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Invited Commentary

Invited Commentary: Sleep Disturbances—Another Threat to Male Fecundity?

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In a cross-sectional study among 953 young Danish men (2008–2011), Jensen et al. reported that sleep disturbances showed inverse U-shaped associations with semen parameters and testis size (*Am J Epidemiol.* 2013;177(10):1027–1037). Sleep disturbances were associated with several factors likely to affect semen parameters (such as history of sexually transmitted infections) that cannot all be efficiently controlled for, leaving room for residual confounding. Future studies could adopt a longitudinal design and rely on objective personal measures of sleep quality and duration using accelerometers. Intervention studies would also be helpful to identify whether sleep disturbances (or improvement of sleep quality) can lead to short-term variations in semen parameters. This study adds another suspect to the list of factors possibly influencing male fecundity potential, which also includes overweight, exposure to tobacco smoke (in adulthood and in utero), exposure to specific persistent (lead, organic pollutants) and nonpersistent (some phthalates, bisphenol A) environmental pollutants, and exposure to atmospheric pollutants. Even if each of these factors has a weak impact at the individual level, the large number of factors and the relatively high prevalence of exposure in the general population make it likely that at the population level, lifestyle and environmental factors put a high burden on male fecundity potential.

environment; fertility; health impact; male; reproduction; semen; stress

In the tale "The Sleeping Beauty in the Wood," Charles Perrault tells us about "a king and a queen who were grieved, more grieved than words can tell, because they had no children" (1). After "trying the waters of every country" and making many pilgrimages, the queen gave birth to a beautiful daughter. Unfortunately, because of an aged fairy who had not been invited to the baptism, the princess fell into a 100-year-long sleep. After this time, a prince, disregarding the fact that her clothes "were like those to which his grandmother had been accustomed," woke her up and married her on the same day. During the 2 years that followed, the couple had 2 children, which is a sign of a lack of fecundity problems.

An audacious interpretation of this tale would be that a good night's sleep is good for fecundity.

Three hundred years after Perrault, Jensen et al. (2) have revisited this hypothesis by testing whether sleep disturbances could be associated with altered male fecundity parameters. In this issue of the *American Journal of Epidemiology*, they report an inverse U-shaped association between sleep disturbances and sperm concentration, proportion of motile and morphologically normal spermatozoa, and testis size (2). The study was based on a Danish study of military conscripts, a well-designed cross-sectional study of male reproductive health with continuous recruitment of young men since 1996 (3); the focus in this new publication is on men recruited between 2008 and 2011, when a questionnaire on sleep disturbances was added to the design.

IS THIS REAL?

Let us first discuss the potential bias. The authors rightly indicate that reverse causation is not a strong concern in their study. The recruited men were young (77% of them were aged 18–20 years), and only 7% had already attempted to have a child. It is therefore unlikely that sleep disturbances had been caused by any knowledge about poor fecundity potential. Selection bias is a general concern in semen studies, which often have low participation rates (usually in the 10%–30% range) or are based on self-selected

populations (e.g., sperm donors), preventing estimation of participation rates. In other populations, willingness to deliver a semen sample is sometimes associated with characteristics linked to fertility status (4–6). In the present study, the participation rate was approximately 30%, which is in the higher range of generally observed values (2); shortly after the study set-up in 1996, a comparison of testosterone levels between men agreeing to deliver semen and blood samples and men accepting only blood sampling (with a participation rate of 78% for this group) was done. Testosterone serum levels were similar between the two groups of men (7), limiting the plausibility of a selection bias related to fecundity level; this is further supported by the above-mentioned fact that most of the men were aged 18–20 years and that very few had previously made a pregnancy attempt.

Measurement error is a clear concern. The study benefited from a centralized assessment of semen parameters, with a small number of technicians assessing morphology, and a strict quality control program. Nonetheless, because of the within-man variability of most semen parameters, studies with 2 or more measures per man are usually more efficient than studies with a single assessment of semen parameters, particularly for the most variable parameters such as motility or morphology of the spermatozoa (8). This type of bias is likely to be more limited for sperm concentration and should be expected to attenuate any association with sleep disturbances (8). Concerning the assessment of the latter, the Karolinska Sleep Questionnaire has been validated against electroencephalographic measures and slow eye movement activity (9). Jensen et al. used a 4-item version of this questionnaire and averaged the replies to the 4 questions to obtain a single variable on sleep quality (2), which warrants a more complete assessment of sleep features in future studies. Small and relatively cheap accelerometers can now be conveniently carried by study participants at night to provide an objective measure of sleep duration and quality (10). Their use in future surveys, in addition to subjective questionnaires, would allow investigators to study the impact not only of sleep disturbances but also of sleep duration, which has previously been shown to be associated with various other health outcomes (11).

Finally, the issue of confounding is particularly tricky in this study. Which common causes could sleep disturbance and poor semen quality share? There appear to be many candidates; Figure 1 is an attempt to summarize the relationships between some of these factors. Depression is a potential confounder that was discussed by the authors. It was adjusted for, and exclusion of depressed subjects did not alter associations; as indicated (2), residual confounding cannot be excluded because depression symptoms are possibly underdeclared. Relatedly, it was reported previously in the same study that poor self-rated health is associated with decreased semen quality (12). Many diseases could lead to participants' suffering from sleep disturbances or rating their sleep quality as poor, so that poor (self-rated) health is possibly also associated with sleep disturbances. Thanks to their detailed assessment of subjects' characteristics, Jensen et al. highlighted the observation that men with sleep disturbances had an unhealthier lifestyle (2); indeed, they had a higher body mass index, more often smoked, were more often exposed to smoking in utero, and more often suffered from sexually transmitted infections. All of these characteristics are known or supposed to influence semen quality, and the limitations of questionnaires to accurately assess them leaves room for residual confounding. Exposures to specific environmental factors constitute other potential candidates; some of them, including polychlorinated biphenyls (13), could affect semen parameters, in the context of either early-life or adulthood exposures. Toxicological studies have also found effects of polychlorinated biphenyls on (pentobarbital-induced) sleep duration in animal models (14); to my knowledge, this possible effect has been little considered in humans. The issue of confounding also needs to be discussed in light of the reported association between sleep disturbances and testis volume (2); testis volume is indeed less likely than semen parameters to vary in the short term, outside the context of acute shocks or disorders. This association favors sleep disturbances assessed at the time of semen examination being a marker for earlier events more directly related to semen quality. In other words, the associations observed by Jensen et al. (2) could be partly due to an effect on male fecundity parameters of poor sleep quality during childhood or the teenage period, or of early life exposures.

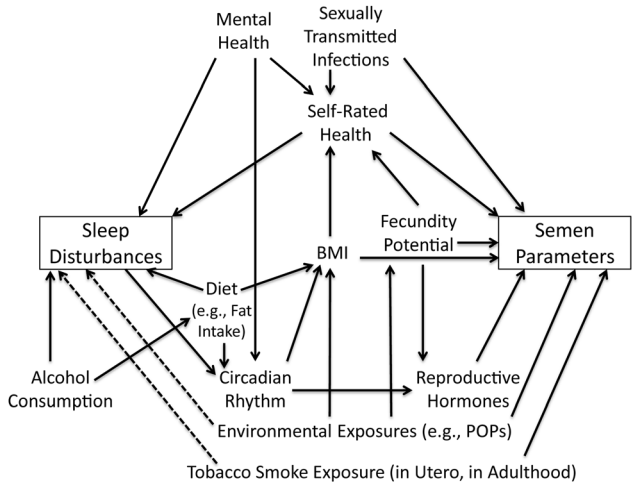

Figure 1. Hypothesized relationships between sleep duration, semen parameters (e.g., sperm concentration), and selected potential confounders or intermediate factors. The figure does not contain all relevant factors or all possible relationships. The dashed arrows correspond to associations that are little documented or merely plausible. BMI, body mass index; POP, persistent organic pollutant.

For factors halfway between physical health, mental health, and behaviors such as sleep quality, the complexity of the causal web (Figure 1) will probably remain a challenge in terms of residual confounding for observational studies. Consequently, the types of small intervention studies mentioned by Jensen et al. aiming at checking whether improved sleeping patterns restore semen quality (what could be seen as a "Sleeping Beauty"-type experiment) would be very relevant, at least to document short-term effects.

The existence of potential bias should not preclude a discussion on the potential underlying mechanisms and on the possible implications of such an association.

Sleep disturbances could perturb the circadian rhythm of reproductive hormones, which would in turn affect the production of spermatozoa. As was suggested in an experiment on 10 men, the nocturnal testosterone rhythm can be disrupted by sleep fragmentation (15), which is a feature of what people consider sleep disturbances. Jensen et al. also noted an intervention study in which sleep restriction for 1 week caused a decrease in testosterone levels (16). The assessment of other reproductive hormones implied in the regulation of sperm production in a longitudinal context would allow discussion of the plausibility of this "endocrine disruption" pathway. In the Jensen et al. study, sleep disturbances were not associated with alterations in reproductive hormone levels (2), but their intraindividual variability (despite assessment in a very narrow time window between 9:30 AM and 10:30 AM for most men) may be even larger than that of semen parameters, further limiting statistical power. In addition, the usual regression approach in which each hormone level is separately regressed on sleep disturbance might not be efficient in the case of a complex system with retroaction loops such as the endocrine system. Joint modeling of all hormone levels simultaneously might be more relevant, ideally in the context of repeated hormone measurements.

POSSIBLE IMPLICATIONS

What could be the consequences for couples of an alteration in semen characteristics in relation to sleep disturbances? Would a decrease of 20%–30% in sperm concentration affect the ability to achieve pregnancy? The answer is not straightforward, because the association between sperm concentration and ability to achieve pregnancy has a threshold. A rough estimate is that fecundability, the monthly probability of pregnancy, would decrease by about 10% following a decrease of 20%–30% in mean sperm concentration (17). As was shown in a simulation study, the proportion of couples suffering from 12-month involuntary infertility could consequently increase by 10%–50% (18). Sleep disturbances could also alter male libido, which might entail an additional burden on time to pregnancy.

We can also consider these results in the wider context of the falling sperm count hypothesis. This hypothesis, first formulated in the 1970s (19), has attracted the attention of the scientific community after an ecological analysis suggested a decline of 50% in mean sperm concentration over a 45-year period (20). Since then, many reports have been published—the most recent ones describing a decline in sperm concentration among Finnish young men (21) and among partners of sterile women resorting to assisted reproduction technologies in France (22), no change among Swedish men from the general population (23), and an increase (starting from a low mean value in 1996) among the Danish military conscripts (3) considered here. The debate is unlikely to find a resolution with the sole reliance on such approaches, if only because temporal trends can vary between regions, because few well-designed monitoring systems exist outside Scandinavian countries, and because of the already-noted concern about (self-) selection bias in semen studies.

However, the results presented by Jensen et al. allow us to tackle this issue in an indirect way. Sleeping duration has probably shortened in Western populations, and it is possible that sleep disturbances are more frequent now than in earlier times (24). If we assume that the prevalence of sleep disorders has increased by, say, 40% over the past several decades, then a decrease of approximately 25% in mean sperm concentration at the individual level among men with sleep disturbances would translate into a decrease of 10% in mean sperm concentration during the same period at the population level (25). This would be a rather minor impact; however, sleeping disturbances are not alone on the list of factors possibly influencing semen characteristics whose prevalence has increased during the last few decades. This list, which Dr. Jensen and her colleagues have contributed to building, includes active smoking in adulthood (26), maternal smoking during pregnancy (27), overweight (28), possibly heat (if we consider that scrotal temperature tends to increase as a result of men spending more time sitting and being less active) (29), exposure to persistent organic pollutants (13), exposure to heavy metals such as lead (30) (although the trend in exposure prevalence may have reversed recently in countries where lead has been banned from gasoline), exposure to less persistent pollutants such as bisphenol A and phthalates during the developmental period (31, 32) or in adulthood (33, 34), and exposure to atmospheric pollutants (35). Let us assume that this list of suspects includes 8 factors, each entailing on average a decrease of 20% in sperm concentration among exposed men, and that the prevalence of exposure to each factor increased by 40% during the period considered. If we disregard any other time-varying risk factor, the population impact of these 8 factors as a whole would be a decrease in sperm concentration of approximately 50% (25).

This basic health impact assessment exercise does not tell us that sperm concentration has indeed declined, but it indicates that these factors may altogether put a very heavy burden on the (male) fecundity potential of contemporary populations.

Let us do our best to address this question, so that we are not doomed to wait 100 years before an exhaustive evaluation of the impact of the environment as a whole (including all lifestyle factors and, more strictly, environmental factors at all ages) on fecundity is available.

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