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EDITORIAL COMMENTARY

# Much a do about nothing or male sperm in peril? Are sugar-sweetened beverages to blame?

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There has been much written of late on the state of male fertility and the postulated declining sperm count trends across populations. A growing body of evidence points to a number of environmental, nutritional and lifestyle factors contributing to falling sperm counts. However, the clinical and public health relevancy remains in question. In a large cross-sectional study, Nassan *et al.* (2021) examined intake of sugar-sweetened beverages (SSBs), artificially sweetened beverages (ASBs), fruit juice and energy drinks in relation to testicular function, semen quality parameters, testicular volume and serum reproductive hormones among 2935 young Danish men (median age, 19 years). The authors hypothesised that higher intake of SSB, but not of ASB, fruit juice or energy drinks, would be associated with poorer overall testicular function, and suggested potential mechanisms via glucose-related oxidative stress, cellular ageing, hypothalamus–pituitary–adrenal axis dysregulation, insulin resistance or possible changes in glucose receptors in sperm motility and post-ejaculation maturation. Beverage consumption was assessed through a self-administered validated food frequency questionnaire. Semen quality parameters were measured conventionally, testicular volume was assessed via ultrasound, and biomarkers of reproductive hormones were quantified in serum. All exposure and outcome data were collected at a single time point, on the study visit day, among a group of young Danish men evaluated for military service fitness from 2008 to 2017. Non-consumers were compared to all other levels of consumption across individual quartiles. Nassan *et al.* used quantile regression models to assess the median change (95% CI) in outcome across quartiles relative to non-consumers as the reference.

Comparing non-consumers to all other levels of SSB intake, a relationship was observed between SSB and total sperm count and sperm concentration and reproductive hormones, i.e. the inhibin B/FSH ratio. In multivariable regression, the median sperm concentration for men in the highest quartile of SSB intake was 13.0 (95% CI: −21, −5.5) million/ml lower than in the non-consuming reference group. Men in the highest category of intake consumed 220 ml of SSB per day (median) with a range of 140–1720 ml/day. Similarly, sperm counts were also lower among all levels of SSB intake compared to the reference group. For example, compared to non-drinkers, the highest quartile of SSB consumption had sperm counts of 28 million (95% CI: −48, −9) fewer and lower inhibin B/FSH ratios (−9; 95% CI: −18, 0). ASB consumption was associated with lower sperm motility, while energy drinkers had improved sperm morphology and higher E2 and LH concentrations. No other meaningful associations were reported for other semen quality parameters, testicular volume or serum hormone concentrations.

While there are only three previous studies (Jensen *et al.*, 2010; Chiu *et al.*, 2014; Yang *et al.*, 2015) from which to compare, the results were consistent only in that higher cola or SSB consumption was associated with any one individual sperm parameter. However, there was limited consistency with respect to which parameter was influenced and the magnitude of associations varied widely. Nevertheless, differences in findings across studies are likely owing to variation in study populations, design, sample size and measurement of exposure and outcomes. One related study by Hatch *et al.* (2018) reported that men's SSB consumption was associated with delayed time to pregnancy among healthy couples attempting conception, lending some support to a potential effect of SSB on male fertility.

According to Nassan *et al.*, the present work represents the largest study to date on beverage consumption and testicular function, and the authors had high power to conduct the primary analysis as well as additional sensitivities. The results are compelling and suggest that men who drink SSB of any amount compared to abstainers have lower sperm counts and concentrations. Potentially diminished testicular function may be explained by the lower inhibin B/FSH ratio among consumers of SSB. However, there was no association with FSH concentrations nor the other reproductive hormones measured, leaving the pathophysiology of lower sperm production uncertain. While the results are reported as linear across quartiles of consumption, a more critical interpretation can argue that there is indeed little difference across quartiles given the overlapping CIs from quartile one to four. It can be argued that these results represent a plateau response, with

any level of SSB exposure showing lower sperm count and concentrations compared to zero exposure.

Due to the cross-sectional nature of the study design, causal interpretation is strongly cautioned. These data were collected at one point in time and thus temporality of exposure preceding testicular function measurements is not established. Furthermore, it would seem unlikely that SSB differs from fruit juice exposure in biological mechanisms of spermatogenesis; both have higher sugar content with differing amounts of fructose and glucose and both can result in insulin-driven metabolic or other cellular changes. Importantly, residual confounding by cigarette smoking, marijuana and recreational drug use, total energy intake and physical activity is possible given the baseline differences between individuals reporting never drinking SSB with those consuming any SSB. Unmeasured confounding from other lifestyle factors related to SSB consumption also cannot be ruled out. Significantly, muscle enhancing products may be an important confounder that was not adjusted for in the multivariable regression models. The proportion of users of a muscle enhancing product differed substantially: 37% among non-SSB consumers compared with only 17% among individuals in the highest SSB use category. Muscle enhancing products may alter important physiologic and hormonal pathways involved in testicular function among SSB abstainers making the comparison group a healthier reference population.

The most salient question, however, remains: how do we interpret such discrete findings in light of their clinical and public health relevancy? Irrespective of any causal link between beverage consumption and lower sperm counts and concentrations, do such variations in sperm parameters really matter? A critical look at the literature to date on declines in sperm count suggest that sperm count variability is not necessarily pathological nor clinically meaningful (Boulicault *et al.*, 2021). Indeed, men can conceive a pregnancy across a wide range of sperm quality parameters (Cooper et al., 2010; Chiles and Schlegel, 2015). High variability of sperm parameters within an individual man and across men can occur as part of normal healthy testicular function. Fertile women, too, recruit an irregular number of follicles per month and there is between ovary variability as well variations within and across women (Blackwell *et al.*, 2013). Take for example the primary finding that men with the highest consumption of SSB had 28 million fewer sperm (95% CI: −48, −9) compared to men who reported no SSB consumption. When the median sperm count among men in the total sample is reported to be 140 million (95% CI: 133, 146), the reported decrease of 28 million among men with the highest exposure to SSB would still put them within the normal range of this semen quality parameter. Although the authors used quantile regression, it may be more clinically relevant to examine the difference in semen quality parameters at the lower tail of the distributions (low percentiles) instead of the medians in relation to levels of SSB intake. Indeed, some of observed declines in sperm parameters may very well be non-pathological and of no concern clinically, but represent variations within a population with differing lifestyle factors. This could be interpreted as akin to differences in vitamin D status, haemoglobin levels and other laboratory blood measurements, where lifestyle, diet and environmental and other factors contribute to blood biomarker profiles of physiological health.

So is sperm in peril and is SSB consumption partially to blame? The recent debate on falling sperm counts suggests male reproduction is in a dire state; however, the evidence of its true impact may suggest otherwise. Male fertility is not in decline and infertility has not increased among couples over the time (Chandra *et al.*, 2013). Even if findings between SSB intake and sperm count and concentrations were causal, the findings will still need to be interpreted in light of their clinical relevancy. Nevertheless, advocating for a healthy lifestyle, including a diet rich in vitamins and omega-fatty acids, exercise and a reduction of tobacco, alcohol and recreational drug use, as well as steps to reduce exposure to environmental toxins, remains a prudent preconception clinical recommendation among both members of the couple planning a conception. In the end, what is good for the goose is also good for the gander.

## Authors' roles

C.M. drafted the commentary. Y.Z. researched and cited evidence for the commentary, and provided critical feedback. Both authors approved the final copy.

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## Conflict of interest

None declared.

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