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Semen quality of young men in Switzerland: a nationwide cross-sectional population-based study

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ABSTRACT

Background: Sperm counts have been steadily decreasing over the past five decades with regional differences in the Western world. The reasons behind these trends are complex, but numerous insights indicate that environmental and lifestyle factors are important players.

Objective: To evaluate semen quality and male reproductive health in Switzerland.

Materials and methods: A nationwide cross-sectional study was conducted on 2523 young men coming from all regions of Switzerland, recruited during military conscription. Semen volume, sperm concentration, motility, and morphology were analyzed. Anatomy of the genital area and testicular volume was recorded. Testicular cancer incidence rates in the general population were retrieved from Swiss regional registries.

Results: Median sperm concentration adjusted for period of sexual abstinence was 48 million/mL. Comparing with the 5th percentile of the WHO reference values for fertile men, 17% of men had sperm concentration below 15 million/mL, 25% had less than 40% motile spermatozoa, and 43% had less than 4% normal forms. Disparities in semen quality among geographic regions, urbanization rates, and linguistic areas were limited. A larger proportion of men with poor semen quality had been exposed in utero to maternal smoking. Furthermore, testicular cancer incidence rates in the Swiss general population increased significantly between 1980 and 2014.

Discussion: For the first time, a systematic sampling among young men has confirmed that semen quality is affected on a national level. The median sperm concentration measured is among the lowest observed in Europe. No specific geographical differences could be identified. Further studies are needed to determine to what extent the fertility of Swiss men is compromised and to evaluate the impact of environmental and lifestyle factors.

Conclusion: A significant proportion of Swiss young men display suboptimal semen quality with only 38% having sperm concentration, motility, and morphology values that met WHO semen reference criteria.

INTRODUCTION

One of the first studies demonstrating a decline in sperm count over a fifty years’ time period was published in the nineties (Carlsen et al., 1992). The causes of the increasing number of men with low semen quality remained, however, marginally addressed, in part because of advancements reached concomitantly by medically assisted reproductive technologies (Palermo et al., 1992). A quarter of a century later, a meta-analysis evaluating temporal trends in sperm count confirmed earlier findings and reported a continuous significant decrease in sperm concentration in the Western world for the past twenty years (Levine et al., 2017).

The observed decrease in semen quality is more likely to be related to environmental factors rather than genetics. Some
studies aiming at evaluating the impact of environmental and lifestyle factors on semen quality have been conducted on fertile men or partners of infertile women. Swan et al. (2003) evaluated differences in semen quality of fertile men in four American states with different urbanization levels (Missouri, California, Minnesota, and New York). Reduced semen quality was observed in semirural and agricultural areas, the highest median sperm count being in the state of New York with zero agriculture surfaces. A study on male partners of infertile women consulting fertility clinics in France showed that the lowest sperm concentrations were in regions with high agricultural surfaces (Le Moal et al., 2014). These studies highlighted the importance of environmental factors, but a potential selection bias in the choice of the study population was often discussed whereby results were thought not to necessarily reflect the situation in the general population (Muller et al., 2004; Hauser et al., 2005; Deonandan & Jaleel, 2012).

Another set of studies on populations where men had no previous knowledge of their fertility status were conducted in several European countries, the USA, and Japan. Subjects were young men from the general population, aged 18–24 years, and often recruited in the context of military conscription. These studies reported median sperm concentration of 41–67 Mio/mL and revealed important regional differences in semen quality underlying once more the relevance of environmental or lifestyle factors (Andersen et al., 2000; Jorgensen, 2001, 2002; Punab et al., 2002; Richthoff et al., 2002; Tsarev et al., 2005; Paasch et al., 2008; Mendiola et al., 2011, 2013; Fernandez et al., 2012; Iwamoto et al., 2013; Erenpreiss et al., 2017; Priskorn et al., 2018; Rodprasert et al., 2019). However, most of these studies were conducted in one single, often urban, region, leading to results that cannot necessarily be generalized to represent the situation in the whole country. The impact of geographical variations within one country cannot be evaluated in such a study design. Nevertheless, the incidence of testicular cancer in the previously mentioned studies has frequently been shown to correlate with low semen quality trends (Serrano et al., 2013; Skakkebaek et al., 2016).

The main purpose of the present work was to carry out the first standardized nationwide cross-sectional study on young men from the general population in order to evaluate semen quality in Switzerland and determine the impact of geographical factors. The incidence rate of testicular cancer was also extracted from the general population in order to evaluate semen quality and the incidence of testicular cancer in the previously mentioned populations. These studies highlighted the importance of environmental factors, but a potential selection bias in the choice of the study population was often discussed whereby results were thought not to necessarily reflect the situation in the general population (Muller et al., 2004; Hauser et al., 2005; Deonandan & Jaleel, 2012).

A correction factor of 1.5 was determined using Bland–Altman analysis and was applied to these measures. Tanner stages of pubic hair were recorded from one to six, as previously described (Garn, 1956). Varicocele was determined according to the international grading system; grade 0 representing the absence of varicocele and grades 1 to 3 representing increasing severity of the enlarged vessels, as previously described (Dubin & Ameral, 1970; Kim & Goldstein, 2008). Grade 1 was notably determined after the Valsalva maneuver. Military physicians measured the men’s weight and height during their visit to the recruitment centers, and BMI was calculated (kg/m²). Participants were asked to provide a semen sample obtained by masturbation in a private room at the andrology laboratory after a recommended period of sexual abstinence of at least two days. The ejaculate was collected in a sterile and non-toxic 15-mL tube mounted with a funnel (Spermo-Sampler, Verridial, Blonay VD, Switzerland).

Questionnaires
Participants completed a questionnaire covering personal information divided into four sections: (i) Residence and general health information—such as previously diagnosed diseases and pharmacological drug intake during the 3 months immediately prior to participating in the study; (ii) health of their urogenital system such as occurrence of varicocele, as well as records on diagnosed and treated malformations such as cryptorchidism and hypospadias; (iii) lifestyle and diet—such as alcohol consumption and smoking; (iv) education. The mothers completed a separate questionnaire focusing on the time period close to conception, fetal life, and birth of the study volunteers.

Physical examination and sample collection
Trained urologists assessed the anatomy of the genital area, i.e., the presence of surgical scars, hypospadias, cryptorchidism, and varicocele. The testicular volume was measured by palpation using Praders orchidometer and/or by ultrasound (Logic 400 CL, GE Healthcare, Glattbrugg/ZH, Switzerland), and gynecomastia was evaluated by palpation. A significant correlation was observed between the two types of testicular volume measurement, but as expected values recorded with ultrasound were lower (Salim et al., 1995; Sakamoto et al., 2007). A correction factor of 1.5 was determined using Bland–Altman analysis and was applied to these measures. Tanner stages of pubic hair were recorded from one to six, as previously described (Garn, 1956). Varicocele was determined according to the international grading system; grade 0 representing the absence of varicocele and grades 1 to 3 representing increasing severity of the enlarged vessels, as previously described (Dubin & Ameral, 1970; Kim & Goldstein, 2008). Grade 1 was notably determined after the Valsalva maneuver. Military physicians measured the men’s weight and height during their visit to the recruitment centers, and BMI was calculated (kg/m²). Participants were asked to provide a semen sample obtained by masturbation in a private room at the andrology laboratory after a recommended period of sexual abstinence of at least two days. The ejaculate was collected in a sterile and non-toxic 15-mL tube mounted with a funnel (Spermo-Sampler, Verridial, Blonay VD, Switzerland).

Semen analyses
Date and time of the last ejaculation were recorded, and the abstinence period was calculated. Semen volume was determined by weighing the tube before and after collection. Samples were incubated for 20–40 min at 37 °C to allow liquefaction and then thoroughly homogenized using a disposable Pasteur

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pipette. Sperm concentration was assessed using the Computer Assisted Sperm Analyzer (CASA; Sperm Class Analyzer—SCA, MICROPTIC, Barcelona, Spain), and dilutions were made using a commercialized HEPES buffered with 0.4% HSA sperm medium (IVF basics, Gynotec B.V., GC Malden, The Netherlands) when needed. Aliquots (5 μL) of the diluted sample were transferred in a 20-μm-deep counting chamber (Leja Products, GN Nieuw-Vennep, The Netherlands) that was placed on a thermostatic (37 °C) microscope stage. Observations were made with a 10× phase contrast objective at a final 100× magnification. For each sample, a minimum of 400 sperm cell tracks were captured at a rate of 25 images per second using the CASA. Sperm concentration and kinetic parameters were recorded and the video sequences stored. For sperm morphology analysis, smears on glass slides were air-dried and sent to a central laboratory where they were Papanicolaou-stained. One hundred and fifty sperm cells were captured for each volunteer and automatically classified as normal or abnormal by an algorithm that was developed by Microptic based on the stricter criteria following WHO guidelines (Menkveld et al., 1990). The majority of the slides were analyzed using the CASA system (n = 2218), however some slides (n = 101) were analyzed by a single trained technician conforming to the evaluation standards of the CASA with a high correlation between the two methods of assessment.

Quality assurance and quality control
A set of standard operating procedures (SOPs) were established at the beginning of the data collection. Every collaborating andrology laboratory applied the same protocols for semen analysis according to the guidelines dictated by the World Health Organization in 1999 (sample collection, initial macroscopic examination, and microscopic investigations). Sperm concentration, motility, and kinematic parameters were determined using the CASA system in order to avoid interpersonal variations in assessing concentration and motility. Identical CASA systems were used in all study locations, and very strict instructions were followed for recording the sequences such as frame rate, sperm concentration, and counting chamber depth. All the video sequences were then carefully examined and validated by two trained technicians throughout the whole study period. Internal quality control for the CASA assessment was performed before each session using latex beads of known concentrations (QC beads, BioScreen, New York, NY, USA), and external quality control for the technician’s assessment was regularly performed to evaluate sperm concentration, motility, and morphology (UKNEQAS; https://ukneqas.org.uk, EQColline : https://www.eqcolline.org).

Statistical analysis
Medians with the 5th and 95th percentiles were used to describe continuous variables, and frequencies were employed to describe categorical variables. Descriptive results are shown for the entire population as well as after stratification of men in three groups according to the measured sperm concentrations: <15 Mio/mL, 15–40 Mio/mL, and >40 Mio/mL. The first cutoff was chosen based on the 5th percentile published by the WHO for fertile men (Cooper et al., 2010). The second cutoff was chosen based on consensus between several ‘time to pregnancy’ (TTP) studies where the TTP was shown to increase for sperm concentration up to a threshold of 40–50 Mio/mL (Bonde et al., 1998; Guzick et al., 2001; Slama et al., 2002). Differences between the three groups were tested using the Kruskal–Wallis test for continuous variables and chi-square for categorical variables. Linear regression analysis was carried out to obtain adjusted semen values corrected for confounding factors (see below). To correct for skewed distribution, sperm concentration and total sperm counts were normalized by a cubic root transformation and sperm motility was normalized by natural logarithmic transformation. Volume and sperm morphology were included untransformed. Duration of abstinence (standardized to 96 h) was taken into account for values of semen volume, sperm concentration, and total sperm count. The time between the delivery of the semen sample and the start of motility analysis (standardized to 30 min) was taken into account for the percentage of motile spermatozoa. No seasonal variation or any effect of the collection site could be detected for the semen parameters. Further adjustments for explanatory factors such as lifestyle factors (BMI, smoking, alcohol consumption) or genital malformations were not performed in order to represent the situation as it is in the cohort. However, semen parameters were separately evaluated for a subgroup of 1115 men who were not exposed to maternal smoking in utero and who were not diagnosed with varicocele or cryptorchidism. Men were stratified in groups according to their place of living in (i) the three geographic regions characteristic of the Swiss territory (Jura, Plateau, and Alps), (ii) the three urbanization rates (urban, intermediate, and rural), and (iii) the linguistic regions (French, Italian, and German), in order to explore potential effects of geographical and lifestyle factors on the observed semen quality. Data on geographic regions, urbanization categories, and linguistic areas were obtained from the Office of Federal Statistics (OFS) (Viktor Goebel, 2014; OFS, 2016) and cross-linked with the residence data in our questionnaires. A p-value below 0.05 was considered statistically significant. Data were analyzed using a commercially available package (IBM SPSS Statistics 23, NY, USA).

Testicular cancer incidence trend analysis in Switzerland
Incidence trend analysis was performed on testicular cancer data obtained from the National Institute for Cancer Epidemiology and Registration (NICER), which combines data from cantonal cancer registries. Data registered for at least five years from the last available diagnosis year (2014) were selected. Rates were age-standardized with the direct method by using the European standard population of 2013. Annual percentage change (APC) in incidence rates for cases pooled bi-annually to reduce variability was estimated with the Joinpoint Regression Program (version 4.6.0.0, August 2018; Statistical Research and Applications Branch, American National Cancer Institute). Complete-ness of case ascertainment and data quality among Swiss cancer registries have been recently assessed without detecting signs of over- or under-registration (Lorez et al., 2017).

RESULTS
Basic description of the study population
The general characteristics and reproductive parameters of the study population are summarized in Table 1. The majority of the study participants was healthy, had an educational level higher than obligatory school (ending at age 15 in Switzerland), and did not have prior knowledge of their fertility status. These traits did not differ according to groups of sperm concentration (Table 1; A). Similarly, no significant differences were observed...
Semen quality of young men in Switzerland

The median sperm concentration and total sperm count were 47 Mio/mL and 128 Mio, respectively (Table 1; F). When adjusted to a period of abstinence of 96 h, the median sperm concentration was 48 Mio/mL (Table 2). Comparing with the reference level set by the WHO for fertile men, 17% of men had sperm concentration below 15 Mio/mL and 17% had less than 39 million as total sperm counts in their ejaculate (Fig. 1A,B). In terms of motility, 25% displayed low values with less than 40% motile sperms and 43% had less than 4% morphologically normal sperms cells (Fig. 1C,D). Overall, sixty-two percent had one or more semen parameters that fell below the WHO thresholds.

Stratification of men according to geography, urbanization rate, and linguistic region

We evaluated geographic differences in sperm concentration across the three major landscapes in Switzerland according to

| Table 1 | Basic description of the total number of men and of groups of men stratified according to their sperm concentration. Results are presented as medians (5th–95th percentiles) for continuous variables or percentages for categorical variables. Testicular volume is represented as mean (±SD) |
|---|---|---|---|---|
| N with data | Total population (N = 2523) | Sperm concentration (Mio/mL) | p-value* |
| | | Group 1 | Group 2 | Group 3 |
| | | <15 (N = 425, 17%) | 15–40 (N = 683, 27%) | >40 (N = 1415, 56%) |
| A: General characteristics | | | | |
| Age (years) | 2523 | 19 (18–21) | 20 (18–21) | 19 (18–22) | 0.4 |
| Height (cm) | 2267 | 179 (169–190) | 178 (169–189) | 179 (169–190) | 0.8 |
| Weight (kg) | 2269 | 72 (59–93) | 73 (59–94) | 72 (59–95) | 0.9 |
| BMI (kg/m²) | 2267 | 22.6 (18–29) | 22.5 (19–29) | 22.6 (18–29) | 0.8 |
| Self Reported Health – excellent or very good (%) | 2164 | 97.5 (96.7–98.3) | 97.5 (96.7–98.3) | 97.5 (96.7–98.3) | 0.9 |
| Self Reported Health – good or good enough (%) | 2164 | 2.5 (1.7–3.2) | 2.5 (1.7–3.2) | 2.5 (1.7–3.2) | 0.9 |
| Medication last 3 months (%) | 2150 | 9.4 (7.9–11.0) | 9.4 (7.9–11.0) | 9.4 (7.9–11.0) | 0.3 |
| Ever fathered a child (%) | 2144 | 1.5 (0.9–2.1) | 1.5 (0.9–2.1) | 1.5 (0.9–2.1) | 1.0 |
| Experienced fertility problem (%) | 2127 | 0.1 (0.0–0.3) | 0.1 (0.0–0.3) | 0.1 (0.0–0.3) | 0.6 |
| Educational level, higher than obligatory school (%) | 2155 | 85.8 (84.1–87.5) | 85.0 (83.3–86.7) | 85.8 (84.1–87.5) | 0.8 |
| B: Lifestyle factors | | | | |
| Cigarette smokers (%) | 2156 | 26.3 (24.5–28.1) | 26.0 (24.4–27.7) | 24.6 (22.9–26.3) | 0.03 |
| Cigarettes/day, smokers only | 568 | 10 (1–20) | 10 (1–23) | 10 (1–20) | 0.02 |
| Alcohol consumers (%) | 2156 | 83.0 (81.2–84.8) | 80.0 (78.3–81.7) | 83.0 (81.2–84.8) | 0.2 |
| Alcohol, consumers only (units/week) | 1789 | 5.0 (1–24) | 5.0 (1–18) | 5.0 (1–25) | 0.1 |
| | | | | |
| Maternal BMI at conception (kg/m²) | 1511 | 21.2 (18.9–23.6) | 21.8 (19.7–23.8) | 22.1 (19.9–24.1) | 0.5 |
| Maternal age at conception (years) | 1413 | 29 (23–37) | 30 (26–39) | 29 (22–37) | 0.5 |
| Paternal age at conception (years) | 1464 | 32 (25–43) | 32 (25–44) | 32 (25–43) | 0.9 |
| Mother smoked during pregnancy (%) | 1657 | 13.0 (10.8–15.3) | 15.6 (13.4–17.9) | 12.6 (10.4–14.8) | 0.008 |
| C: Parental parameters | | | | |
| Asthma (%) | 2089 | 10.4 (8.6–12.2) | 9.6 (7.8–11.4) | 10.6 (8.8–12.4) | 0.9 |
| Other diseases (%) | 2031 | 11.7 (9.8–13.7) | 12.8 (10.9–14.8) | 11.8 (10.0–13.6) | 0.6 |
| STD (chlamydia &/or gonorrhoea) treated (%) | 2144 | 0.7 (0.3–1.2) | 0.9 (0.5–1.3) | 0.9 (0.5–1.3) | 0.6 |
| Cryptorchidism treated (%) | 1698 | 3.8 (2.8–5.0) | 5.6 (4.6–6.7) | 6.4 (5.5–7.4) | 0.001 |
| Varicocele operated (%) | 2133 | 1.0 (0.5–1.5) | 2.0 (1.5–2.5) | 3.0 (2.5–3.5) | 0.04 |
| D: Previously diagnosed/treated | | | | |
| Gynecomastia (%) | 1373 | 6.8 (5.5–8.1) | 6.8 (5.5–8.1) | 6.8 (5.5–8.1) | 0.5 |
| Pubic hair, stage 5–6 (%) | 1386 | 86.3 (83.8–88.8) | 86.7 (84.3–89.2) | 86.6 (83.8–88.8) | 0.4 |
| Hydorchiole (%) | 1411 | 2.4 (1.8–3.0) | 2.4 (1.8–3.0) | 2.4 (1.8–3.0) | 0.7 |
| Varicocele (%) | 1413 | 18.0 (16.0–20.0) | 18.2 (16.6–19.8) | 18.2 (16.6–19.8) | 0.001 |
| Testicular volume, mean ± SD (mL) | 1406 | 17.5 (15.9–19.1) | 16.2 (14.6–17.8) | 17.0 (15.4–18.6) | <0.001 |
| E: Physical examination | | | | |
| Ejaculation abstinence (days) | 2523 | 2.8 (1.5–6.8) | 2.8 (1.5–6.8) | 2.8 (1.5–6.8) | <0.001 |
| Volume (mL) | 2523 | 2.8 (1.0–5.6) | 2.8 (1.0–5.6) | 2.8 (1.0–5.6) | <0.001 |
| Sperm Concentration (Mio/mL) | 2523 | 47 (35–178) | 70 (41–149) | 70 (41–149) | <0.001 |
| Total sperm count (Mio) | 2523 | 128 (7.7–524.5) | 170 (100–200) | 170 (100–200) | <0.001 |
| Motile sperm (%) | 2523 | 51 (18.2–83.4) | 53 (24.7–73.5) | 53 (24.7–73.5) | <0.001 |
| Normal morphology (%) | 2319 | 4 (0–17) | 4 (0–17) | 4 (0–17) | <0.001 |

*Taken any medication during the 3 months immediately prior to participating in the study. Unable to conceive a child despite their willingness. Sum of intake of beer, wine and strong alcohol in recent weeks prior to participation in the study. Suffering from autoimmune diseases and/or cancer and/or diabetes and/or hepatitis and/or hypertension and/or thyroid. Mean of the right and left testicular volumes measured with Prader’s Orchidometer and/or ultrasound. A correction factor of 1.5 was applied to correct for under-estimated values measured with ultrasound. p-value for comparison of results between semen quality categories. Kruskal–Wallis test has been used for continuous variables and chi-square test for categorical variables. A p-value below 0.05 was considered statistically significant and was highlighted in bold.
Table 2: Adjusted semen parameters of total population and subgroup of men not diagnosed with varicocele, treated for cryptorchidism, or having been exposed in-utero to maternal smoking. Adjusted results are presented as medians (5–95% confidence interval) calculated by linear regression analysis.

| Parameter                      | Total population (N = 2523) | Subgroup (N = 1115) |
|--------------------------------|-----------------------------|---------------------|
| Ejaculation abstinence (days)  | 2.8 (1.5–6.8)               | 2.9 (1.5–7)         |
| Volume (mL)                    | 3 (2.9–3.1)                 | 3 (2.9–3.3)         |
| Sperm concentration (Mio/mL)   | 48 (42–55)                  | 51 (49–60)          |
| Total sperm count (Mio)        | 136 (121–145)               | 151 (124–173)       |
| Motile sperm (%)               | 51 (50–52)                  | 50 (48–51)          |
| Normal morphology (%)          | 5 (0–17)                    | 5 (0–17)            |

*Volume, sperm concentration and total sperm count are adjusted to a period of abstinence of 96 h; sperm motility is adjusted to 30 min between delivery of semen sample and start of motility analysis. Morphology was unadjusted and median is presented with 5–95th percentiles.

DISCUSSION

In this standardized nationwide cross-sectional study, we describe semen quality at a national level for the first time. We found that the adjusted median sperm concentration (48 Mio/mL) is among the lowest in Europe. When compared to the WHO reference levels, 62% of men had semen parameters associated with a prolonged waiting time to pregnancy (Guzick et al., 2001; Cooper et al., 2010). An evaluation of geographical factors, urbanization rates, or linguistic regions revealed no major differences in semen quality.

An important matter to primarily address concerns the relatively low participation rate (5.3%) of the invited subjects. More than 97% of Swiss young men were invited to participate in the study accounting for 92,274 individual over a twelve years’ time period. A self-selection bias cannot be excluded, but because the aim of our study is to evaluate male reproductive health, we first evaluated the presence of potential bias with this respect. We found that 99.9% of the volunteers had no prior knowledge of...
their reproductive capacities with only 0.1% having experienced fertility problems. The frequency of men diagnosed with varicocele during the physical examination in the study was of 18% compared with values ranging between 15 and 18% in the general Swiss population (Reinberg, 2007) pointing therefore to the absence of selection bias in terms of fertility status or reproductive health. Evaluation of general traits such as BMI shows that values in our cohort (22.6 kg/m²) correspond almost exactly to what has been reported in a population of Swiss conscript (22.8 kg/m²) (Staub et al., 2010) and to what have been reported...
by the Swiss Office of Federal Statistics OFS (21.5 kg/m²) (OFS, 2018a). Additionally, the percentage of men having an educational level higher than obligatory school (86%) was very similar to the one in the general population (88%) as reported by the OFS (OFS, 2018b). We, thus, think that volunteers that participated in our study are also not self-selected in terms of BMI and education. It might also be argued that this group of young men does not represent the adult population as a whole. However, it has been reported that full sperm capacity is on average achieved by the age of 20 (Perheentupa et al., 2016). As many as 86% were fully masculinized, having normal adult pubic hair—at least Tanner stage 5 (Garn, 1956)—and a mean testicular volume within the normal range (17.5 mL) (Bahk et al., 2010). Thus, the immaturity of the volunteers could not explain the observed values.

According to a small survey, we conducted on the men who did not participate in the biological part of the study; the low participation rate can be partially explained by practical aspects such as difficulties in reaching the andrology laboratories from the army recruitment centers because of poor public transport connections, and the disappointment of some subjects following the military decision about their enrollment. Some men also mentioned being uncomfortable in donating a semen sample and having to undergo a genital examination or not being psychologically ready to learn the results.

Epidemiologically, the Testicular Dysgenesis Syndrome (TDS) hypothesis is corroborated by observations of generally lower semen quality among men from countries with high incidences of testicular cancer (Skakkebaek et al., 2001). Indeed, a large set of countries within Europe including Germany, Denmark, and Norway reported both low-median sperm concentration and high testicular cancer rates. In countries such as Finland, Estonia, Lithuania, Latvia, and Spain, higher-median sperm concentration was observed with lower testicular cancer rates (Serrano et al., 2013; Skakkebaek et al., 2016). Consistently, we also observed a high incidence of testicular cancer along with an adjusted median sperm concentration that ranges among the lowest in Europe (Jørgensen et al., 2011). The frequency of genital malformation such as cryptorchidism is not well reported in Switzerland, but comparison of the values we observed in our cohort (3.8%) with European and international reports reveals no differences (2.5–6%) (Boisen et al., 2004; Ly et al., 2008; Hart et al., 2015).

A higher proportion of men with low sperm concentration was found to have been exposed to in utero maternal smoking and had suffered from previously diagnosed cryptorchidism and varicocele, in accordance with formerly published data (Storgaard et al., 2003; Jensen et al., 2005; Ramblau-Hansen et al., 2007; Ravnborg et al., 2011; Damsgaard et al., 2016). Excluding those men did not change significantly the median sperm concentration, therefore indicating that impaired semen quality is not only because of the presence of those men in the study population. More importantly, this shows that, besides those previously described, many factors impacting semen quality remain unknown.

Compared with other European studies performed in urban places, one of the strengths of the present study is that reproductive health of young men was evaluated at a national level, with participants coming from every geographical region of the country. Because of the method used to sample each region proportionally to the density of its residing male population, some regions had a low number of subjects. This made it difficult to compare data between regions and therefore hindered geographical analysis. We still attempted to identify possible factors that might affect semen quality either directly or indirectly. Differences according to the geographic region, urbanization rates, and linguistic regions were investigated. Our analysis revealed only subtle geographic variations with significant differences between Jura and Plateau among the three sperm concentration categories. We thus believe that more refined studies should be applied to improve our understanding of the influence of geographical factors during fetal and adult life on semen quality.

In conclusion, a significant proportion of Swiss young men display suboptimal semen quality, with only 38% of the men having sperm concentration, motility, and morphology values that are above the WHO reference values. A consequence will likely be prolonged waiting time to pregnancy and an increased risk of seeking fertility treatment.

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CONFLICT OF INTEREST
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.
AUTHOR’S CONTRIBUTIONS
R.R., A.S., E.S., M.G., and S.N. designed the study. R.R., A.S., E.S. M.V.d.B., J.V., A.F. collected the data. R.R., L.P., A.S., R.G., L.M., T.K.J., N.E.S., N.J., and S.N. analyzed and interpreted the data. R.R., A.S, N.J., and S.N. wrote the paper. All authors were involved in paper revision and gave final approval.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Locations of the Swiss army recruitment centers. Name of cantons are indicated in red and name of centers in black.

Figure S2. Number of volunteers contacted and the participation rate according to their type of participation in the study.

Table S1. Description of Swiss men according to geographical stratification in three regions.

Table S2. Description of Swiss men according to urbanization rates.

Table S3. Description of Swiss men according to linguistic regions.