003)
United States	Cohort study	551	25-59	↑	Chen et al. (2003)
United States	Cohort study	201	20-45	↓ ($p < .0001$)	Toft, Pedersen, and Bonde (2003)
Brazil	Infertility patients	889	A. ≤45; B. >45	↓	Pasqualotto, Sobreiro, Hallak, Pasqualotto, and Lucon (2005)
Denmark	Cohort study	551	≤35	↑	Carlsen, Swan, Petersen, and Skakkebæk (2005)
United States	Andrology laboratory	1,174	>45	↓	Hellstrom et al. (2006)
India	Andrology laboratory	368	25-59	↓	Pal et al. (2006)
Japan	Cohort study	324	25-40	↓ ($p < .0001$)	Iwamoto et al. (2006)
India	Infertility clinic	7,770	20-45	↓ ($p < .001$)	Adiga, Jayaraman, Kalthur, Upadhya, and Kumar (2008)
Nigeria	Infertility clinic	170	25-40	↓ ($p < .001$)	Ugwuja, Ugwu, and Ejikeme (2008)
Australia	Infertility clinic	225	>30	↓	Stewart et al. (2009)
Germany	Fertility center	320	A. <30; B. 30-35; C. 36-39; D. >40	↔ (NS)	Winkle, Rosenbusch, Gagsteiger, Paiss, and Zoller (2009)
Tunisia	Infertility clinic	2,940	20-45	↓ ($p < .001$)	Feki et al. (2009)
India	Andrology laboratory	3,729	A. 33; B. 35 (of two decades)	↓ ($p < .005$)	Mukhopadhyay et al. (2010)
Korea	Andrology laboratory	1,139	A. 19-27; B. >54	↓	Bahk, Jung, Jin, and Min (2010)
Argentina	Cohort study	9,168	20-77	↓ ($p < .05$)	Molina et al. (2010)
Netherlands	Periconceptional prospective cohort study	227	26-59	↓ ($p < .01$)	Hammiche et al. (2011)
Sweden	Andrology laboratory	511	25-40	↔ (NS)	Axelsson, Rylander, Rignell-Hydbom, and Giwercman (2011)
Australia	Infertility clinic	114	23-64	↓ ($p < .01$)	Giles et al. (2011)
Nigeria	Cohort study	106	20-45	↓ ($p < .01$)	Akande, Isah, Sekoni, and Pam (2011)

(continued)

Table 1. (continued)

Country	Population	Sample size (*n*)	Male age definition (range/mean/group, in years)	Direction of effect with increasing age	Study
Finland	Andrology laboratory	858	18-19	↓ ($p < .01$)	Jorgensen et al. (2011)
China	Andrology laboratory	104	A. <35; B. 35-39; C. ≥40	↔ (NS)	Nie et al. (2012)
Denmark	Danish one-center study	4,867	A. 18-19; B. >54	↑ ($p < .02$)	Jorgensen et al. (2012)
France	Andrology laboratory	10,932	A. ≤35; B. >35	↓ ($p < .05$)	Geoffroy-Siraudin et al. (2012)
Nigeria	Infertility clinic	316	20-40	↓ ($p < .05$)	Jimoh, Olawui, and Olaiya Omotoso (2012)
China	Infertility clinic	201	A. 20-40; B. 40-60; C. >60	↓	Diao et al. (2013)
India	Infertility clinic	100	A. ≤30; B. >30	↓	Jajoo and Kalyani (2013)
Brazil	Infertility clinic	2,300	33-39	↓ ($p < .001$)	Borges et al. (2013)
Japan	Cohort study	792	20-45	↓ ($p < .01$)	Iwamoto et al. (2013)
France	Cohort study	26,609	18-70	↓ ($p < .05$)	Rolland et al. (2013)
China	Fertility clinic	1,152	18-50	↓ ($p < .01$)	Tang et al. (2013)
United States	Infertility clinic	5,081	16.5-72.3	↓	Stone, Alex, Werlin, and Marrs (2013)
India	Fertility clinic	435	31-44	↓ ($p < .05$)	Nirupa et al. (2014)
United States	Cohort study	10,665	No age data	↓ ($p < .05$)	Belloc et al. (2014)
United States	Cohort study	11,935	Mean age 36.6	↓	Eisenberg et al. (2014)
Spain	Cohort study	992	25-40	↓ ($p < .05$)	Romero-Otero et al. (2015)
United States	Observational prospective cohort	501	Mean age 31.8	↓ ($p < .05$)	Eisenberg, Chen, Ye, and Buck Louis (2015)
China	Cohort study	1,213	No age data	↓	Tang et al. (2015)
Tunisia	Andrology laboratory	116	Males of mean age 32.74	↔ (NS)	Hadjkacem Loukil, Hadjkacem, Bahloul, and Ayadi (2015)

Note. Data are represented as mean (*SD*); ↓ = decrease; ↑ = increase; ↔ = no change; NS = not significant at $p < .05$; no p value indicates that no statistical testing was done.

nificant decrease reflecting the aging process that possibly affects spermatogenesis (Mahmoud et al., 2003).

Changes in sperm count can occur after occupational and environmental exposure to toxic agents (Dutta, Joshi, Sengupta, & Bhattacharya, 2013; Sengupta & Banerjee, 2014) or from predisposing factors of the host, such as age (Kidd, Eskenazi, & Wyrobek, 2001). The innumerable evidences, mostly from clinical studies, suggest that age is associated with all the concomitant factors, resulting in diminished sperm concentration (Spandorfer et al., 1998). Men at older ages (e.g., ≥50 years) were underrepresented in many clinical studies, which restricts statistical strength and prevents unveiling of the exact form of relationship between age and sperm concentration. In addition, potential confounders that might explain changes with age, such as smoking history or duration of abstinence, were hardly ever taken into consideration (Wyrobek et al., 1983).

A detailed scrutiny of diverse studies from specific cites reveals evidence of decline in sperm concentration, but a worldwide decline has not been demonstrated. It is arduous to execute a systematic, scientific study regarding the decline in human semen quality. Thus, the objective of the current review is to build up a substantial idea regarding alterations in sperm concentration in humans by picking the huge scattered reports of the past 35 years, molding them in sequential pattern, and statistically analyzing and correlating the worldwide declining sperm count trend with male fertility.

Data Extraction and Data Analysis

Research articles on humans published in English from 1980 through July 2015 were included in the current report. The authors also included 32 of 61 reports of the study by Carlsen et al. (1992), that is, reports from 1980 to 1992. The authors selected publications about sperm concentration with predefined criteria for inclusion and exclusion, as follows. (1) The non-Carlsen studies published during 1980 to July 2015 were identified by using Medical Subject Headings (MeSH) of electronic databases, which included Medline, National Library of Medicine, Bethesda, MD, with the following key words: sperm count, sperm density, sperm concentration, semen quality, male infertility, and semen analysis. (2) Relevant literature on changes of sperm concentration and its influence on future natural and assisted conception cycles were retrieved. (3) Data on subjects with clinical problems were been excluded. (4) Studies with insufficient numbers of subjects ($n < 5$) were excluded. In each case, sperm concentration and its outcome were evaluated. Analytic epidemiological studies were emphasized. Therefore, the current analysis was based on 138 studies published in from 1980 to 2015 (July). In the Results section, the relative changes in the outcome with age are represented. Whenever possible, the differences between younger men (i.e., ages ≤30 years) and older men (i.e., ages ≥50 years) were summarized. The authors also analyzed the correlation of age with mean sperm concentration obtained from the published studies with proper age data. For simple statistical analyses (calculation of mean sperm concentration, median values, and Box-and-Whisker plots), Microsoft Excel 2013 was used. Correlation and regression analyses of data were done using StatSoft (2011). Correlation coefficient was considered to be significant if p was <.05 or <.001 (Fisher & Yates, 1974). Mean sperm concentrations of all 138 reports were also analyzed with linear regression weighted by number of subjects included in the individual publications.

Description of Data

During the retrieval of relevant documents, the authors found a total of 138 studies that reported temporal decline in sperm concentration in the past 35 years. The outcomes of these studies are represented in Table 1. Most of the reports are based on andrology laboratories or assisted conception populations (44.20%) and epidemiological studies (28.26%), while others used volunteers recruited from sperm banks or advertisements (6.52%) and infertility clinics (16.67%). Among the 138 published research works discussed in this article from 1980 through 2015, most were carried out in Europe, North America, and Asia, while others were carried out in South America, Australia, and Africa. Most of the studies used sample sizes less than 500 subjects (68.12%) and ≥1,000 (21.01%), while a few studies used sample sizes between 500 and 1,000 subjects (10.87%). Five reports used an extraordinarily large sample size (>10,000; Andolz et al., 1999; Belloc et al., 2014; Eisenberg et al., 2014; Geoffroy-Siraudin et al., 2012; Rolland et al., 2013). Out of 138 reports, 80.43% provided data about the age of subjects. No significant alterations in sperm concentration was identified in 15.94% of the reports, only 3.62% reports identified a significant increase, and 80.43% reports identified a significant decrease in sperm concentration from 1980 to 2015. While only the reports identifying significant decrease were taken into consideration, it was observed that out of 111 studies, 23.42% of reports identified strong significance. The current report also enlisted interval studies published during the reporting period of the current article, which proclaims alterations in sperm concentrations during 1980 to 2015 (Table 2).

State of Affairs: Past 35 Years

Worldwide Variations

Mean sperm concentrations were obtained either directly from the published articles or in some cases arithmetic mean was calculated from median or geometric mean. Linear regression analysis identified a significant decrease between 1980 and 2015 from 91.65×10^6/mL to 39.34×10^6/mL ($r = -.313$, $p = .0002$). This reflected

Table 2. Summary of Interval Studies Reporting Decline in Sperm Concentration Published Within the Study Period of the Current Report.

Publication date	Author	Location	Study period	Sample size
1996	Irvine, Carwood, Richardson, MacDonald, and Aitken	Scotland	1984-1995	577
1996	De Mouzon et al.	France	1989-1994	7,714
1997	Berling and Wolner-Hanssen	Sweden	1985-1995	718
1997	Benshushan et al.	Israel	1980-1995	188
1998	Younglai et al.	Canada	1984-1995	48,968
1998	Bonde et al.	Denmark	1986-1995	1,196
1999	Zorn et al.	Slovenia	1983-1996	2,343
1999	Bilotta et al.	Italy	1981-1995	1,068
1999	Zhang et al.	China	1983-1996	9,292
2002	Costello et al.	Australia	1983-2001	448
2003	Almagor et al.	Israel	1990-2000	2,638
2003	Chen et al.	United States	1989-2000	551
2003	Marimuthu et al.	India	1990-2000	97
2003	Vicari et al.	Italy	1982-1999	716
2005	Lackner et al.	Austria	1986-2003	7,780
2007	Sripada et al.	Scotland	1994-2005	4,832
2008	Liang et al.	China	1980-2005	5,834
2009	Feki et al.	Tunisia	1996-2007	2,940
2010	Molina et al.	Argentina	1994-2004	9,168
2012	Geoffroy-Siraudin et al.	France	1988-2007	10,932
2012	Haimov-Kochman et al.	Israel	1995-2009	2,182
2013	Menidola et al.	Spain	2001-2011	273

almost a 57% decline in sperm count worldwide from 1980 (Figure 1A). The current study also identifies that recruitment of a larger population for this type of study increased predominantly after 1995.

Median values of sperm concentrations were calculated in seven different intervals (from 1980-1985 to 2010-2015). The median value was reported to be 71.6×10^6/mL during the study period. These values are plotted in the Box-and-Whisker plot in Figure 1B, which also identifies a significant decline from 1980-1985 to 2010-2015 ($y = -3.92x + 87.72$, $R^2 = .460$).

Regional Variations

Recent studies on the male reproductive system bring conflicting evidence to the forefront regarding sperm counts, with some reporting significant decline while some have reported no change. North America, Europe, Asia, and Africa are more prone to a declining trend of sperm counts over the years, whereas studies based in South America and Australia do not depict such a trend (Figures 2 and 3). An overview of the sperm counts obtained from data produced by various regions of the world is reported in Figure 1, which identifies that there was a significant decline in sperm concentrations from 1980 to 2015. However, a striking feature of much of the data is the surfacing of regional differences in semen quality. It has been suggested that these regional differences in sperm counts possibly are biologically meaningful. Most of the controversies that have aroused from past clinical studies about semen quality may be partly due to involvement of only few selected groups of men. In many studies, historical data collected for other purposes have been used without close attention to important and specific factors relevant to an analysis of secular or geographical trends.

North America. Numerous studies conducted in the United States have demonstrated a declining trend of mean sperm concentration in different regions over the years 1980 to 2015 ($r = -.435$, $p = .007$; Figure 2A). Data on sperm counts procured from several studies from 1938 to 1980 (following the report of Saidi et al., 1999) also depicts a significant decrease in sperm count ($r = -.635$, $p = .004$) in North American men until 1980. Thus, from these two findings it can be resolved that North American states are going on with the trend of declining sperm counts from 1938 until 2015. The authors also evaluated the mean sperm concentrations in 1980-1985 and 2010-2015, which identified a 36.49% decline in sperm concentration over the last 35 years (Figure 2C). The current study also compares the mean sperm concentrations of 2015 with the report of Carlsen et al. published in 1992. It reveals an additional 28.25% decline in mean sperm concentration after 1992 in North American men (Figure 2E).

Various scattered reports were brought under one analytical review by Saidi et al. (1999) using 29 studies based in the

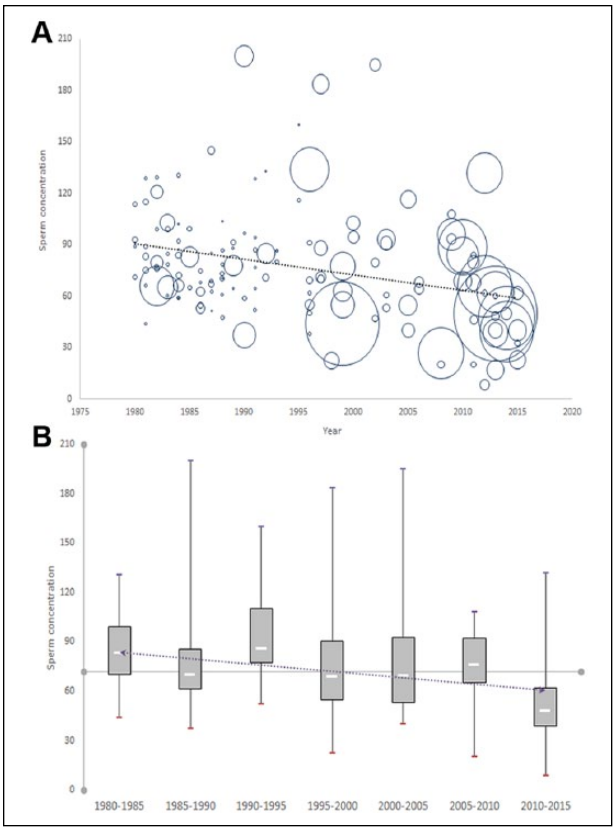

Figure 1. (A) Temporal decline in sperm concentration ($\times 10^6$/mL) ($r = -.313$, $p = .0002$, $R^2 = .098$); bubble size corresponds to the number of men in study. (B) Changes in sperm concentrations from 1980 to 2015 shown as Box-and-Whisker plots. White bands indicate the median values for each duration. The *Y*-intercept shows median (71.6×10^6/mL), and the regression band ($y = -3.92x + 87.72$, $R^2 = .460$) indicates significant decline from 1980 to 2015.

United States from 1938 to 1996, which analyzed semen of 9,612 fertile men. The mean sperm concentrations of selected geographic locations were determined with analysis of variance (ANOVA), and any alterations were gauged with time using linear regression analysis. From that study, it was perceptible that New York had the highest value for mean sperm concentration as compared to the other sates of the United States (as also reported by Fisch & Goluboff, 1996). It can be explained through Figure 2F, which attempts to describe the variations in sperm count among states in North America and also indicates that New York and Connecticut have the highest sperm count in the United States. Thus, sperm concentrations were reported to vary with geographical areas in the United States, the maximum being that of New York whose exact reason is yet to be identified, but factors like climate, socioeconomic status, ethnicity, and other environmental and social factors should be considered.

South America. Only a handful of studies have been conducted involving regions of South America to assess the trend of declining, increasing, or static sperm counts as well as changes of the same from place to place across the continent (Borges et al., 2013; Oliva, Spira, & Multigner, 2001; Pasqualotto et al., 2005; Tortolero et al., 1999). A study in Venezuela, carried out on the male partners of infertile couples, suggested that the proportion of men presenting azoospermia or oligospermia showed no change from 1981 and 1995 (Tortolero et al., 1999). Studies also focused on the impact of chemical exposures on various characteristics of sperm among the populations of male partners of infertile couples during the period 1995 to 1998 in the southern coastal region of Argentina (Oliva et al., 2001).

Studies retrieved during the current analysis identified that most of the reports were from Brazil and Argentina. These reports indicated no such significant alteration in sperm count in South American men ($r = -.155$, $p = .688$; Figure 2B). The mean sperm concentrations have declined from 66×10^6/mL to 63.4×10^6/mL, which is only 4.22% relative to that of 1980 (Figure 2D). A presumption about the role of environmental and occupational factors on male reproductive health can be drawn through the above-mentioned studies (Oliva et al., 2001; Tortolero et al., 1999) and the declining trend of the sperm count (though not significant at p of .05). For example, agricultural zones of South America are cursed by exposure to organochlorine pesticides and other endocrine disruptors, which might be more detrimental to fertility in the coming years.

Europe. Europe is a continent of geographic diversities. The current report included 50 studies carried out from 1980 to 2015. Most of these were conducted in the United Kingdom, France, Denmark, and Finland. The analysis revealed a significant decline in sperm concentrations over time ($r = -.307$, $p = .02$; Figure 3A), and the mean sperm concentration have declined more than 39% compared to 1980 (Figure 3A). Among the European countries, the United Kingdom and Denmark had the maximum sperm concentrations, while Spanish men were reported to have the least sperm counts. Similar cross-sectional studies were performed by Møller and Skakkebæk (1999) and Skakkebæk et al. (1998) to investigate the possible geographical differences in sperm count, involving subjects who were male partners of pregnant women from Denmark, France, Scotland, and Finland and young men from the general populations in Denmark, Norway, Finland, Estonia, and Lithuania. These studies identified a significantly better semen quality in Finland, Estonia, and Lithuania from which an East-West gradient is revealed in the European area. A major factor that has an immense impact on sperm count is seasonal changes, which is evident from the fact that sperm count differed by about 30% in summer from that in winter in all the four countries. This fact is also supported by all other previous studies, some including men of known fertility and some of known subfertility, which observed seasonal variations in

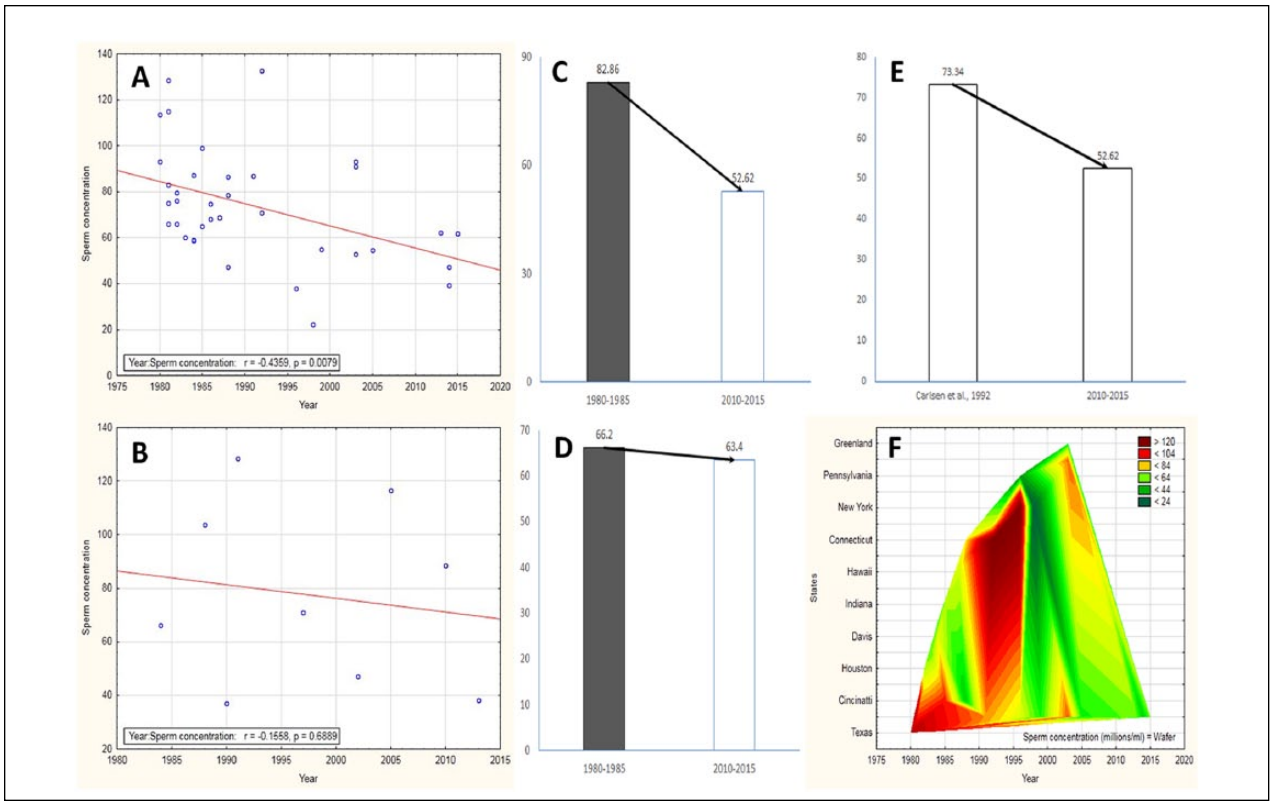

Figure 2. (A) Correlation plot shows significant decline in sperm concentration in North America ($r = -.435$, $p = .007$), but no such alteration in South America (B). It has decreased 36.49% in North America (C) and only 4.22% in South America (D) from 1980 to 2015. A comparative overview of Carlsen et al., 1992 and this study reveals a further 28.25% decline after that report in North America (E). Wafer plot reveals that New York and Connecticut have the highest sperm count (F).

sperm count being lowest during the summer and highest during autumn or winter (Gyllenborg et al., 1999; Maier, Newbold, & McLachlan, 1985; Spira, 1984; Tjoa et al., 1982). There are a few studies that could not detect any seasonal variations (e.g., Mallidis, Howard, & Baker, 1991).

Time trends in semen quality are interestingly related with almost identical patterns in the occurrence of testicular cancer, which is rising worldwide. It was reported that the incidence of this disease is five times higher among Danish men than it is among Finnish men (Adami *et al.*, 1994; Forman & Møller, 1994), while in the previously discussed study the former had a much better sperm count. Such inverse relationship between sperm count and the risk of testicular cancer is not only apparent from the cohort studies but is also observed in individuals (Møller & Skakkebæk, 1999). This could also be supported by the study that predicts that men born in Scandinavia during the Second World War had a comparatively lower risk of developing testicular cancer in adult life than men who were born before or after the war (Adami et al., 1994; Møller & Skakkebæk, 1999). Sperm counts are thought to decline with a more recent year of birth as is suggested by a couple of studies (Irvine et al., 1996; Skakkebæk et al., 1998), for which a possible causative agent could be exogenous factors that interfere with the functions and multiplication of the fetal Sertoli cells resulting in a syndrome of reduced sperm count, hypospadias, undescended testis, and testicular cancer (Bergman, Brandt, & Brouwer, 1996; Sharpe & Skakkebæk, 1993). In this respect, it is noteworthy that the gradient in the incidence of hypospadias between Denmark and Finland is apparently parallel to the gradient of the testicular cancer in these regions (Toppari et al., 1996). Thus, it can be concluded that European cities suffer from robust variations in sperm count, which is even related to sperm production and testicular cancer. These variations might be due to differences in life styles, environmental factors, endocrine disruptions, or other factors.

Asia. Most of the Asian studies were carried out in China (Diao et al., 2013; Nie et al., 2012; ; Tang et al., 2013; Tang et al., 2015; Wang et al., 1985) and India (Jajoo & Kalyani, 2013; Marimuthu et al., 2003; Mehta, Makwana, Ranga, Srinivasan, & Virk, 2006; Mukhopadhyay et al., 2010; Pal et al., 2006), and a few in Japan (Iwamoto et al., 2013), Israel (Benshushan et al., 1997; Homonnai et al., 1982; Laufer et al., 1985; Singer et al., 1990), and Saudi Arabia (el Shoura et al., 1995).

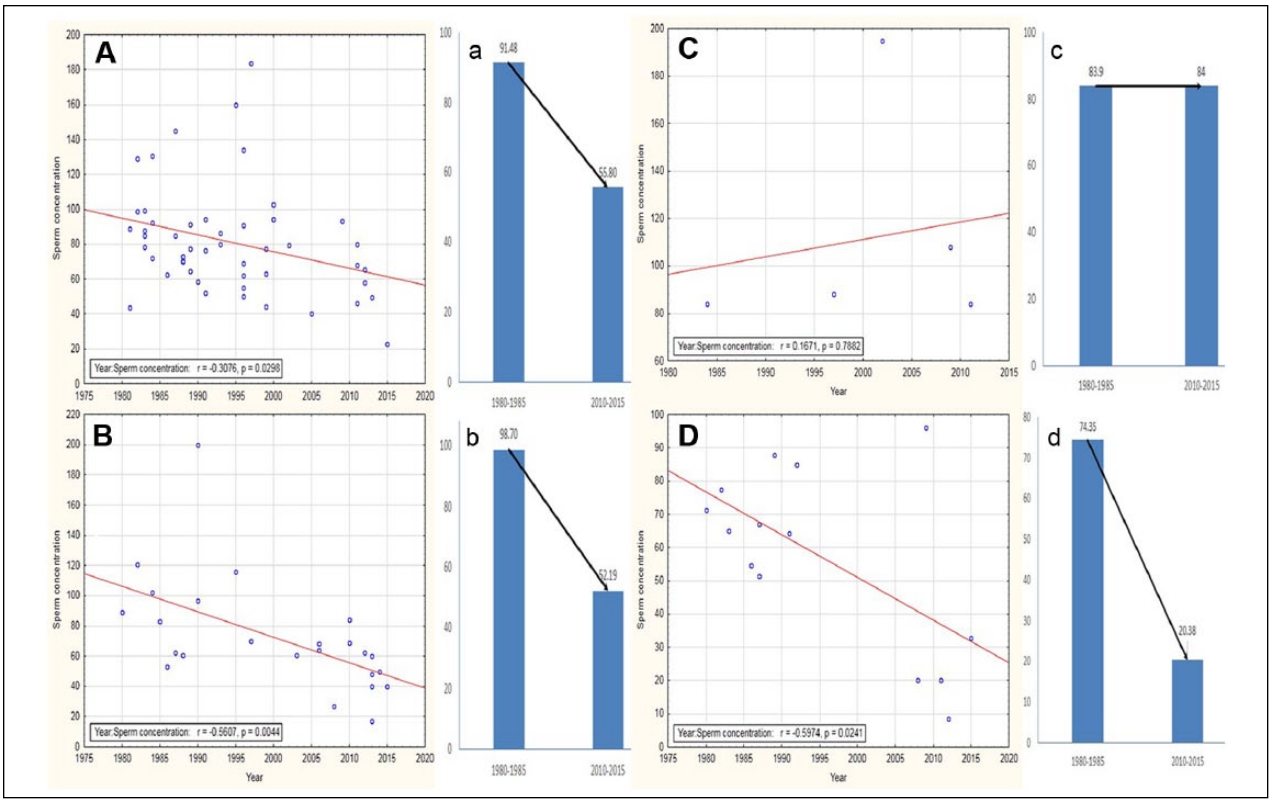

Figure 3. (A) Correlation plots of non-American continents showed significant reduction in sperm concentrations in Europe ($r = -.307$, $p = .02$) (A), Asia ($r = -.560$, $p = .004$) (B), and Africa ($r = -.597$, $p = .02$) (D), while Australia showed an increasing trend in sperm concentration over time ($r = .167$, $p = .788$) (C). Mean sperm concentrations reflected similar trends (a-d).

In 1980, Wang and Yeung first reported a decline in sperm count in Chinese men. Later, numerous studies reported similar observations (Diao et al., 2013; Nie et al., 2012). In Japan, studies on altering sperm concentrations in males are scarce. Thus, very limited information could be gathered regarding male reproductive status. A severe declining trend or variations in sperm quality has been reported by few cross-sectional studies in Japan (Iwamoto et al., 2013). India has a medley of cultures, religions, life styles, and most importantly geographic and climatic diversities according to which the physical attributes of the people belonging to each region have been molded. Therefore, variations in physicality and thereby reproductive health status of men are most likely to occur among different regions of this country. Not many studies have been done to analyze such predictions (Jajoo & Kalyani, 2013; Marimuthu et al., 2003; Mukhopadhyay et al., 2010; Pal et al., 2006). However, a relevant study was conducted in laboratories at five different cities, namely, Bangalore, Kurnool, Mumbai, Jalandhar, and Jodhpur, using sperm samples from male partners of infertile couples. Samples were analyzed for sperm concentrations using standardized methods recommended by the World Health Organization (WHO). The outcome of the study suggested that prevalence of both azoospermia and oligozoospermia was highest in Kurnool, being 38.2% and 51%, respectively. The observation from the mean sperm counts in normospermic men depicts lower values for the metropolitan cities like Mumbai and Bangalore than other small cities (Mehta et al., 2006).

Current analysis reveals a similar trend of declining sperm count in males based in Asia, which is similar to the U.S. and European countries. The current report identifies a significant decline in mean sperm concentration (47.12%) from 1980 to 2015 ($r = -.560$, $p = .004$; Figure 3B-b). This may be attributable to lifestyle, food habits, and the extensive use of fertilizers in cultivation. Gui-Yuan, Meng-Chun, Jin-Lai, and Wen-Qing (1989) demonstrated that a probable cause of such declining sperm concentrations in India might be due to extensive use of Gossypol (a phenol compound isolated from the seeds, stems, and roots of the cotton plant) and other pesticides.

Africa. In 1991, the WHO had estimated that almost 20 to 35 million couples were infertile in Africa. Nigeria is suggested to have been suffering from highest infertility problems among the other African regions, with the male infertility factor accounting for 40% to 50%. The degree of infertility and its cause vary from place to place. This is evident from the study pursued in mid-western Nigeria,

which reported that about 50% of the 780 couples under evaluation differed in the causes of their infertility (Okonofua, Menakaya, Onemu, Omo-Aghaja, & Bergstrom, 2005). A study associated with south-western Nigeria had reported that 42.4% of infertility resulted from the male factor (Ikechebula, Adinma, Orie, & Ikegwuonu, 2003).

In the current analysis, the authors identified that most of the studies on sperm count in Africa was carried out in Nigeria (Akande et al., 2011; Jimoh et al., 2012; Lapido, 1980; Nnatu et al., 1991; Osegbe et al., 1986; Sobowale & Akiwumi, 1989; Ugwuja et al., 2008). A time-dependent decline in sperm concentration was observed from 1980 to 2015 ($r = -.597$, $p = .02$; Figure 3D) that reflected an overall 72.58% decrease in sperm concentration (Figure 3D-d). It is thus understandable that regional variations in reproductive status prevails in Africa and the high rates of male infertility in Nigeria is thought to be due to infections, sexually transmitted diseases, and hormonal abnormalities (Akinloye, Grommok, Nieschlag, & Simoni, 2009; Emokpae, Uadia, Omale-Itodo, & Orok, 2007).

The organochlorine pesticide DDT (1,1,1-trichloro-2,2-bis (chlorodiphenyl)ethane) is one of the most persistent organic pollutants that is known to be toxic, persistent, and bioaccumulative and has been used for malaria vector in South Africa since 1945. According to a cross-sectional study in an endemic malaria area (Limpopo Province, South Africa), DDT concentrations and sperm counts were negatively correlated among African men (Jager, Aneck-Hahn, Bornman, Farias, & Spanò, 2012). Therefore, sperm counts vary in different regions of Africa based on environmental factors, chemicals, and infections that each region offers.

Australia. There are very few reports on changes in sperm count of Australian men. In 1984, the report of Handelsman et al. about the semen quality of sperm donors first predicted that there is no alteration in the sperm count of Australian men. Later, several studies reported no alteration in semen quality (Costello et al., 2002; Stewart et al., 2009). In the current analysis, the authors identified a mild increase in sperm concentration from 1980 to 2015 ($r = .167$, $p = .788$; Figure 3C) that reflected 0.11% increase in sperm concentration in Australian men (Figure 3C-c).

Links With Possible Factors

These observed trends in sperm concentration might be linked to the effects of environmental factors, including endocrine disruptors. They might also be linked to other known semen altering factors, like an increase in body mass index (BMI), stress, nutrition, or sometimes systemic pathologies, such as diabetes, cancer, or systemic infection. In previous reports, the authors mentioned various environmental, occupational, and lifestyle factors that can alter sperm count (Dutta et al., 2013; Sengupta & Banerjee, 2014; Figure 4). In addition, aging increases the risk of oxidative stress and other systemic diseases, which can also contribute to a reduction in sperm count ($R^2 = .979$, $p > .001$).

Environmental and Lifestyle Factors: Direct Action on Spermatogenesis

Since 1961, dibromochloropropane (DBCP), a nematocide employed on various tropical crops, has been known to affect testicular functions. Torkelson (1961) reported that DBCP caused testicular atrophy in laboratory animals. Later, in 1977, Whorton, Krauss, Marshall, and Milby published an article that reported DBCP had rendered thousands of agricultural workers sterile in many countries worldwide. Since that report, many other chemical substances have been reported to have the potential to decrease sperm count in men (Bonde, 1996). These substances include pesticides such as ethylene dibromide (Ratcliffe et al., 1987) and carbaryl (Wyrobek, Watchmaker, et al., 1981), solvents such as glycol ethers (Welch et al., 1988), carbon disulfide (Lancranjan, 1972), and 2-bromopropane (Kim et al., 1996; Table 3), and heavy metals (Lancranjan, Popescu, Gavanescu, Klepsch, & Serbanescu, 1975; Sengupta, 2013; Sengupta, 2014b; Sengupta, Banerjee, Nath, Das, & Banerjee, 2015; Table 4). Along with these agents, thousands of chemicals should be included with experimental evidence that have demonstrated testicular toxicity in animals but for which data are not available for humans (Bonde, 1996; Łepecka-Klusek, Wdowiak, Pilewska-Kozak, Syty, & Jakiel, 2011; Sundaram & Witorsch, 1995). Rosenstock, Liptzin, Six, and Tomich (2013) reported a significant increase of pesticide use from 1980 to 2010 proclaiming that these chemicals play a pivotal role in declining sperm count in different age groups of males. Among thousands of chemicals that we are exposed to environmentally or occupationally, very few have been evaluated for reproductive toxicity, specifically in various age groups of men. It is known that the susceptibility to this chemical assault increases with age.

Besides chemical assault, researchers must also consider physical factors like ionizing radiation and heat. Spermatogenesis requires the temperature in the scrotum to be at least 3°C lower than body temperature. An increase in scrotal temperature disturbs spermatogenesis (Mieusset, Bujan, Mansat, Grandjean, & Pontonnier, 1991). Prolonged exposure to sources of radiant heat may lead to significant changes in sperm concentrations (Figa-Talamanca et al., 1992; Thonneau, Bujan, Multigner, & Mieusset, 1998). Other physical agents, such as high-frequency electromagnetic fields, may also affect testicular function (Weyandt et al., 1996; Table 5). As the use of cell phones, laptops, and Wi-Fi has increased tremendously in past three decades (Lenhart, Purcell, Smith, & Zickuhr, 2010), the possibility of radiation-induced decline in sperm count increases.

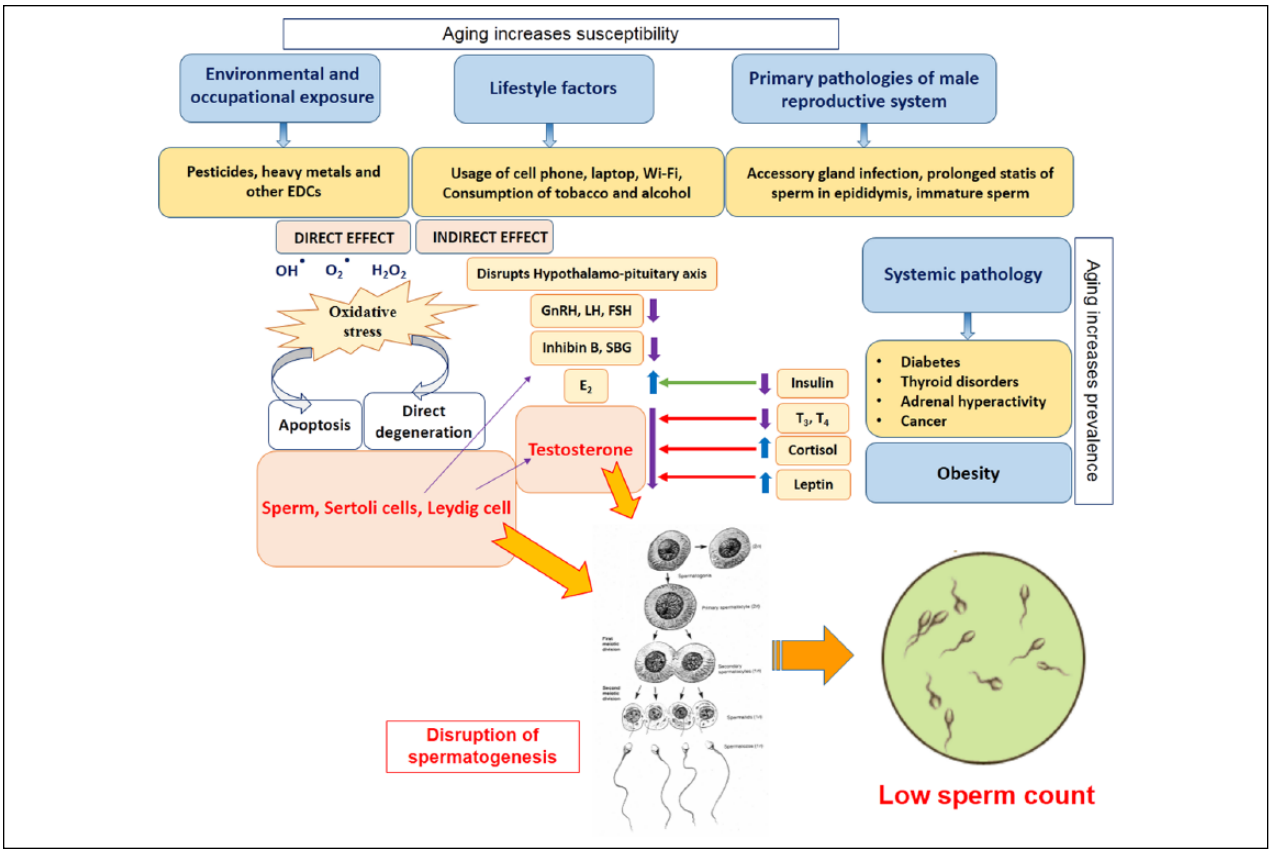

Figure 4. Possible mechanism of action of environmental toxicants, lifestyle factors, obesity, and systemic diseases in lowering sperm count in ageing male (red arrows show inhibition, blue arrows show stimulation, purple arrows indicate decrease, and blue arrows indicate increase in hormone levels).

Finally, the effects of regular consumption of tobacco or alcohol, both of which are on the brink of disturbing spermatogenesis, should not be ignored (Bonde, 1996; Multigner & Spira, 1997). Stress, which is very hard to assess, has also been set forth as a factor that may have a negative impact on sperm production (Fenster et al., 1997; Negro-Vilar, 1993). In a report of the Royal College of Physicians (2012), researchers documented a massive change in consumption of tobacco from 1962 to 2007. They described an increase in tobacco consumption from 1962 to 2000 and a gentle fall from 2000 to 2012. They also recorded that this decrease is prevalent in the United Kingdom and other European countries, but in the rest of the world there are no data of decreasing active or passive consumption, specifically in developing countries, which could be related to the worldwide decrease in sperm count even in 2015. Another relevant Federal Survey (2013) reported that males in the 18 to 35 years age group are mostly addicted to tobacco consumption, followed by the age group of 35 to 60. This is of great concern in relation to declining sperm counts in aging males.

Major alterations in sperm counts have been observed in populations following changes in other diverse factors, such as catastrophes. The Kobe earthquake decreased sperm count of local men significantly (Fukuda, Fukuda, Shimazu, Yomura, & Shimizu, 1996). Clearly, a large number of environmental factors are likely to affect spermatogenesis in humans. However, most of the studies cited above were carried out in a professional environment in circumstances in which the level of chemical and physical exposure is generally high. This accounts for a nonnegligible proportion of the adult male population. In addition, given the widespread use of chemical substances in particular, it is legitimate to raise questions concerning the consequences for the general population of their accidental or deliberate release into the environment.

Effect of Endocrine Disruptors

There are numerous reports that identify the role of endocrine disrupting chemicals (EDCs) for secular changes in sperm count. These EDCs are liable to have adverse effects on individual organisms through primary effects on endocrine systems. These substances, via their estrogenic or anti-androgenic activities, are likely to hinder testicular development in the fetus and the postnatal functions of the testes (Sharpe, 1993). In 1938, estrogenic activity for a range of man-made chemicals was first documented

Table 3. Studies on Pesticides and Sperm Concentration of Past Two Decades.

Study	Compound	Subjects	Age	Compound concentration	Sperm concentration ($\times 10^6$ cells/mL)
Ayotte et al. (2001)	*p,p′*-DDE	24 Healthy males	16-28	77.9 mg/g lipid	Decreased $p < .05$
Duty et al. (2003)	MBP	168 Male partners of subfertile couples	36	16.1 ng/mL	Decreased $p < .05$
	MEP			175.5 ng/mL	No change
	MEHP			7.6 ng/mL	No association
Rignell-Hydbom et al. (2005)	*p,p′*-DDE	195 Healthy males	24-65	240 ng/g lipid (80-887)	No change
Charlier and Foidart (2005)	*p,p′*-DDE	73 Healthy males	25	1.05 µg/g lipid	No change
Hauser, Williams, Altshul, and Calafat (2005)	MBP	463 Male partners of subfertile couples	36	17.3 ng/mL	Decreased $p < .05$
	MEP			180 ng/mL	No association
	MEHP			8.0 ng/mL	No association
	MMP			3.6 ng/mL	No change
	p,p′-DDE			220 ng/g lipid (72.5-7776)	No relationship
Pant et al. (2008)	DEP	300 Healthy males	29	0.64-3.11 µg/mL	Decreased $p < .05$
	DBP			0.18-1.65 µg/mL	Decreased $p < .05$
Wirth et al. (2008)	MEP	45 Male partners of subfertile couples	35	121.9 ng/mL	Decreased $p < .05$
	MBP			26.9 ng/mL	No association
	MMP			1.1 ng/mL	No change
	MEHP			11.5 ng/mL	No association
Mendiola et al. (2010)	BPA	375 Male partners of pregnant women	18-53	1.5 µg/L	No association
Meeker et al. (2010)	BPA	190 Males from infertility clinic	36	1.3 ng/mL	Decreased $p < .05$
Li et al. (2011)	BPA	218 Healthy males	No data	1.6-5.9 mg/L	Decreased $p < .05$
Knez, Kranvog, Breznik, Voncina, and Vlaisavljevic (2013)	BPA	142 Male partners of subfertile couples	34	1.55 ng/mL	Decreased $p < .05$
Jurewicz et al. (2013)	MEP	269 Males from infertility clinic	32	153.6 µg/mL	No alteration

Note. MBP = mono-*n*-butyl phthalate; MEP = mono-ethyl phthalate; MMP = mono-methyl phthalate; MEHP = mono-2-ethylhexyl phthalate; BPA = biphenol-A; DBP = di-*n*-butyl phthalate; DEP = di-ethyl phthalate; *p,p′*-DDE = *p,p′*-Dichlorodiphenyldichloroethylene.

(Dodds & Lawson, 1938). Since the 1960s, it has been known that synthetic compounds such as the chlorinated insecticides methoxychlor and DDT and polychlorinated biphenyls (PCBs) may have estrogenic activity in laboratory animals (Bitman, Cecil, Harris, & Fries, 1968; Tullner, 1961). It has been known for some time that some xenobiotics may act in a similar way to hormones (xenohormones), thereby affecting endocrine regulations. The list of chemical substances with hormonal activity in vitro or in vivo has not stopped growing in the past few decades. In addition to those already mentioned, they include insecticides (lindane), fungicides (vinchlozoline), surfactants (alkylphenols), plastics (bisphenol-A, phthalates), and industrial by-products (dioxins; reviewed in Colborn, Vomsaal, & Soto, 1993; Toppari et al., 1996). Experiments in vivo in laboratory animals have identified that the administration of methoxychlor, octylphenol, butyl phthalate, or dioxin during gestation or lactation causes a significant decrease in sperm production in the adult (Gray, 1982; Mably, Bjerke, Moore, Gendron-Fitzpatrick, & Peterson, 1992; Sharpe, Fisher, Millar, Jobling, & Sumpter, 1995). Several observations support the idea that EDCs may be involved in changes of sperm quality in humans and that these disrupting effects increase with the progression of age. Thus, the trend of declining sperm counts in aging males from 1980 to 2015 may be attributed to the persistently increased exposure of these EDCs.

Obesity Can Affect Spermatogenesis

The association between high adiposity and alterations in sperm count has not been clearly demonstrated in men. Data from large-scale epidemiological studies suggest an elevated risk for infertility among couples when the male

Table 4. Studies on Heavy Metals and Sperm Concentration.

Agent	Study	Concentration of agent in seminal plasma	Sperm concentration ($\times 10^6$ cells/mL)	Criteria
Lead	Hovatta et al. (1998)	2.5 µg/dL	96 × 10^6 cells/mL	1992 criteria
	Telisman et al. (2000)	36.7 µg/dL	Decreased $p < .05$	1987 criteria
	Hernández-Ochoa et al. (2005)	0.2 µ/dL	11 × 10^6 cells/mL	1999 criteria
	Meeker et al. (2008)	1.5 µg/dL	42.7 × 10^6 cells/mL	1999 criteria
	Fatima et al. (2010)	>40 µg/dL	≥20 × 10^6 cells/mL	1999 criteria
	Mendiola et al. (2011)	2.93 µ/dL	≥20 × 10^6 cells/mL	1999 criteria
Cadmium	Hovatta et al. (1998)	0.15 µ/dL	96 × 10^6 cells/mL	1992 criteria
	Akinloye, Arowojolu, Shittu, and Anetor (2006)	65 µg/dL	42.7 × 10^6 cells/mL	1999 criteria
	Meeker et al. (2008)	0.04 µ/dL	42.7 × 10^6 cells/mL	1999 criteria
	Benoff et al. (2009)	0.028 µ/dL	Decreased $p < .05$	1992 criteria
	Mendiola *et al.* (2011)	0.10 µ/dL	≥20 × 10^6 cells/mL	1999 criteria
Mercury	Choy et al. (2002)	40.6 mmol/L	≤20 × 10^6 cells/mL	1999 criteria
	Rignell-Hydbom (2007)	0.225 µg/dL	48 × 10^6 cells/mL	1999 criteria
	Mendiola et al. (2011)	1.99 µg/dL	≥20 × 10^6 cells/mL	1999 criteria

Table 5. Reports on Cell Phone Usage and Sperm Concentration.

Study	Sample size	Age (years, mean ± *SD*)	Exposure	Sperm concentration ($\times 10^6$/mL)
Fejes, Závaczki, et al. (2005)	371	30.8 ± 4.4	[Retrospective] Two groups: low transmitters (<15 min/day), high transmitters (>60 min/day)	Decreased sperm count (and motility)
Erogul et al. (2006)	27	Males of reproductive age	RF-EMR 900 MHz for 5 min	Significantly decreased ($p < .05$) sperm count (motility, morphology, and viability)
Wdowiak, Wdowiak, and Wiktor (2007)	304	Males of reproductive age visiting infertility clinic	[Retrospective] three groups: No cell phone use, sporadic cell phone use over last 1-2 years, regular cell phone use for more than 2 years	Decreased sperm count (motility, morphology and viability)
Agarwal, Deepinder, Sharma, Ranga, and Li (2008)	361	31.81 ± 6.12	[Retrospective] Four groups: no use, little use (<2 h), mid use (2-4 h), high use (>4 h)	Decreased sperm count (motility, morphology and viability)
Falzone et al. (2008)	NA	NA	RF-EMR 900 MHz at 2 W/kg and 5.7 W/kg SAR. Incubated for 21°C for 16 h	Significantly decreased sperm count
De Iuliis, Newey, King, and Aitken (2009)	22	24.1 ± 1.1	RF-EMR 1.8 GHz at 0.4 W/kg to 27.5 W/kg SAR. Incubated for 21°C for 16 h	Decreased sperm count (motility and viability)
Agarwal et al. (2009)	32	28.2 ± 4.1	RF-EMR 850 MHz at 1.46 W/kg. Exposed at distance of 2.5 cm for 60 min	Decreased sperm count (motility and viability), increased ROS level
Falzone, Huyser, Franken, and Leszczynski (2010)	12	Males of reproductive age (healthy non-smoking donor)	RF-EMR 900 MHz at 2 W/kg and 5.7 W/kg SAR. Incubated for 21°C for 16 h	Significantly decreased ($p < .05$) sperm count, increased ROS level
Falzone, Huyser, Becker, Leszczynski, and Franken (2011)	12	31.8 ± 12.5	RF-EMR 900 MHz for 60 min	Significantly decreased ($p < .05$) sperm count

Note. RF-EMR = radiofrequency-electromagnetic radiation; SAR, specific absorption rate.

partner is overweight or obese (Nguyen, Wilcox, Skjaerven, & Baird, 2007; Ramlau-Hansen et al., 2007; Sallmen, Sandler, Hoppin, Blair, & Baird, 2006). Several studies have reported an inverse correlation between BMI and sperm concentration or total sperm count (Jensen et al., 2004; Paasch, Grunewald, Kratzsch, & Glander,

2010), but other reports have failed to document this relationship (Aggerholm, Thulstrup, Toft, Ramlau-Hansen, & Bonde, 2008; Duits, van Wely, van der Veen, & Gianotten, 2010). The current report collected data from the past few decades regarding the association between BMI and sperm concentration and identified that overweight and obesity were associated with an increased risk of oligozoospermia or azoospermia (Table 6).

Regarding the correlation between obesity and alteration of sperm concentration, different hypotheses have been raised. First, alterations of the hypothalamo-

pituitary-gonadal axis have been reported to be involved in this process. Aromatization of steroids to estrogens in peripheral tissues leads to the hypogonadotropic hyperestrogenic hypogonadism previously described in obese men (Schneider, Kirschner, Berkowitz, & Ertel, 1979), with a significant decline in total and free testosterone levels (with increased leptin) and increase in estradiol (E_2), both leading to deleterious effects on spermatogenesis. Moreover, reports have identified a decrease of sex hormone-binding globulin among obese men, notably mediated by hyperinsulinemia, emphasizing the negative feedback effect of elevated total E_2 levels (Stellato, Feldman, Hamdy, Horton, & McKinlay, 2000). Obesity is also associated with an increase of endorphins, leading to a both lower LH pulse amplitude and GnRH production (Bhattarai, Chaudhuri, Bhattacharya, & Sengupta, 2014; Bhattarai, Bhattacharya, Chaudhuri & Sengupta, 2014; Blank, Clark, Heymsfield, Rudman, & Blank, 1994; Dutta et al., 2013; Krajewska-Kulak & Sengupta, 2013). In an earlier report, the authors described that the role of thyroid hormones in men can also contribute to decreased sperm count (Krajewska-Kulak & Sengupta, 2013). A decreased level of circulating triiodo-thyronine (T_3) may affect testicular production of testosterone, and thus affects spermatogenesis (Krajewska-Kulak & Sengupta, 2013). Some authors have also reported that obesity may directly alter spermatogenesis and Sertoli cell function (Winters et al., 2006) by the more severe diminution of inhibin B levels compared with the decrease of follicle-stimulating hormone. Another hypothesis is the increase of scrotal temperature caused by hip and abdominal fat tissue accumulation, or even scrotal fat deposition (Shafik & Olfat, 1981), would involve spermatogenesis disturbances. Preferential accumulation in fatty tissue of toxic substances and liposoluble EDCs would amplify those alterations, as indicated by serum organochlorine levels being correlated with BMI (Magnusdottir et al., 2005).

In 2007, Johnson et al. reported that obesity prevalence had increased tremendously in the second half of the 1900s, which can be correlated with the trend of declining sperm count in men. The WHO (2014) also reported the prevalence of obesity (BMI $\geq$30 kg/m^2) had increased remarkably worldwide by 2014, and notably in the United States, where a decline in sperm count is more significant than in the rest of the world. The WHO reported worldwide obesity had more than doubled since 1980. They also reported, in 2014, that more than 1.9 billion adults 18 years and older were overweight. Of these, over 600 million were obese. In 2014, 39% of adults aged 18 years and over (38% of men) were overweight (WHO, 2014), and the prevalence of obesity increases with age. This is reassuring the data of declining sperm counts in aging males presented in this report.

Conclusion

The current study, with strong experimental evidences extracted by analyzing multitudinous studies, reports a declining trend in sperm concentration over the past 35 years with perceptions of the reasons of such deterioration in male reproductive health. These variations of sperm concentrations are observed by taking into account the different geographical regions. The outcome of this review is a systematic, concisely arranged scientific report on sperm concentration and the factors involved, from 1980 to 2015 from all over the world; statistical analysis of significant declining trend of sperm concentration over the said time period; and correlation of male health with the declining pattern of sperm count trend considering the age of an individual. With the development of more biomarkers to relate age with sperm concentrations and with upcoming studies investigating the causes of the decreasing quality of sperm parameters, greater knowledge could be developed to explore the possible remedies to overcome this expanding threat of infertility to the next generations.

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Table 6. Body Mass Index (BMI), Obesity, and Sperm Concentration.

Study	Country	Population	Age (years, mean ± *SD*)	Percentage by BMI category (kg/m^2)					Percentage by total sperm count category		
				<18.5 (%)	18.5-24.9 (%)	25-29.9 (%)	30-39.9 (%)	>40 (%)	Azoospermia (%)	Oligozoospermia (%)	Normozoospermia (%)
Eskenazi et al. (2003)	United States	97 Nonsmoking male volunteers without known fertility problems	46.4 ± 15.9	0	50.5	42.3	7.2	0	4.1	12.4	83.5
Jensen et al. (2004)	Denmark	1,558 Young military recruits	19.5 ± 1.3	3.5	77.3	15.4	3.7	0.1	0.3	45.2	54.5
Koloszar et al. (2005); Fejes, Koloszar, Szollosi, Zavaczki, and Pal (2005); Fejes et al. (2006)	Hungary	473 Male partners from subfertile couple attending infertility center	29.5 ± 3.6	6.3	33.6	32.4	22.0	5.7	44.0	30.0	65.6
Magnusdottir, Thorsteinsson, Thorsteinsdottir, Heimisdottir, and Olafsdottir (2005)	Iceland	72 Male partners from subfertile couple attending infertility center	37.4 ± 5.4	0	36.1	44.4	15.3	4.2	2.8	27.8	69.4
Zorn, Osredkar, Meden-Vrtovec, and Majdic (2007)	Slovenia	189 Male partners from subfertile couple attending infertility center	34.4 ± 5.8	0	43.9	41.8	14.3	0	22.2	11.7	61.1
Aggerholm et al. (2008)	Denmark	1,669 Male volunteers from general population	33.9 ± 8.8	0.5	52.0	39.4	8.1	0	1.2	11.1	87.7
Vujkovic et al. (2009) and Hammiche et al. (2011)	Netherland	225 Male partners from subfertile couples during IVF or ICSI cycles	37.5 ± 5.3	0.9	45.3	45.3	8.5	0	—	40.9	59.1
Duits et al. (2010)	Netherland	1,401 male partners from subfertile couple attending infertility center	36.4 ± 6.5	0.4	47.3	41.9	9.7	0.7	6.3	17.5	76.2
Martini et al. (2010)	Argentina	793 Male partners from subfertile couples	34.9 ± 6.2	—	31.0	49.4	18.5	1.1	1.9	52.7	45.4
Ramlau-Hansen et al. (2010)	Denmark	259 Sons of mothers recruited during their pregnancy in 1984-1987	20.1 ± 0.8	3.9	72.2	17.8	6.1	0	0.8	20.5	78.7
Chavarro, Toth, Wright, Meeker, and Auser (2010)	United States	483 Male partners from subfertile couple attending infertility center	36.3 ± 5.4	—	25.5	48.2	23.8	2.5	—	10.8	89.2
Keltz et al. (2010) and Relwani et al. (2011)	United States	185 Male partners from sub-fertile couples during IVF or ICSI cycles	37.5 ± 8.0	0.5	22.2	47.0	29.2	1.1	—	44.9	55.1
Tunc, Bakos, and Tremellen (2011)	Australia	81 Male partners from subfertile couple attending infertility center	36.8 ± 5.2	0	25.9	45.7	28.4	0	—	28.4	71.6
Shayeb, Harrild, Mathers, and Bhattacharya (2011)	United Kingdom	1,966 Male partners from subfertile couple attending infertility center	33.1 ± 6.0	0.9	40.8	44.9	12.5	0.9	—	18.2	81.8
Lotti et al. (2011)	Italy	222 Male partners from subfertile couple attending infertility center	35.8 ± 7.0	0	59.0	32.0	9.0	0	20.3	37.8	41.9
La Vignera, Condorelli, Vicari, and Calogero (2012)	Italy	150 Nonsmoking male volunteers	31.4 ± 2.3	0	33.3	33.3	26.7	6.7	2.7	41.3	56.0
Eskandar et al. (2012)	Saudi Arabia	500 Male partners from subfertile couple attending infertility center	34.8 ± 7.7	11.0	13.4	24.0	26.4	25.2	1.4	29.6	69.6
Hammiche et al. (2012)	Netherlands	449 Male partners from subfertile couple attending infertility center	35.4 ± 6.5	1.1	34.1	49.2	15.2	0.4	5.8	35.2	59.0
Braga et al. (2012)	Brazil	250 Male partners from subfertile couples during IVF or ICSI cycles	38.4 ± 9.3	2.0	50.0	40.0	4.0	4.0	—	34.4	65.6

Note. IVF = in vitro fertilization; ICSI = intracytoplasmic sperm injection.

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