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REVIEW ARTICLE

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Trend of change of sperm count and concentration over the last two decades: A systematic review and meta-regression analysis

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Abstract

Background: Since the 1970s, several studies found that sperm concentration (SC) and total sperm count (TSC) constantly worsened over time, mainly in high-income countries.

Objectives: To evaluate whether the decreasing trend in sperm count is continuing in Western European countries and USA, we performed a systematic review and meta-regression analysis.

Materials and methods: Embase and Pubmed/Medline were searched papers published in English in the 2000–2020 period limiting the search to data collected in the USA and Western European countries.

Results: We identified 62 articles and pooled information on 24,196 men (range 10–2,523), collected from 1993 to 2018. Considering all the studies, random-effects meta-regression analyses showed no significant trend for SC (slope per year −0.07 mil/mL, *p*-value = 0.86). Negative trends of SC were detected in Scandinavian countries (slope per year −1.11 mil/mL, 95% CI: −2.40 to +0.19; *p*-value = 0.09), but the findings were statistically not significant. No significant trends of SC were detected in Central Europe (slope per year +0.23, 95% CI −2.51 to +2.96; *p*-value = 0.87), the USA (slope per year +1.08, 95% CI −0.42 to +2.57; *p*-value = 0.16), and Southern Europe (slope per year +0.19, 95% CI −0.99 to +1.37; *p*-value = 0.75).

We have analyzed separately findings from studies including sperm donors, fertile men, young unselected men (unselected men, study mean age < 25 years) and unselected men (unselected men, study mean age ≥ 25 years). No significant trends of SC were observed among sperm donors (slope per year −2.80, 95% CI −6.76 to +1.17; *p*-value 0.16), unselected men (slope per year −0.23, 95% CI −1.58 to +1.12; *p*-value 0.73), young unselected men (slope per year −0.49, 95% CI −1.76 to +0.79; *p*-value 0.45), fertile men (slope per year +0.29, 95% CI −1.09 to +1.67; *p*-value 0.68).

Discussion and conclusion: The results of this analysis show no significant trends in SC, in USA, and selected Western European countries.

KEYWORDS
andrology, Europe, sperm concentration, total sperm count, trend, USA

1 | INTRODUCTION

Since the 1970s, several studies suggested that sperm count, motility, and morphology constantly worsened over time.[1–3] In 1992, a comprehensive review[1] of data from the general population detected a decline in semen quality between 1938 and 1991. This trend was confirmed both by Swan et al.,[2] and Levine et al. (2017)[3] in papers that considered studies published till 2013. Very recently Levine et al. (2022)[4] published a systematic review that included studies till 2019. In Levine et al.,[3] the sperm count negative trend was mainly due to a 50%–60% decline among men unselected by fertility from high-income countries including North America, Europe, Australia, and New Zealand. In Levine et al. (2022), the sperm count negative trend was −2.48% per year, considering studies published in all the world from 2000 onward. Changes in multiple environmental (endocrine disrupting chemicals,[5,6] pesticides,[7] heat[8] and lifestyle factors (diet,[9,10] stress,[11,12] smoking[13] and body mass index (BMI)[14,15]) have been suggested to explain these trends. However, methodological concerns shed doubts on the interpretation, since several studies included selected populations such as infertile men,[16,17] sperm donors,[18] or men undergoing vasectomy.[19] The awareness about fertility problems has also increased over time. This awareness may cause biases in evaluating the trends in sperm count. Easier access to sperm count, for men with fertility problems, could increase the proportion of men with known low semen quality. Conversely, the same increased awareness may push the men to have their semen quality assessed, increasing the rate of evaluations in men with normal semen quality. A way to reduce this potential selection and diagnostic bias is to analyze recent sperm count trends among populations with widespread access to diagnostic resources.Europe and North America are high-income areas, where availability of diagnostic and treatment resources for male and female fertility problems remained widely unchanged over the last 10–20 years. To evaluate whether the decreasing trend in sperm count is continuing in high-income areas, we conducted a systematic search of the literature with the same search criteria used in Levine et al. (2017),[3] and we summarized the results of studies conducted in the USA and Europe and published between the 2000 and 2020.

2 | METHODS

The report of this systematic review follows the MOOSE (Meta-analysis in Observational Studies in Epidemiology)[20] and PRISMA 2020 (Preferred Reporting Items for Systematic reviews and Meta-Analysis) guidelines.[21] This systematic review was registered in Prospero database (registration number CRD42021261111). Taking into account the review of Levine et al.,[3] we performed a systematic search of the literature for studies published from 2014 onward. Embase and Pubmed/Medline were searched using “sperm count” OR “sperm density” OR “sperm concentration” (SC), as search string with predefined criteria for inclusion and exclusion (Supporting information Search), and we limited the literature search to data collected in the USA and Western European countries. We considered studies published from 2014 to October 2020 using the search string reported in the Supporting information (Supporting information Search).The search (performed on October 23, 2020) retrieved 2,552 articles from Pubmed/MEDLINE and 185 articles from EMBASE (selecting those not in MEDLINE). Editorials, reviews, conferences, abstracts, and protocols were excluded. We selected 125 articles eligible for full-text retrieval. We excluded studies on subjects with clinical problems, as well as studies with small-sample size ($n < 10$). Studies targeting specific populations (e.g., men with a specific disease) or investigating treatments or outcomes of the condition were also excluded, unless they reported baseline data. If multiple reports from the same study were published, only the more recent one was considered. Two authors reviewed the papers and independently selected the articles eligible for systematic review, and discrepancies were resolved by discussion. Then, we selected 19 papers[22–40] published in the 2000–2013 period. As regards the articles published in the 2000–2013 period, we identified 46 papers from the review by Levine et al. (2017).[41–86] Finally, 65 studies were included in the qualitative synthesis.

2.1 | Data extraction

From included articles, we extracted relevant information including authors, year of publication, year of data collection, study design, study population, subjects’ age, BMI, semen volume, SC, and total sperm count (TSC). When results from more than one period or more than one group were reported, we included multiple records for the study. For the purpose of our meta-analysis, subjects included in the original studies were classified “fertile men” (men with proven fertility), “sperm donors,” “young unselected men” (men included in studies with mean age less than 25 from an unselected or a healthy population), and “unselected men” (men included in studies with mean age equal or greater than 25 from an unselected or a healthy population). We also classified studies according to four geographical areas: Scandinavian countries (Denmark, Finland, Sweden and Norway), Central Europe (France, Germany, Switzerland, the Netherlands), Southern Europe (Italy, Greece, Spain), and the USA.

2.2 | Statistical analysis

We used point estimates of mean SC or mean TSC, from individual studies, to model time trends during the study period, as measured by slope of SC or TSC per calendar year in a linear regression model. The midpoint of the sample collection period was the independent variable in all analyses and, in adjusted models, we also included geographical area and population type. We reported the parameter estimate ± its standard error and/or *p*-value. The interaction term between study population and year of collection was evaluated, for both SC and TSC, in multiple regression models. In studies where the sample collection period was not provided, we estimated it by subtracting, from the publication year, the mean difference between collection and publication year from studies with known information. Units were million/mL for

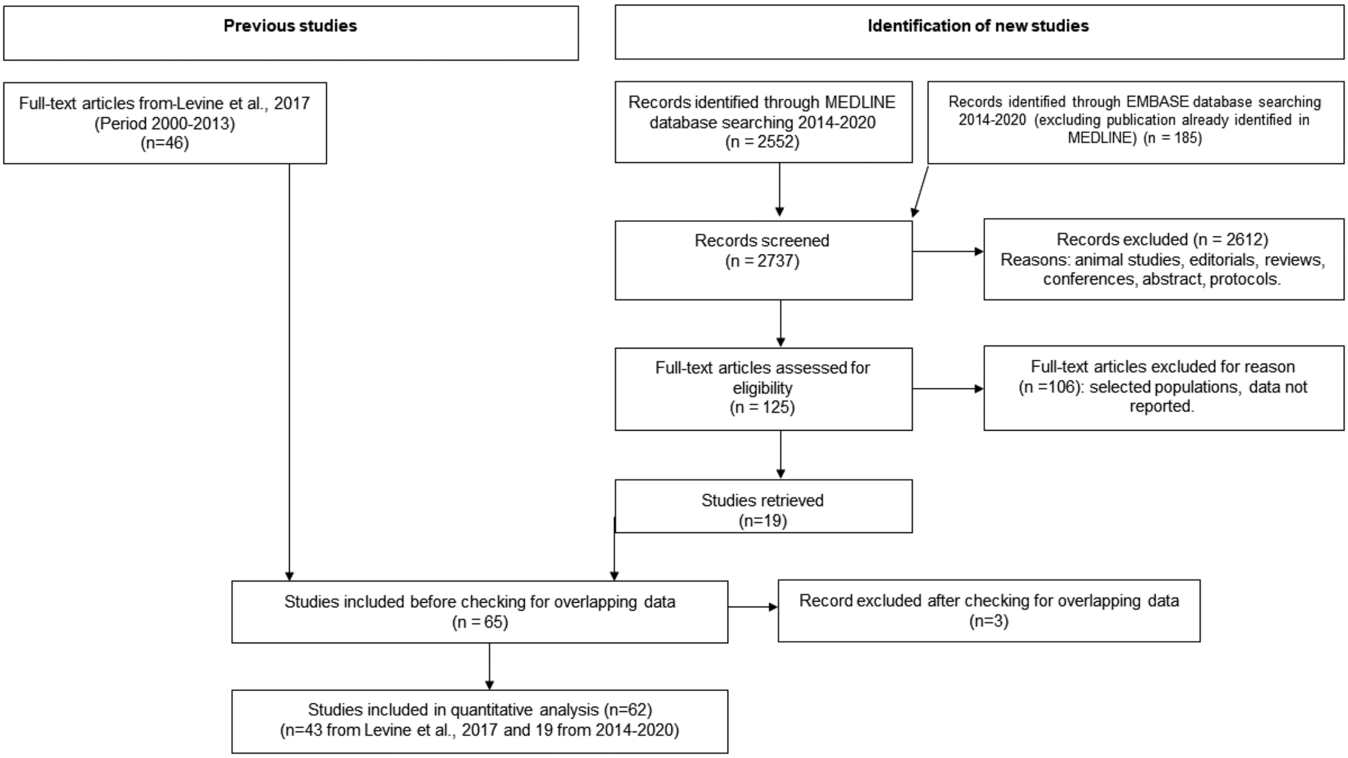

FIGURE 1 Flow chart of literature search (PRISMA 2020).

SC and million for TSC (defined as SC × sample volume) and all slopes denote unit change per calendar year. For example, for studies that reported median SC or TSC, we estimated the mean by adding the average difference between the mean and median in studies for which both were reported. In studies that did not report the range or midpoint year of sample collection, the midpoint was estimated by subtracting, from the publication year, the average difference between the year of publication and the midpoint year of sample collection of studies for which both were reported.

When the standard deviation (SD) but not the standard error (SE) of the mean of SC or TSC was reported, the SE was calculated by dividing the SD by the square root of the sample size. For studies that did not report the SD, we estimated the SD using the mean SD from others. Since this procedure may leads to a bias, for each meta-regression model we also computed a sensitivity analysis by excluding studies in which the SD was imputed because not available.[87] If mean TSC was not reported, it was calculated by multiplying mean SC by mean semen volume.

The SGplot SAS procedure was used to plot SC mean (million/mL) and TSC mean (million) of each study, and the trends across the study period. Graphs were obtained for the overall sample and by area (USA, Scandinavian countries, Central Europe, Southern Europe) and study population (fertile, sperm donors, unselected men, young unselected men). In the graphs, the size of the study is indicated by the size of the circle. The type of study population is represented by each dot by assigning each group different colors.

Random effect meta-regression analyses were performed to estimate slope coefficients. SC mean and TSC mean were included in turn as dependent variables and modeled as function of time (year of collection). To obtain trend estimates for each item of the independent variable (in turn area or study population), we built two series of dichotomous variables with value equal 0 or year of collection. The models were adjusted in turn for area or study population. We reported parameter estimates and relative 95% confidence interval. Percentages of residual variation due to heterogeneity were also reported.

Analyses were performed in STATA (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.) and SAS 9.4 (SAS Institute, Cary, NC, USA).

3 | RESULTS

We selected 65 studies regarding four geographical areas (USA, Scandinavian Countries, Central Europe and Southern Europe). Forty-six papers were published in the 2000–2013 period (selected from the review of Levine et al.) and further 19 papers were identified during the period 2014–2020[22–40] (Figure 1).

After checking for possible overlapping data, we excluded the studies of Lundwall et al. (2003)[85] (excluded because reported the same data as Richtoff et al.[49]), Toft et al. [84] (excluded because reported the same data as Rignell-Hydbom et al.[62]) and Rylander et al.[83] (excluded because reported the same data as Malm et al.[35]). We also excluded data concerning Denmark and Finland (but not Norway) from Jørgensen et al.[46] (because they overlapped the data of Jørgensen et al.[75]) (Table S2).

TABLE 1 Regression analyses.

	No. of records*	No. of men	Beta (trend)	Standard error	*p*-Value
SC					
Univariate	85	24,196	−0.05	0.40	0.83
Adjusted for area and study population	85	24,196	+0.08	0.41	0.85
TSC					
Univariate	73	22,840	−1.34	1.73	0.44
Adjusted for area and study population	73	22,840	−0.92	1.76	0.60

*Number of records: in some studies, reporting data concerning different period of collection or different countries, we included more than one record (one record for each period of collection/country).

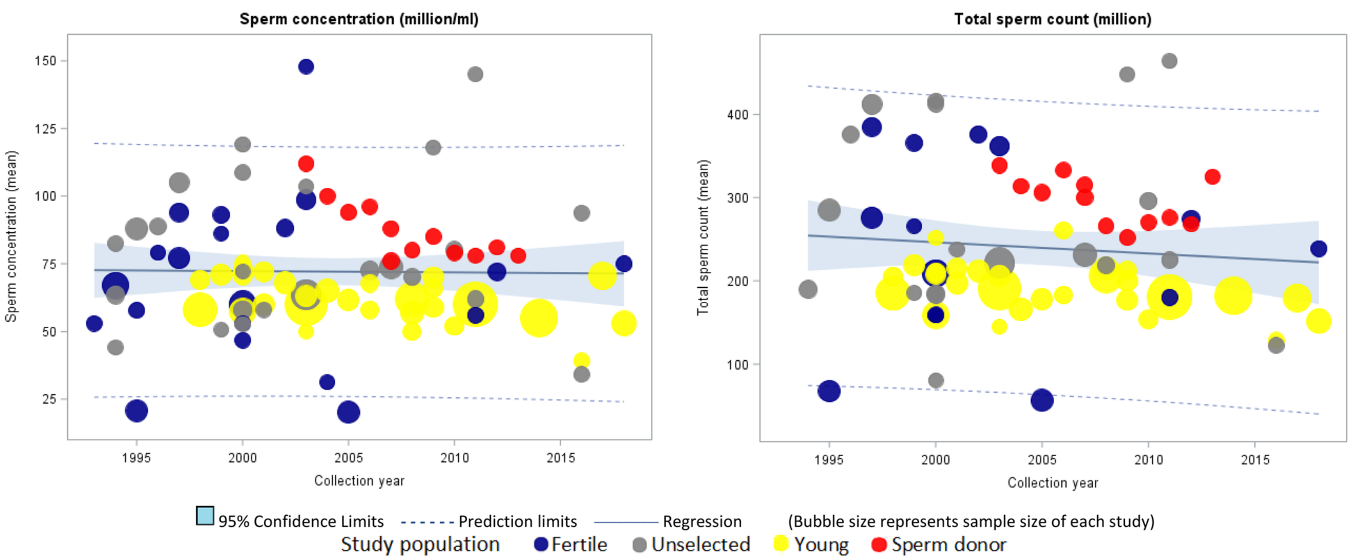

FIGURE 2 Trends in sperm concentration and total sperm count, 1993-2018 (simple linear regression).

Thus, we included 62 papers published between 2000 and 2020.

According to data extraction criteria, multiple information was retrieved from papers reporting data on several time periods. Thus, from 62 publications, we extracted 85 records for SC and 73 for TSC. Then, main characteristics of selected studies are reported in Table S1.

Overall, the considered studies reported information on 24,196 men. The lowest number of men included in a study was 10[66], the highest 2,523.[36] The mean or median age ranged from 17.9 to 65 years, and the BMI from 21.0 to 29.8 kg/m^2.

3.1 | Findings from all identified studies

As per selection criteria, selected articles were published in the 2000–2020 period, with data collection period ranging from 1993 to 2018. Mean or median values for SC and TSC widely varied by country, by study population included in the study, and by age. The overall analysis (simple linear regression) for SC showed statistically no significant trends of SC (slope per year −0.05 ± 0.40 mil/mL, *p*-value = 0.83) and TSC (slope per year −1.34 ± 1.73 mil, *p*-value = 0.44) (Table 1, Figure 2). Since both geographical area and study population were significantly associated with SC (*p*-value = 0.01 and < 0.0001, respectively) and TSC (*p*-value = 0.001 and < 0.0001), they were included in the multivariable model, showing no significant trend in SC (slope per year +0.08 ± 0.41 mil/mL, *p*-value = 0.85). The TSC decline was less marked (slope per year -0.92 ± 1.76 mil, *p*-value = 0.60) than in the univariate analysis, without significance for both the models (Table 1). Including abstinence hours and BMI, in turn, where these variables were reported, did not substantially change these estimates (data not shown).

We also computed a regression model that included the interaction term between study population and year of collection. For both SC and TSC, the interaction terms were not significant (*p*-value = 0.17 and 0.28, respectively) (data not shown). For this reason, we decided not to include the interaction term in the regression models. Anyway, we computed a regression model to evaluate the trend in the different study populations and included the "study population" variable to adjust the trend in each area. The meta-regression model, including area and study population, showed no significant trend of SC (slope per

TABLE 2 Meta-regression analyses.

	No. or records*	Number of men	Mean ± SD	Beta (trend)	*p*-Value	% residual variation due to heterogeneity (I^2)
SC						
Model including area and study population	85	24196	72.1 ± 22.9	−0.07	0.86	97.5%
Area (dicotomic variables)**						96.0%
USA	20	3,067	81.4 ± 16.6	+1.08	0.16	
Scandinavian Countries	28	12,873	68.8 ± 14.8	−1.11	0.09	
Central Europe	16	4,179	79.7 ± 25.7	+0.23	0.87	
Southern Europe	21	4,077	61.7 ± 29.7	+0.19	0.75	
Study population (dicotomic variables)***						97.1%
Fertile	20	3,793	68.8 ± 29.7	+0.29	0.68	
Sperm donors	12	582	87.3 ± 11.1	−2.80	0.16	
Unselected men	24	3,482	79.5 ± 26.9	−0.23	0.73	
Young unselected men	29	16,339	61.9 ± 8.4	−0.49	0.45	
TSC						
Model including area and study population	73	22,840	239.9 ± 87.4	−1.10	0.52	97.7%
Area (dicotomic variables)**						96.8%
USA	16	2,083	284.6 ± 63.6	+4.65	0.27	
Scandinavian Countries	27	12,707	234.0 ± 74.9	−4.30	0.08	
Central Europe	15	4,147	263.0 ± 115.3	+4.00	0.44	
Southern Europe	15	3,903	179.5 ± 66.6	−0.14	0.96	
Study population (dicotomic variables)***						96.6%
Fertile	14	2,928	241.0 ± 109.0	+0.23	0.94	
Sperm donors	12	582	297.0 ± 29.4	−4.50	0.56	
Unselected men	19	3,157	273.3 ± 115.1	−1.12	0.70	
Young unselected men	28	16,173	192.1 ± 29.8	−1.40	0.58	

*Number of records: in some studies, reporting data concerning different period of collection or different countries, we included more than one record (one record for each period of collection/country).
**Model including area (dicotomic variables), area (dummy with Central Europe as reference category), study population (categorical variable).
***Model including study population (dicotomic variables), study population (dummy variable with Fertile as reference category), area (categorical variable).

year −0.07 mil/mL, *p*-value = 0.86, I^2 = 97.5%) and TSC (slope per year −1.10 mil, *p*-value = 0.52, I^2 = 97.7%) (Table 2). We also performed a sensitivity analysis, for both SC and TSC, by excluding the studies which did not report the SD (30 records excluded in SC and 34 in TSC). The multivariate meta-regression model of SC showed no significant trend (slope per year +0.41 mil/mL, *p*-value = 0.50, I^2 = 98.0%) and no significant trend of TSC was confirmed (slope per year −0.20 mil, *p*-value = 0.93, I^2 = 98.0%) (data not shown).

3.2 | Findings according to geographic areas

Using simple linear regression, SC appeared to increase, though not significantly, in Central Europe (*p*-value = 0.46) and the USA (*p*-value = 0.11), was stable in Southern Europe (*p*-value = 0.82), and decreased significantly in Scandinavian countries (*p*-value = 0.01) (Figure 3). In the simple linear regression models for TSC by geographical area, the USA and Central Europe showed no significant trend (*p*-value = 0.20 and 0.64, respectively) and a stable trend was found in Southern Europe (*p*-value = 0.71), whereas Scandinavian countries reported no significant decline (*p*-value = 0.05) (Figure 4).

We further computed random effects meta-regression analyses to estimate SC and TSC trends according to geographic area (USA, Scandinavian Countries, Central and Southern Europe) (Table 2). No significant trends of SC were detected in the USA (slope per year +1.08, 95% CI −0.42 to +2.57; *p*-value = 0.16), Central Europe (slope per year +0.23. 95% CI −2.51 to +2.96, *p*-value = 0.87), Southern Europe (slope per year +0.19, 95% CI −0.99 to +1.37; *p*-value = 0.75), and Scandinavian countries (slope per year −1.11 mil/mL, 95% CI: 95% CI −2.40 to +0.19; *p*-value = 0.09) (Table 2).

TSC showed no significant trend in Scandinavian Countries (slope per year −4.30 mil, 95% CI −9.18 to +0.59; *p*-value = 0.08), Southern Europe (slope per year −0.14, 95% CI −5.27 to +4.99; *p*-value = 0.96), the USA (slope per year +4.65, 95%CI −3.61 to +12.9; *p*-value = 0.27), and Central Europe (slope per year +4.00, 95% CI −6.33 to +14.33; *p*-value = 0.44) (Table 2).

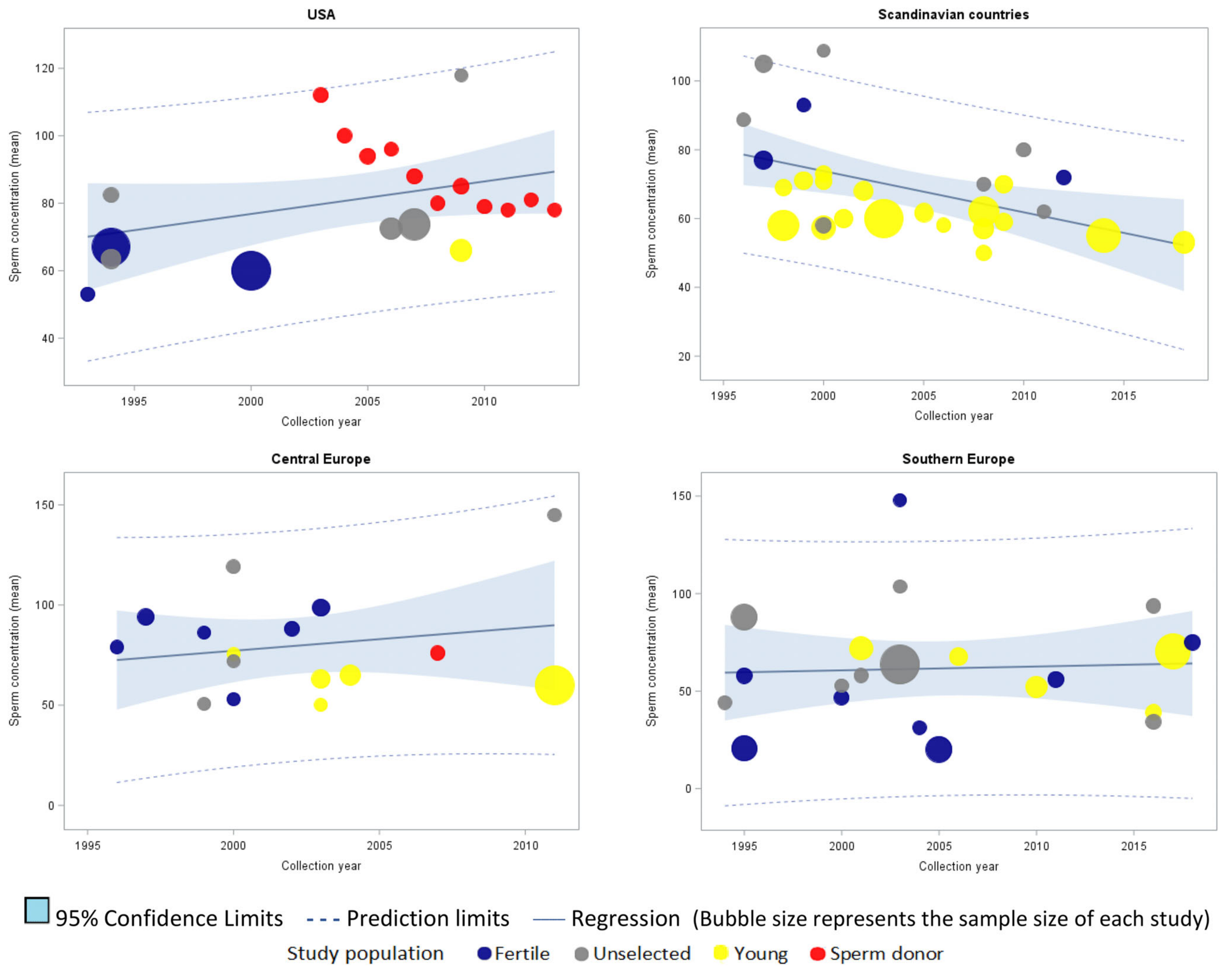

FIGURE 3 Trends in sperm concentration by area, 1993-2018 (simple linear regression model).

3.3 | Findings from studies including sperm donors, fertile men, and unselected men (unselected young men and unselected men)

In fertile and unselected men, the SC trend (simple regression analysis) was stable (*p*-value = 0.81 and 0.66, respectively), whereas it was decreasing in young unselected men (*p*-value = 0.01) and sperm donors (*p*-value = 0.001) (Figure 5). Considering the results of the meta-regression analysis, no significant trends of SC were detected in sperm donors (slope per year −2.80, 95% CI −6.76 to +1.17; *p*-value = 0.16), young unselected men (slope per year −0.49, 95% CI −1.76 to +0.79; *p*-value = 0.45), unselected men (slope per year −0.23, 95% CI −1.58 to +1.12; *p*-value = 0.73), and fertile men (slope per year +0.29, 95% CI −1.09 to +1.67; *p*-value = 0.68) (Table 2).

In the simple linear regression model, a decrease in TSC over time was observed in all populations (Figure 6), and was significant in men < 25 years old (*p*-value = 0.02).

Considering the results of the meta-regression analysis, TSC showed no significant trend in sperm donors (slope per year −4.50, 95% CI −19.73 to +10.74; *p*-value = 0.56), young unselected men (slope per year −1.40, 95% CI −6.34 to +3.55; *p*-value 0.58), unselected men (slope per year −1.12, 95% CI −6.93 to +4.69; *p*-value = 0.70), and fertile populations (slope per year +0.23, 95% CI −6.18 to +6.65; *p*-value = 0.94). All the meta-regression models showed high heterogeneity, with the percentages of residual variation ranging from 96.0% to 97.7% (Table 2).

4 | DISCUSSION

In this systematic review of the change of sperm counts over the last two decades, we observed no significant trend of TSC. Separately considering different geographic areas, Scandinavian countries showed a declining trend of SC, though the finding was not significant after taking into account the study population. Likewise, no statistically significant declining of TSC was observed. The declining trend tended to be more marked in Scandinavian countries and in sperm donors, young unselected men, and unselected men, but the findings were statistically non-significant.

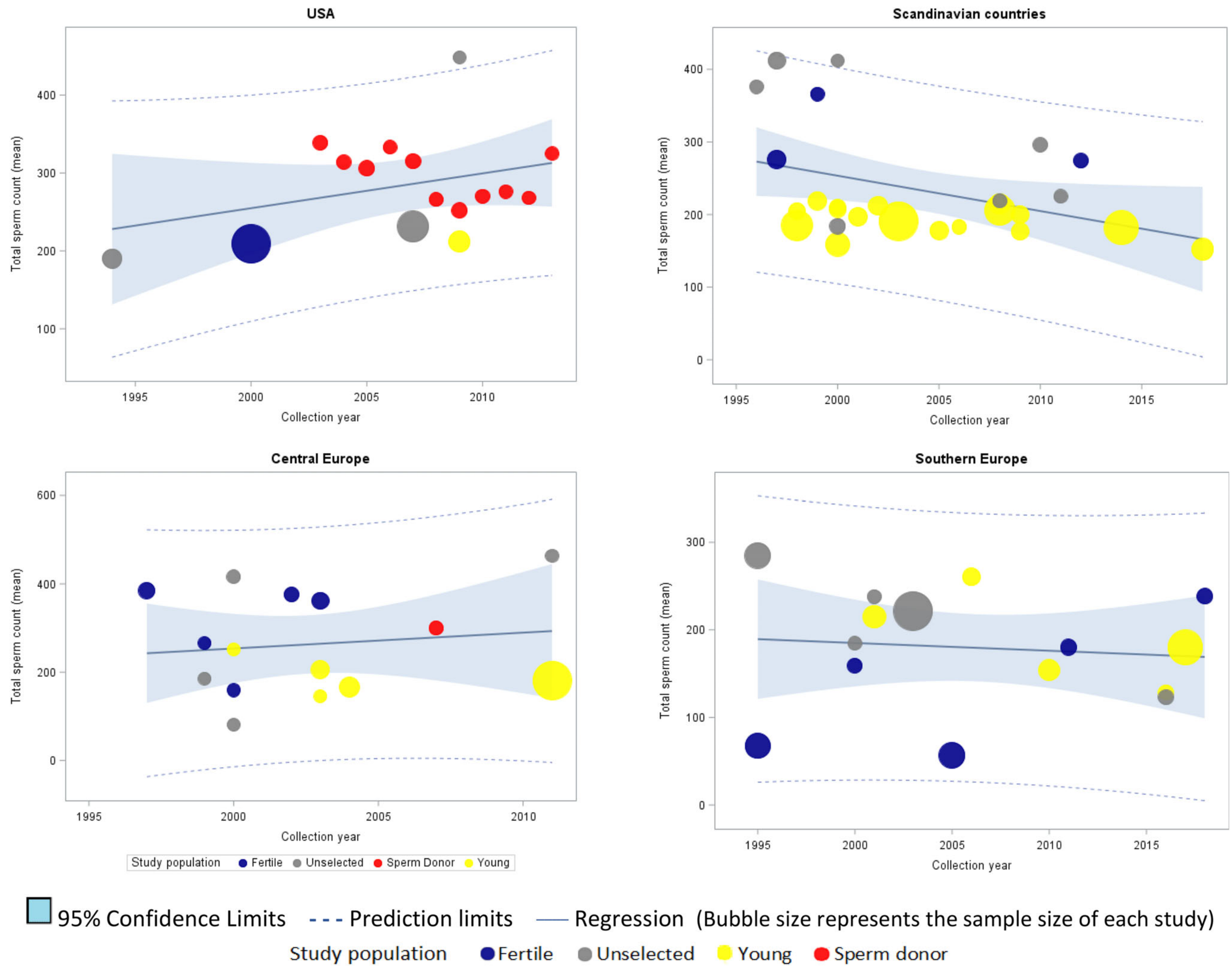

FIGURE 4 Trends in total sperm count by area, 1993-2018 (simple linear regression model).

These findings are not totally consistent with previous reports. For example, Sengupta et al.[88] estimated in European countries an overall 32% decrease in SC in the period 1965–2017.

A comprehensive review[3] including studies published between 1973 and 2011 concluded that SC declined significantly among men from Europe and North America, with the most severe decline in men unselected by fertility. Along this line an update of that review,[4] including also data from South/Central America–Asia and Africa confirmed a declining trend worldwide. Levine et al., however, presented data referred to large geographic areas. We analyzed available information for specific countries in high developed areas. Thus, it is possible that different trends may emerge in specific countries or areas. These differences may disappear when we analyze trends for continents or wide geographic areas.

Our general analysis showed a decreasing trend, but the findings for the period 2000–2020 were not significant. Interestingly, the decline in sperm count tended to be more marked in studies from Scandinavian countries.

The different trends observed in distinct study populations and geographic areas are not easy to explain. For example, the SC value tended to increase in fertile men, but no decreasing trend was observed in unselected men. This finding can be due to selection bias: assuming a downward trend, men with poor semen quality will be less likely to enter the fertile group and thus we would expect a less pronounced decline in this group compared to unselected men.

Otherwise, young men reported a more marked decrease than older unselected men. It is difficult to explain these findings, but it is conceivable that exposure in utero may be increased in younger generations, and human exposure to hormonal disruptors during pregnancy is associated with lower sperm counts in "exposed" (fetal) males in adulthood.[89]

Further, since the high prevalence of obesity among young men is increasing in most high-income countries, it is possible that the obesity epidemic may be having an impact on spermatogenesis among young men, and it may also render such individuals more susceptible to damaging effects of other lifestyle or environmental exposure.[90] Some differences in SC and TSC trends emerged in our analysis, although not statistically significant, among geographic areas. In particular, we observed an SC decreasing trend only in Scandinavian Countries.

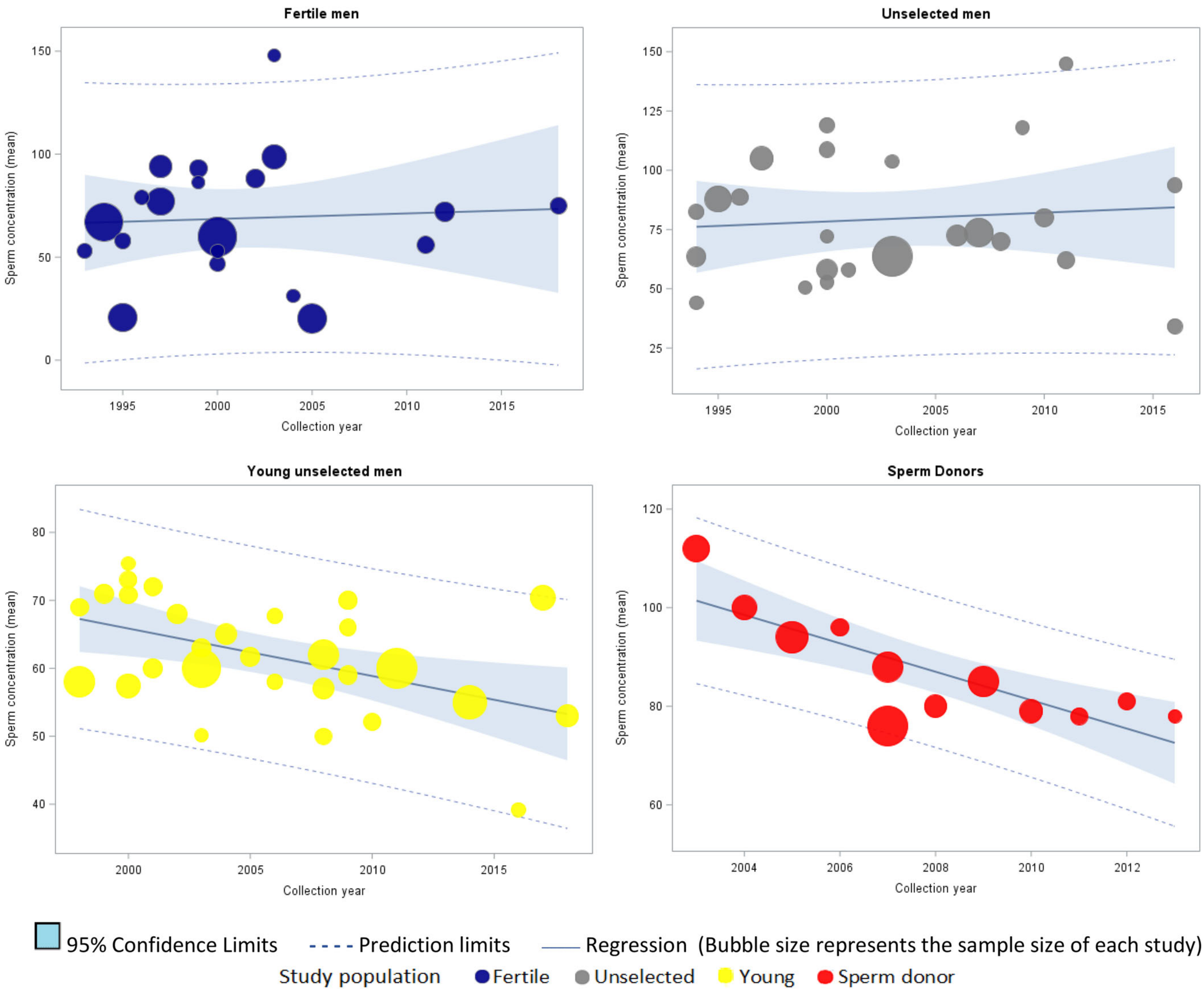

FIGURE 5 Trends in sperm concentration by study population, 1993-2018 (simple linear regression model).

In Europe, regional variation in semen quality has been reported in the late 1990s, with the lowest SCs and total counts being observed for Danish men, followed by French and Scottish men, and Finnish men having the highest sperm counts.[86]

In general, it is conceivable that TSC trend may differ among high-income populations due to different exposure to environmental and lifestyle factors. Along this line, unhealthy diets,[91,92] low physical activity, and hours of TV watching[93] have been associated with worse semen quality, and some studies suggested that the prevalence of overweight and obesity among adults is increasing in Northern Europe.[94] However, it is difficult to explain the observed differences, since it is unlikely the lifestyles in these parts of Europe developed markedly in different directions, thus explaining the effects seen. Other exposures such as traffic pollutants (nitrogen dioxide, sulfur compounds, and sulfur oxides, lead), environmental pollutants (sulfur dioxide, nitric dioxide, nitric oxides, carbon monoxide, ozone, methane, nonmethane hydrocarbons, and volatile organic compounds)[95] and endocrine disrupting compounds[96] may also compromise male reproductive function. Reproductive health risk in men after exposure of bisphenol A (BPA) and pesticides has been reported.[97] Different exposures to pollutants may also explain at least in part the different regional trends.

4.1 | Limitation

To give an overall evaluation and to increase the number of considered subjects, we have included in the general analysis and in the analysis for geographic areas all identified studies, thus this analysis includes data from fertile men, sperm donors, and unselected men (young and not young). As previously reported, different slopes in different populations have been observed. Thus, the inclusion in the same analysis of all populations may introduce biases. This point, with the observation of a high heterogeneity among the studies, should be borne in mind in the interpretation of the general results.

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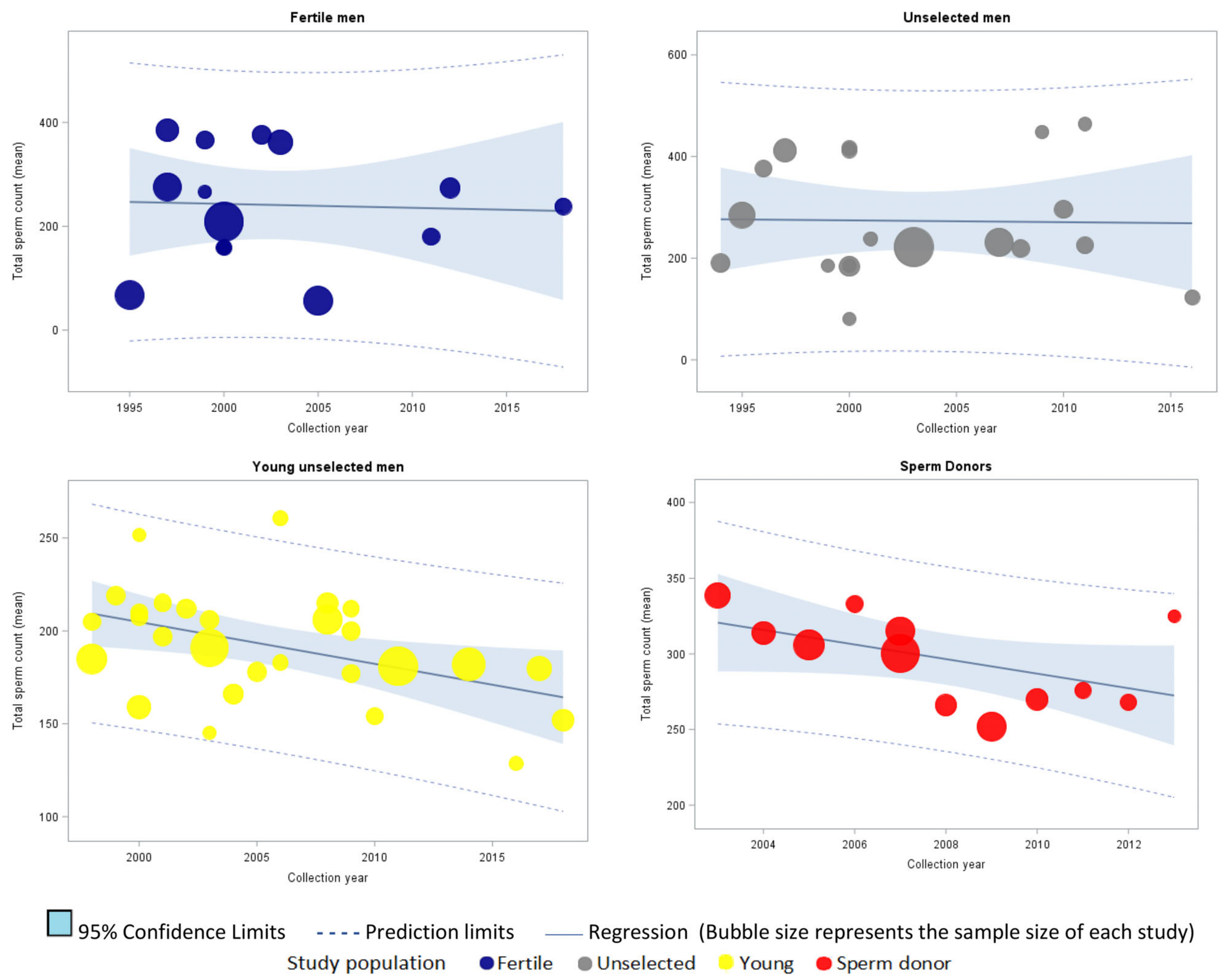

FIGURE 6 Trends in total sperm count by study population, 1993-2018 (simple linear regression model).

To give information of the role of different populations in general trends, we have identified with different colors in figures the different populations.

Among other potential limitations, we analyzed SC and TSC but not sperm motility and morphology. Information regarding these two variables were seldom available. Moreover, the recommended methods and criteria for motility and morphology substantially changed over time, making a reliable comparison impossible. The assessment of SC by hemocytometer has been recommended by the World Health Organization since 1980 (World Health Organization, 2010), but there are still huge variations among individuals and laboratories analyzing the same sample. These differences cannot be taken into account in the analysis, however SC is considered the most reliable endpoint for epidemiological analysis.[98]

5 | CONCLUSIONS

This systematic review including data collected between 1993 and 2019 showed no significant trends in SC in USA and selected Western European countries. The findings, however, are limited and not totally consistent among different populations. To monitor sperm quality in different geographic areas over time is needed.

AUTHOR CONTRIBUTIONS

Sonia Cipriani, Elena Ricci, Giovanna Esposito, and Eva Negri analyzed the data. Sonia Cipriani, Elena Ricci, Francesca Chiaffarino, and Michela Dalmartello wrote the paper. Elena Ricci and Giovanna Esposito selected the articles. Carlo La Vecchia, Eva Negri, and Fabio Parazzini designed the research study and wrote the paper.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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