Semen quality in the 21st century

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Abstract | Although semen quality is an important determinant of fertility, defining clear thresholds for normal ranges has proven difficult. According to 'time to pregnancy' studies, fecundity starts to decline when sperm concentrations fall below $30–55 \times 10^6$/ml, whereas the WHO criterion for normal values is currently 15×10^6/ml. Multiple studies over the past 15 years have reported median sperm concentrations of $41–55 \times 10^6$/ml in young men (mean age 18–21 years) from the general population, suggesting that many of them have suboptimal semen quality. Sperm numbers remain fairly constant between 19 and 29 years of age, which points to the importance of developmental effects. Discussion on whether population semen quality has declined has continued for decades, as regional differences in trends have been noted. The reasons for poor semen quality and adverse trends are not well established, but some associations suggest a causal relationship, for example, with maternal smoking during pregnancy. The role of chemical exposures leading to endocrine disruption and detrimental reproductive effects has been in the focus of research during the past 20 years. Identification of exposures that affect fertility could provide opportunities for effective prevention of reproductive health problems.

Several original studies published since 2000 in various countries have evaluated possible time trends in sperm concentration or total sperm count in different populations (TABLE 1). These studies have suggested a decreasing trend in sperm concentration and/or total sperm count of young men[1,2], male partners in infertile couples[3–8], fertile men[9,10] and semen donors[11–13] or semen donor candidates[14–17]. However, studies reporting no significant decrease or, indeed, that found a slightly increasing trend, have also been published[18–24]

Change in sperm concentration over time (1938–2013) was evaluated in a systematic review and meta-analysis investigating the effect of age on semen quality[25]. Altogether, 124 measurements of mean sperm concentration were included in the analysis, and a significant decline in sperm concentration over years 1938–2013 and also over years 1994–2013 was observed ($P<0.001$ and $P<0.02$, respectively). However, the latter decline was no longer significant when possible confounding factors — such as mean age, sample source, abstinence control, and gross domestic product for the country of the study — were taken into account[25]. Furthermore, an analysis studying 1994–2013 only included studies that were identified when looking for data on the associations between male ageing and semen quality. Thus, a meta-analysis focusing specifically on evaluating time trends in semen quality in the 21st century is needed in the future. In addition to studies of time trends in semen quality, original studies have also suggested regional differences in semen quality in the 21st century.

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Geographical differences in semen quality

At the end of the 1990s, two coordinated cross-sectional studies using standardized investigation procedures were performed in Europe to study possible regional differences in the semen quality of young men and of partners of pregnant women[26,27]. Study protocols similar to those used in these two reports[26,27] have been used in several further studies published since 2000 (TABLE 2, FIGS 1,2).

Young men

One of the above mentioned coordinated studies evaluated semen quality among young men in Denmark, Finland, Estonia and Norway, and showed that sperm concentrations and total sperm counts were significantly higher among young Finnish or Estonian men than among young Danish or Norwegian men (Finland versus Denmark 95% CI for difference 1.08–1.59, Finland versus Norway 95% CI for difference 1.06–1.60, Estonia versus Denmark 95% CI for difference 1.07–1.79, Estonia versus Norway 95% CI for difference 1.05–1.82) when adjusted to the Danish laboratory level and abstinence time. No significant differences between Finnish and Estonian men or between Danish and Norwegian men were observed[27]. In 2002, young Swedish men aged 18–21 years were reported to have significantly higher sperm concentrations than young Danish men (mean difference 13.4×10^6/ml, 95% CI 4.1–22.7). However, no reference laboratory was used in the study and potential interlaboratory differences in evaluation of sperm concentration could not, therefore,

Key points

- Downward trends in sperm concentrations have been described in several geographical areas during this century
- In several countries, sperm concentration of a considerable proportion of young men has been described to be on a level that has been associated with prolonged time to pregnancy
- Longitudinal studies suggest that almost full sperm production capacity is achieved around the age of 20 years, which points to the importance of earlier developmental phases in establishment of spermatogenic capacity
- Environmental factors are likely to have contributed to the declining trends in sperm concentrations; however, identifying the most important factors causing adverse effects remains a challenge

be taken into account when calculating the difference in sperm concentrations between countries[28,29]. Punab *et al.*[30] studied semen quality among military conscripts in Estonia and Lithuania, and sperm concentrations seemed to be higher in Estonian men. Sperm concentrations among Latvian military conscripts have also been reported to be somewhat higher than in Swedish young men, but significantly higher than in Danish men (mean difference 17×10^6/ml, 95% CI for difference: $3.2–31 \times 10^6$/ml)[28,29,31]. However, these data came from a small study and the results were not adjusted to the Danish reference laboratory level[31]. Around the turn of the century, adjusted sperm concentrations in young men from Japan, Lithuania, and Southern Spain seemed to be higher than in young men from Norway and Denmark[27,30,32,33], and German young men seemed to have similar sperm concentrations as Danish and Norwegian young men[27,34]. No difference in sperm concentration was observed between young men from Eastern and Western Germany[34]. When compared with Danish men examined in 2006–2010, Faroese young men had lower sperm concentrations ($P<0.001$) when adjusted for duration of abstinence[35]; however, the Faroese men were significantly older than the Danish men (median age 24 years versus 19 years, respectively, $P<0.001$)[35]. Around 2010, sperm concentrations of young men from USA and a Western Australian birth cohort were also studied, but adjusted results were not provided and no statistical comparison to the sperm concentration in the European countries has been reported[36,37].

The previously reported difference in sperm parameters between Finland and Denmark seems to be narrowing, as sperm concentrations seem to be decreasing in Finland and increasing in Denmark[2,20]. Similar trends have also been observed when excluding men with previous or current andrological disorders[2,20]. The increase in sperm numbers among the Danish men was statistically significant ($P=0.02$ for sperm concentration in 1996–2000 versus 2006–2010), but, from a biological point of view, rather small. Thus, future studies will have to address whether this possible trend is continuing or whether it is due to random fluctuation that is often seen in population-based studies. The difference between sperm counts in Sweden and Denmark seems to have diminished less, as no decrease in sperm concentrations has been reported from Sweden[19,20,28]. Time trend studies also suggest that sperm concentrations in young Spanish men might have declined in the twenty-first century[1]. Thus, possible differences between birth cohorts in each country should also be taken into account, when studying geographical differences in sperm concentrations. In a longitudinal study of Finnish men who provided semen samples four times over a 10-year period, sperm concentration remained fairly similar between the ages of 19 and 29 years[38]. These data are in line with a previous longitudinal study, which observed no significant change in sperm concentration during 4-year follow-up period of Danish young men, with median age at entry of 19 years[39]. Thus, cross-sectional data on sperm concentrations of 19-year-old men do seem to represent their adult spermatogenic capacity. Semen quality varies regionally and temporally, suggesting both genetic and environmental effects behind the trends.

Fertile men

When evaluating semen quality of male partners of pregnant women in four European cities in a cross-sectional coordinated study, Jørgensen *et al.*[26] observed that Danish men had the lowest sperm concentrations, followed by French and Scottish men, and Finnish men had the highest sperm concentrations when adjusted for possible confounders (age, abstinence time, and season). No significant differences between the four laboratories were observed in the assessment of sperm concentration according to a quality control study[26]. In a study designed in collaboration with that of Jørgensen and colleagues, significantly lower sperm concentrations were observed among male partners of pregnant women from Columbia than among partners of pregnant women from New York, Minneapolis, or Los Angeles ($P=0.001$, $P<0.001$, and $P=0.060$, respectively, when using haemacytometer for determination of sperm concentration and $P=0.002$, $P<0.001$, and $P=0.005$, respectively when using μ-cell disposable counting chamber)[40]. The final data analysis of the US study included increased number of men, and also included men from Iowa; the finding that the lowest sperm concentrations in the USA are observed in men from Missouri was confirmed[41]. A further study on urine pesticide metabolite levels showed a significant association between high pesticide levels and risk of poor semen quality among partners of pregnant women from Missouri but not among similar men from Minnesota[42]. No statistical comparisons between the sperm concentrations in USA and Europe have been reported.

Iwamoto *et al.*[43] evaluated semen quality in Japanese fertile men using a protocol harmonized with the European study by Jørgensen[26]. Men from the Kawasaki and Yokohama areas of Japan had significantly lower sperm concentrations than men from Scotland (Edinburgh) and Finland (Turku) ($P=0.0008$ and $P<0.0001$, respectively), but similar to levels of men from Denmark (Copenhagen) and France (Paris)[26,43]. In a subsequent study on semen quality in fertile Japanese men, statistically significant differences in sperm concentrations were observed between four urban areas (Sapporo, Osaka, Kanazawa, and Fukuoka) in Japan ($P = 0.04$)[44]. Adjusted sperm concentrations seemed higher than in the previous Japanese study and similar to the adjusted sperm concentrations in previous study on fertile European men.

Semen quality in fertile Australian men was determined as a part of the WHO surveillance study[45] and Haugen *et al.*[46] determined semen variables in fertile Norwegian men. However, no adjusted sperm concentrations have been reported and no statistical comparison with the sperm concentration in other countries has been performed. Reasons for the regional differences in semen quality are not known, but lifestyle and environmental factors are likely to have role, in addition to genetic factors.

Lifestyle and environmental factors

Low spermatogenic capacity can be associated with developmental disorders of the male reproductive system, such as cryptorchidism, hypospadias, and testicular germ cell cancer, which are all components of testicular dysgenesis syndrome (TDS)[47]. Increasing rates of TDS components have been reported during past decades in western countries, and it has been suggested that development of TDS is most often associated with exposure of the fetal testis to environmental factors such as endocrine-disrupting chemicals[48]. Exposure to a multitude of endocrine disruptors has emerged during the past century. Thus, besides being possibly affected by concurrent lifestyle factors, semen quality also has developmental determinants.

Smoking

Associations between several lifestyle and environmental factors have been studied. Meta-analyses have suggested that smoking is associated negatively with semen quality[49–51], and is also thought to be associated with increased frequency of sperm aneuploidy and DNA fragmentation[52–54]. Furthermore, prenatal exposure to maternal smoking is also associated with reduced semen quality of adult male offspring — negative associations with sperm concentration, total sperm count, percentage of motile sperm or percentage of morphologically normal sperm, or increased risk of oligozoospermia have been observed[34,55–60] —and men prenatally exposed to smoking are more likely to be smokers themselves[58]. Regular smoking of marijuana has been negatively associated with sperm concentration[61]. Tobacco smoke

Table 1 | **21st century trends in sperm parameters**

Study	Area	Population	Mean age (years)	*n*	Study period	Overall change in sperm concentration	Overall change in total sperm count
Feki *et al.*[5] (2009)	Tunisia	Male partners of infertile couples	36	1,835*	1996–2007	NS	↓
Jiang *et al.*[10] (2014)	China, Sichuan province	Men examined for fertility in sperm bank	Median 32	28,213	2007–2012	↓Fertile men ↓Healthy men ↓Infertile men	NA
Rao *et al.*[12] (2015)	China, Hubei Province, Wuhan	Semen donors (university students)	Range 22–30	1,808	2010–2013	↓	↓
Huang *et al.*[17] (2016)	China, Hunan Province	Semen donor candidates	21.6	3,114	2001–2005	↓	↓
			21.4	10,386	2006–2010		
			21.9	17,136	2011–2015		
Wang *et al.*[13] (2016)	China, Shandong Province	Semen donors	25.8	5,210	2008–2014	↓	↓
Marimuthu *et al.*[23] (2003)	India	Men attending infertility clinic	31.2	1,176	1990–2000	NS‡	NA
Adiga *et al.*[8] (2008)	India	Men evaluated for infertility	NA	7,770	1993–2005	↓	NA
Mukhopadhyay *et al.*[22] (2010)	India	Male partners of infertile couples*	33.2	1752	1981–1985	NS	NA
			35.2	1,977	2001–2006		
Haimov-Kochman *et al.*[11] (2012)	Israel	Healthy semen donors	25.2	58 (2,182 samples)	1995–2009	↓	NA
Lackner *et al.*[3] (2005)	Austria	Men evaluated for infertility (azoospermic men excluded)	Median 31.6	7,780	1986–2003	↓	NA
Jørgensen *et al.*[20] (2012)	Denmark	Young men from the general population	19.4	4,867	1996–2010	↑	↑
Jørgensen *et al.*[2] (2011)	Finland	Young men from the general population	19	858	1998–2006	↓	↓

Table 1 (cont.) | **21st century trends in sperm parameters**

Study	Area	Population	Mean age (years)	n	Study period	Overall change in sperm concentration	Overall change in total sperm count
Geoffroy-Siraudin *et al.*[6] (2012)	France (Marseille)	Male partners of infertile couples	35.1	10,932 7,899§	1988–2007	↓	↓
Rolland *et al.*[7] (2013)	France (126 ART centres)	Male partners of infertile women undergoing first IVF or ICSI	35.2	26,609	1989–2005	↓	NA
Splingart *et al.*[15] (2012)	France (Tours)	Semen donor candidates	35.2	1,114	1976–2009	NA	↓
Sripada *et al.*[4] (2007)	UK	Male partners of subfertile couples*	Range 22–56	4,832	1994–2005	↓	NA
Romero-Otero *et al.*[9] (2015)	Spain	Fertile men undergoing vasectomy	37.8	992	1985–2009	↓	↓
Fernandez *et al.*[32] (2012), Mendiola *et al.*[1] (2013)	Spain	Young men in Almeria	21.3	273	2001–2002	NA	NA
		Healthy university students in Murcia	19.2	215	2010–2011	↓(compared with Fernandez *et al.*[32])	↓(compared with Fernandez *et al.*[32])
Axelsson *et al.*[19] (2011), Richthoff *et al.*[28] (2002)	Sweden	Young native men from the general population	18.2	216	2000–2001	NS	NS
			18.0	295	2008–2010		
Chen *et al.*[18] (2003)	USA	Male partners of infertile couples	36.3; $n = 551$	408	1989–2000	↑(NS)	NA
Centola *et al.*[16] (2016)	USA, Boston area	Semen donor candidates	21.9–25.1	489 (9,425 samples)	2003–2013	↓	↓
Costello *et al.*[21] (2002)	Australia	Semen donor candidates	Range 18–40	448	1983–2001	NA	NS
Shine *et al.*[14] (2008)	New Zealand	Semen donor candidates	Median 36	975	1987–2007	↓	NA
Birdsall *et al.*[24] (2015)	New Zealand	Semen donors	Median 35	285	2008–2014	NS (when compared with period 2001–2007)	NA

NA not available, NS not significant. *Men with sperm concentration >20 M/mL. ‡Men with sperm concentration <10 M/mL excluded. §Men with total sperm count >40M.

contains several hazardous substances and increased oxidative stress, DNA damage, cell apoptosis, and a direct effect on regulation of spermatogenesis have been suggested as possible mechanisms for the adverse effects of smoking on semen quality[60,62]. In addition, marijuana might affect hormone levels, spermatogenesis, and mature sperm cells, as CB1 cannabinoid receptors are expressed in the anterior pituitary, testis, vas deferens, and human sperm cells[61].

Alcohol

According to a meta-analysis, alcohol consumption is negatively associated with semen volume, but not with other measures of semen quality[50]. In a large cross-sectional study of healthy men ($n = 8,344$) from Europe and the USA, no consistent association between semen quality and alcohol consumption during the week preceding the study was observed[63]. However, in a cross-sectional study of young Danish men[64], habitual drinking was associated with reduced sperm concentration, decreased total sperm count, and reduced percentage of spermatozoa with normal morphology, especially with a typical weekly intake of >25 units of alcohol (1 unit of alcohol ≈12 g of ethanol)[64]. An autopsy study of men aged 35–69 years has suggested a dose-dependent association between spermatogenic arrest and alcohol consumption, and an average daily consumption of more than 80 g was associated with a significantly increased risk of spermatogenic arrest[65]. Alcohol consumption might also be associated with sperm aneuploidy[54]. Furthermore, prenatal exposure to alcohol has been negatively associated with sperm concentration in young men. In a Danish pregnancy cohort follow-up study, sons exposed to ≥4.5 drinks per week during pregnancy had approximately one-third lower adjusted mean sperm concentration than sons exposed to <1 drink per week ($P = 0.04$), and an adverse effect of alcohol on fetal Sertoli cells has been suggested as a possible mechanism[66].

Individual smoking and alcohol consumption habits might correlate and, when compared to nonsmokers and nondrinkers, a combination of smoking and alcohol consumption was associated with significantly increased sperm DNA fragmentation ($P < 0.05$) in a study of men who were seeking semen analysis for fertility purposes in an IVF Unit[67]. Promotion of apoptosis was suggested as a

Table 2 | **Sperm concentrations in young and fertile men in different geographical regions***

Study	Area	Mean age (years)	*n*	Study period	Observed median sperm concentration (M/ml)	Adjusted median sperm concentration (M/ml)	Adjusted subgroup median sperm concentration (M/ml)
Young men							
Hart *et al.*[37] (2015)	Australia	20	365	≈2010	45	NA	NA
Andersen *et al.*[29] (2000)	Denmark	19.4	708	1996–1998	• 41 • 45 (abstinence >48 h, *n* = 521)	NA	NA
Jørgensen *et al.*[27] (2002)	Denmark	18.9	300	1997–1999	44	41[‡]	45[‡a]
Jørgensen *et al.*[20] (2012)	Denmark	19.4	4,867	1996–2010	45	NA	NA
		19.6	1,339	1996–2000	43		
		19.3	2,254	2001–2005	45		
		19.4	1,274	2006–2010	48		
Halling *et al.*[35] (2013)	Faroe islands	Median 24.0	481	2007–2010	40	NA	NA
			241	2007–2009	38		
			240	2009–2010	41		
Jørgensen *et al.*[27] (2002)	Estonia	18.8	104	1997–1999	62	57[‡]	63[‡a]
Punab *et al.*[30] (2002)	Estonia	20.4	79	1997–1999	64	67[‡]	66[‡a]
Jørgensen *et al.*[27] (2002)	Finland	18.8	324	1998–2000	61	54[‡]	53[‡a]
Jørgensen *et al.*[2] (2011)	Finland	18.8	338	1998–1999	60	67[#]	65[#c]
		19.0	382	2001–2003	54	60[#]	58[#c]
		19.1	138	2006	50	48[#]	48[#c]
Paasch *et al.*[34] (2008)	Germany (Hamburg)	19.7	334	2003–2004	49	46[‡]	NA
	Germany (Leipzig)	18.9	457	2003–2005	45	42[‡]	
Iwamoto *et al.*[33] (2013)	Japan (total)	21.3	1,559	1999–2003	59	59[‖]	62[‖b]
	Japan (Kawasaki)	20.8	658	1999–2000, 2002–2003	55	57[‖]	58[‖b]
	Japan (Osaka)	21.7	300	2002–2003	60	61[‖]	65[‖b]
	Japan (Kanazawa)	21.8	300	2002–2003	60	61[‖]	61[‖b]
	Japan (Nagasaki)	21.3	301	2002–2003	64	61[‖]	66[‖b]
Tsarev *et al.*[31] (2005)	Latvia	(≈19 years)	133	2001–2002	• 63 • 69 (abstinence ≥48 h, *n* = 100)	NA	NA
Punab *et al.*[30] (2002)	Lithuania	20.7	196	1997–1998	65	55[‡]	51[‡a]
Jørgensen *et al.*[27] (2002)	Norway	17.9	240	1998	53	41[‡]	42[‡a]
Fernandez *et al.*[32] (2012)	Spain	21.3	273	2001–2002	51	62[§]	75[§a]
Mendiola *et al.*[1] (2013)	Spain	19.2	215	2010–2011	44	NA	NA
Richthoff *et al.*[28] (2002)	Sweden	18.2	305	2000–2001	• 53.8 • 51.6 (men born and raised in Sweden, *n* = 248) • 55 (abstinence >48 h, *n* = 223)	NA	NA
Axelsson *et al.*[19] (2011),	Sweden	18.2	216	2000–2001	53	NA	NA
		18.0	295	2008–2010	56		
Mendiola *et al.*[36] (2014)	USA	19.7	221	2009–2010	52	NA	NR
Fertile men (partners of pregnant women)							
Stewart *et al.*[45] (2009)	Australia	35 (*n* = 225)	223	2000–2002	96	NA	NA
Jørgensen *et al.*[26] (2001)	Denmark	31.5	349	1996–1998	61	• 98** (winter) • 69** (summer)	NA

Table 2 (cont.) | **Sperm concentrations in young and fertile men in different geographical regions***

Study	Area	Mean age (years)	*n*	Study period	Observed median sperm concentration (M/ml)	Adjusted median sperm concentration (M/ml)	Adjusted subgroup median sperm concentration (M/ml)
Fertile men (partners of pregnant women) (cont.)							
Jørgensen *et al.*[26] (2001)	Finland	30.0	275	1996–1998	82	• 132** (winter) • 93** (summer)	NR
Jørgensen *et al.*[26] (2001)	France	32.0	207	1997–1998	74	• 103** (winter) • 73** (summer)	NR
Iwamoto *et al.*[43] (2006)	Japan (Kawasaki/ Yokohama)	32.5	324	1998	–	53**	NR
Iwamoto *et al.*[44] (2013)	Japan (total)	31.7	792	1999–2002	84	84¶	NR
	Japan (Sapporo)	30.6	206	2000–2002	95	89¶	
	Japan (Osaka)	32.9	250	1999–2002	76	80¶	
	Japan (Kanazawa)	30.9	233	1999–2001	84	80¶	
	Japan (Fukuoka)	32.6	103	1999–2001	89	98¶	
Haugen *et al.*[46] (2006)	Norway	31	99	NA	70	–	NR
			82‡‡		70		
Jørgensen *et al.*[26] (2001)	Scotland, UK	32.5	251	1996–1997	77	• 119** (winter) • 84** (summer)	NR
Swan *et al.*[40] (2003)	USA (total)	31.3	493	1999–2001	–	NR	NR
	USA (California)	29.8	124	1999–2001	64.8		
	USA (Minnesota)	32.2	155	1999–2001	81.8		
	USA (Missouri)	30.7	176	1999–2001	53.5		
	USA (New York)	36.1	38	1999–2001	88.5		
Redmon *et al.*[41] (2013)	USA (total)	32	763	1999–2005	67	NR	NR
	USA (California)	–	182	1999–2002	Mean 55		
	USA (Iowa)	–	137	2002–2005	Mean 62		
	USA (Minnesota)	–	206	1999–2002	Mean 72		
	USA (Missouri)	–	201	1999–2002	Mean 48		
	USA (New York)	–	37	1999–2002	Mean 85		

*Includes studies that have used similar study protocols. ‡Adjusted to the Danish laboratory level and to an abstinence period of ≥96 h. §adjusted to a period of ejaculation abstinence of 96 h. ‖ Adjusted to a period of ejaculation abstinence of 96 h for a 21-year-old man. ¶Adjusted to a period of ejaculation abstinence of 96 h for a 32-year-old man. # adjusted to a period of ejaculation abstinence of 95 h for a 19-year-old man. **Calculated expected sperm concentration for a 30-year old man having ejaculation abstinence of 96 h. ‡‡Abstinence time 2–7 days and time to pregnancy <12 cycles. [a]Men not taking any medication, and without any previous or current andrological diseases including known fertility problems. [b]Men with no history of reproductive problems. [c]Men without previous or current conditions that could potentially affect the semen quality.

potential mechanism[67]. Also in a study of men attending an andrology laboratory, those who smoked and drank alcohol had significantly lower semen volume, sperm concentration, and percentage of motile spermatozoa when compared with men without these two habits ($P<0.05$)[68].

Obesity

According to the WHO, the worldwide prevalence of obesity in men has doubled between 1980 and 2008. In 2008, 10% of men in the world were obese (BMI ≥30 kg/m^2), compared with 5% for men in 1980 (REF. 69). An extensive 2013 meta-analysis investigating the association between BMI and semen quality described a J-shaped association: overweight and obese men (BMI >25.0) had a significantly increased risk of azoospermia or oligozoospermia compared with men of normal weight (BMI 18.5–24.9)[70]. The meta-analysis included varying study populations, including men from the general population and male partners of subfertile couples. The association between obesity and semen quality is likely to be multifactorial and suggested possible mechanisms include changes in the hypothalamic–pituitary–gonadal axis, direct changes in spermatogenesis and Sertoli cell function, and an increase in scrotal temperature[70]. A cross-sectional study including a large proportion of overweight or obese men from fertility clinics could not confirm such an association[71], but a prospective population-based cohort study on couples attempting to conceive suggested an association between high BMI and prevalence of low semen volume, low sperm concentration, and low total sperm

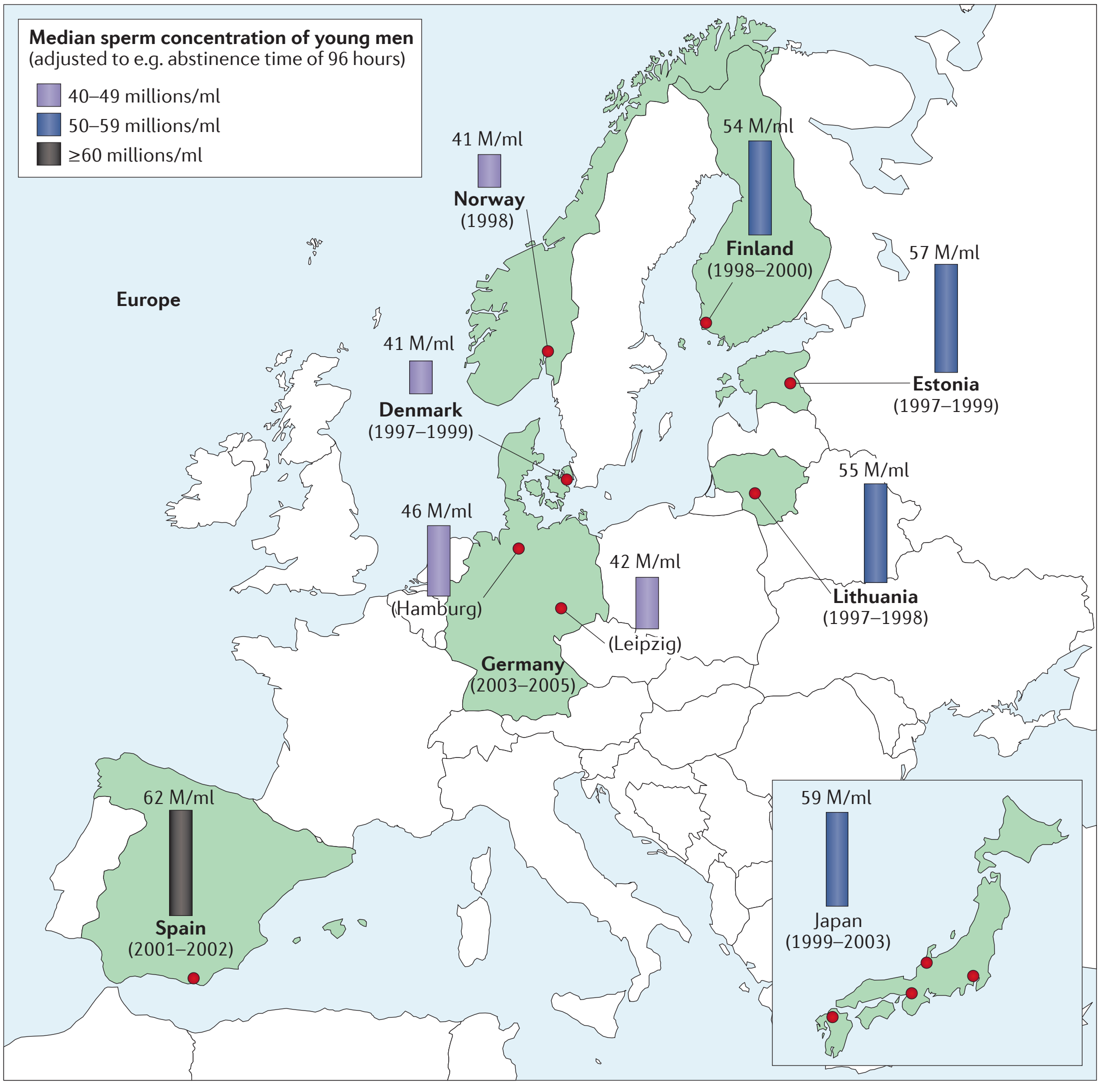

Figure 1 | **Median sperm concentration of young men in different geographical areas in studies using similar study protocols.** The study period and sperm concentration in million/ml (M/ml) is indicated for each area.

count[72]. Furthermore, some more recent studies have reported a negative association between BMI and different parameters of semen quality (semen volume, sperm concentration, total sperm count, motility, normal sperm morphology)[37,73–75], but these results have not been replicated in all recent reports on the topic[76,77].

Stress

A 2011 meta-analysis by Li *et al.*[50] suggested that different forms of psychological stress might be associated with reduced sperm concentration, reduced progressive sperm motility, and abnormal sperm morphology. A similar conclusion was also reached by a large 2016 cross-sectional study of young Danish men from the general population, which suggested a negative association between self-reported stress (stress scores above an intermediate stress level of the study subjects) and sperm concentration, total sperm count, semen volume, and total number of morphologically normal spermatozoa[78]. In the study, 20% of men had been distressed, 13% had had problems in relaxing, 12% had been irritated, and 16% had been tense all the time or a large part of the time during the preceding 4 weeks[78]. A cross-sectional study of the effect of stress in adult men from the general population in Northern California also reported a negative association between perceived stress score and sperm concentration and morphology[79] and a Chinese cross-sectional study on healthy men has also reported a negative association between psychological stress and total sperm count and percentage of sperm with normal morphology[80] It has been speculated that stress could affect semen quality by inducing apoptosis of sensitive germ cells via high glucocorticoid levels[78]. A US study suggested no significant increase in prevalence of psychological distress between 2001 and 2012 (REF. 81) and, therefore, although stress might affect semen quality, increased psychological stress is unlikely to fully explain declining trends in semen quality.

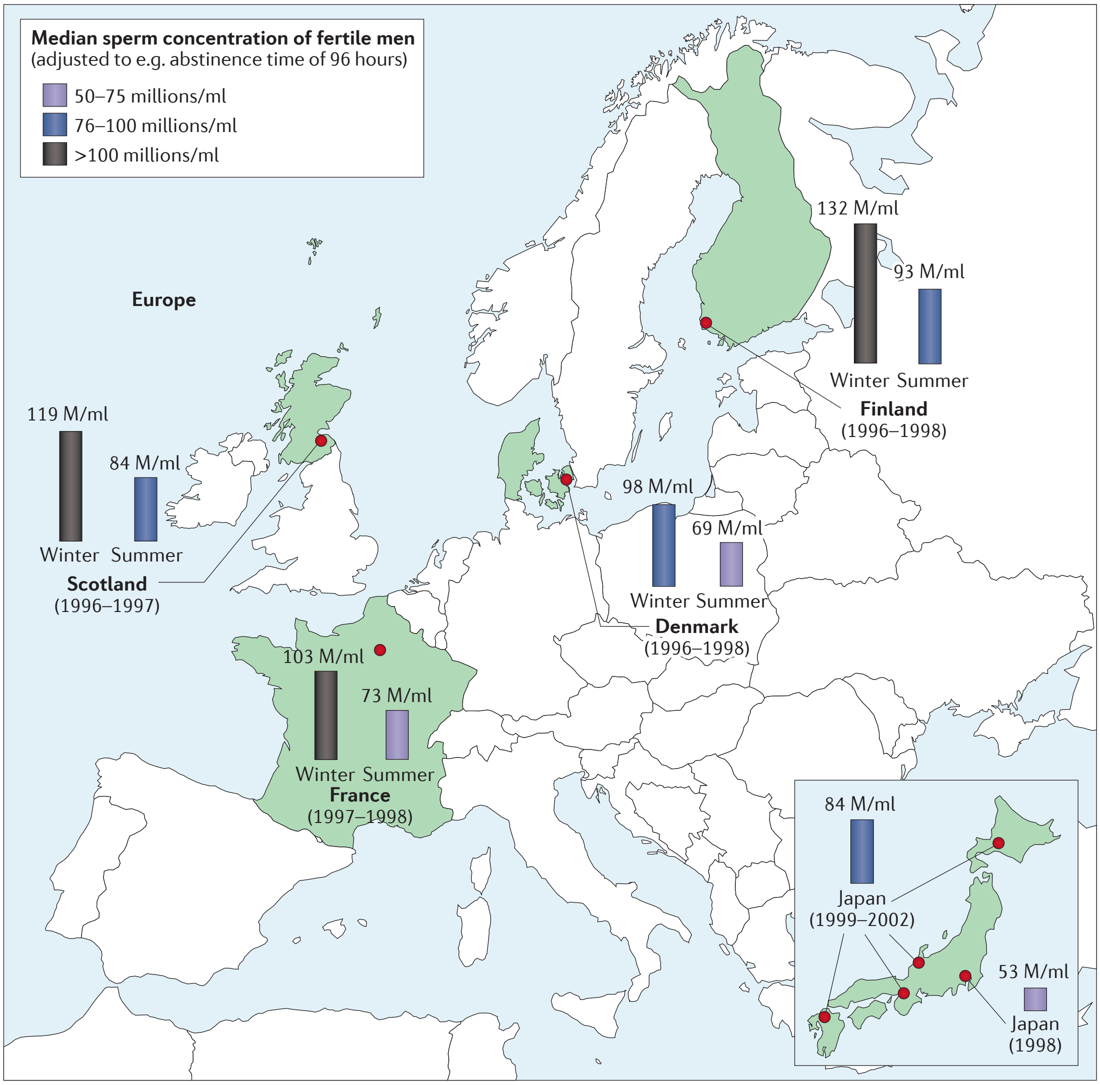

Figure 2 | **Median sperm concentration of fertile men in different geographical areas in studies using similar study protocols.** The study period and sperm concentration in million/ml (M/ml) is indicated for each area. Seasonal differences can be seen in most areas, with sperm concentrations being considerably higher in the winter months.

Endocrine disruptors

Endocrine-disrupting chemicals (EDCs) can influence semen quality and reproductive hormone levels[82–84]. EDCs include environmentally persistent organic pollutants (POPs), which remain intact for long periods and are toxic and widely distributed in the environment, and also other persistent and bioaccumulative chemicals, less persistent and less bioaccumulative compounds, current-use pesticides, pharmaceuticals and personal care product ingredients, metals and organometallic chemicals, natural hormones, and phytoestrogens[82,83]. Humans can be exposed to EDCs via food, water, inhaled air and particles, and via dermal contact.

Persistent chemicals. The persistence of many of the POPs — such as polychlorinated biphenyls (PCBs) — means that they are still major global pollutants even though they have been banned or regulated for years in many countries[82]. Men exposed prenatally to high levels of PCBs and their pyrolytic products (mainly polychlorinated dibenzofurans) in so-called Yu-Cheng (oil-disease) exposure in Taiwan in 1979 had a significantly higher percentage of sperm with abnormal morphology and poorer sperm motility than unexposed controls[85]. Similarly, men exposed prenatally and postnatally via breast milk to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) after the Seveso accident in Italy in 1976 had lower sperm concentrations, total sperm count, and sperm motility than control men, according to a study published in 2011[86]. Men exposed to TCDD at Seveso when they were 1–9 years of age also had reduced sperm concentrations and motility when compared to a control group, whereas such an association was not observed among men exposed to TCDD from the Seveso accident during puberty or in adulthood[87]. *In utero* exposure to background levels of perfluorooctanoic acid (which is a very stable synthetic surfactant) has been associated negatively with sperm concentration and total sperm count, whereas no significant association was seen between *in utero* exposure to background levels of perfluorooctanesulfonic acid, PCBs or dichlorodiphenyldichloroethylene (p,p′-DDE) and semen quality in adulthood[88,89], which suggests that the levels associated with adverse effects varies between chemicals. A detailed review concluded that exposure to PCBs and perfluorinated compounds during adult life seems to be negatively associated with sperm motility and sperm morphology, respectively[84]. Adult exposure levels to PCBs and p,p′-DDE in men have also been positively associated with time to pregnancy[90].

Nonpersistent chemicals. Prenatal exposure to phthalates has been associated negatively with semen volume of young men[91]. Adult exposure to phthalates has also been negatively associated with semen quality. A meta-analysis suggested that exposure to phthalates is associated with decreased sperm concentration, motility and increased sperm DNA damage[92]. Subsequent studies in men representing the general population have also suggested some adverse associations between semen quality and adult exposure to phthalates[93,94]. Increased oxidative stress has been suggested as a possible mechanism for reduced sperm motility related to adult phthalate exposure[93]. However, current literature suggests that the role of adult exposure to phthalates at environmental levels in determining the classical sperm parameters is likely to be small[94]. Bisphenol A, which is used in the production of plastics and epoxy resin liners of canned foods, is a non-persistent chemical that does not bioaccumulate[82]. In a recent review on bisphenol A and male reproductive health it was concluded that, although negative associations between adult urine levels of bisphenol A and various semen quality parameters have been described in some epidemiological studies, the results remain limited and inconclusive[95]. One limitation with studies of chemical exposures is the lack of capacity to consider several concomitant exposures — that is, the mixture effects. This might lead to underestimation of the risks, as individual chemicals might not show a significant association with an adverse outcome, although they might contribute to harmful combined exposure. Animal studies have demonstrated cumulative dose-additive adverse effects of mixtures of antiandrogenic chemicals on male reproductive tract development[96,97]

Use of mobile phone and wireless Internet

Meta-analyses including both *in vivo* and *in vitro* studies have suggested that exposure to mobile phones is associated with reduced sperm motility and sperm viability[98–100]. Increased reactive oxygen species production and increased DNA fragmentation in sperm have been suggested as possible mechanisms for such adverse effects. An association of mobile phone exposure with sperm concentration has been observed in the meta-analysis of animal studies, but the data are equivocal in human studies[98–100] and The National Toxicology Program is currently running a comprehensive study on the effects of mobile phone exposure on health[101]. One *in vitro* study has suggested a negative association between the use of wireless-internet-connected laptops and sperm motility and also suggested increased DNA fragmentation, potentially via a nonthermal effect[102].

Effect of semen quality on fecundity

Semen quality and time to pregnancy

The correlation between semen quality and fecundity is complicated, and no accepted threshold values exist for any semen variables on an individual level[103]. In a multicentre study conducted by the US National Cooperative Reproductive Medicine Network, sperm concentrations of 48×10^6/ml and 13.5×10^6/ml, percentage of motile sperm of 63% and 32%, and percentage of sperm with normal morphology of 12% and 9% defined the lower end of the fertile range and the upper end of the subfertile range, respectively[103]. The men whose sperm variables are in between these limits fall in the grey zone between fertility and subfertility. In a study of couples trying to conceive for the first time, time to pregnancy started to increase when sperm concentration was $<40 \times 10^6$/ml[104]. Percentage of sperm with normal morphology showed also a significant positive association with time to pregnancy[104]. In a large multinational European study of male partners of pregnant women, time to pregnancy increased when sperm concentration was $<55 \times 10^6$/ml or total sperm count was $<145 \times 10^6$, or if the proportion of morphologically normal sperm (using strict criteria suggested by Menkveld *et al.*[105]) was <19%[106]. A prospective US study reported a decline in pregnancy rates in otherwise healthy couples when sperm concentration is $<30 \times 10^6$/ml[107]. The latter two studies included also couples who had previously conceived successfully. A remarkably high proportion of young men all over the world have sperm concentrations below the aforementioned limits (TABLE 2). Percentage of morphologically normal spermatozoa was found to be associated with reduced time to pregnancy, and the percentage of spermatozoa with coiled tail was associated with increased time to pregnancy in a subsequent US study[108,109]. Additional variables, beyond those measured in a conventional semen analysis, have been associated with fecundity. According to a meta-analysis, a high level of sperm DNA fragmentation is associated with decreased pregnancy rate after *in vitro* fertilization (IVF) and increased miscarriage rate after intracytoplasmic sperm injection (ICSI)[110]. Furthermore, studies on presumably fertile couples attempting to achieve a pregnancy and a separate study on couples attempting to conceive for the first time have described an association between sperm chromatin integrity and time to conception[111,112].

Updated WHO criteria for normal semen quality

In 1980, the WHO published a "Laboratory Manual for Examination of Human Semen and Semen-Cervical Mucus Interaction" in response to a growing need for the standardization of procedures for the examination of human semen[113]. Since then the manual has been updated and revised four times and the latest edition, from 2010, listed lower reference values for semen variables[114]. The new values were calculated according to the fifth centile of fertile men and represent semen quality of recent fathers. The lower limit for normal sperm concentration was reduced from 20×10^6/ml to 15×10^6/ml; in the 1940s the normal limit was considered to be 60×10^6/ml[115]. Whether these changes in the reference values reflect improved methodology and knowledge or an actual decline in semen quality at the population level is matter of discussion. The current WHO reference levels do not distinguish between normal and abnormal testis function from a biological point of view, but might instead serve as a tool to identify men who might require fertility treatment in order to procreate.

Conclusions

Studies published in this millennium have clearly shown regional differences in semen quality. In population-based studies of young men, semen quality in many countries is at a level that raises concerns for their fecundity, with a considerable proportion of men having sperm concentrations associated with prolonged time to first pregnancy. Semen quality has certainly declined or stabilized to this low level during the past few decades, possibly owing to modern lifestyle factors, including exposure to environmental chemicals. The search to identify and avoid these preventable causes of reproductive problems continues.

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Competing interests
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