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Sleep: A Nourisher in Life's Feast?

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Despite several decades of basic and clinical research, the functions of sleep remain largely unknown. While sleep is absolutely essential for promoting alertness during the day, the field remains divided on its role in other processes including learning and memory with some supporting and others repudiating such functions (1). In recent years, another livelier debate has emerged on the potential role of sleep in influencing future weight gain. More specifically, the question that has been posed is whether alterations in habitual sleep duration (curtailment or extension) 'cause' or predispose to an increase in body weight? The evidence chronicled in this issue of the journal by Marshall and colleagues addresses the question of whether sleep duration is a 'causal' factor for future weight gain, all other things being equal (2). Given the ever increasing prevalence of obesity, the focus of the review is timely and unquestionably relevant for clinical practice and public health. However, unlike some of the other risk factors that have been associated with obesity (e.g., excess caloric intake, sedentary lifestyle), causally implicating the extremes of sleep duration as an independent intermediary has proved to be challenging.

The question of whether a specific factor (e.g. sedentary lifestyle or sleep duration) orchestrates the predisposition towards future weight gain can be conceptualized using Rothman's framework of sufficient cause (3). A sufficient cause is defined by a set of minimal conditions or events that inevitably will lead to the outcome under consideration (e.g., weight gain). Within this framework, it is readily obvious that factors such as excess caloric intake and sedentary lifestyle represent independent sufficient causes that can increase body weight. If there is concurrence of several sufficient causes (caloric intake + sedentary lifestyle), the risk may be further amplified and could perhaps even exceed the additive sum of the risks attributable to each of the individual factors. Rothman's framework of sufficient cause is not necessarily limited to simple one-to-one relationships. A sufficient cause can certainly be made up of a number of component causes. For example, the occurrence of an outcome may require the concurrence of several factors (e.g., X, Y, and Z). An alternative set of factors (e.g., P, Q, and R) could also serve as a sufficient cause. Thus, the series of X, Y, and Z or P, Q, and R could represent independent causal mechanisms for an outcome (e.g., weight gain, cardiovascular disease). When each of the components from a series exist (i.e., XYZ or PQR), the outcome will occur.

Using the aforementioned framework, it is certainly possible that sleep duration alone may be a sufficient cause by perhaps altering homeostatic mechanisms that promote future weight gain. In fact, Spiegel and colleagues (4) have shown that sleep restriction for even two nights can increase hunger and appetite and alter the diurnal profiles of leptin and ghrelin – factors that

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regulate with satiety and food intake. Such pathophysiological changes, if left unchecked, could certainly increase body weight and anchor short sleep duration as a sufficient cause. If sleep duration in isolation causal, targeting an 'optimal' amount of sleep duration would maintain normal neuroendocrine alterations and minimize additional weight gain beyond that attributable to other well established risk factors. It is, however also possible, and more likely, that sleep duration is a component cause or a marker of other conditions that are associated with being overweight or obese. In this context, sleep duration acts in concert with the other components to form a sufficient cause. For example, sleep duration may influence obesity risk through its association with factors such as socioeconomic position (5). The annual Sleep in America polls have consistently found that survey participants reporting habitually short sleep duration often work longer hours, are more likely to be shift workers, and have more than one job compared to those reporting normal sleep duration (6). Thus, because of imposed demands on their time, these individuals are likely to restrict the amount of nocturnal sleep, resign to poor eating habits, and not engage in a regular exercise program. Although the association between weight gain and long sleep duration is more controversial than with short sleep duration (7;8), the association, if eventually verified as causal, could also be interpreted as component cause. Poor health status and depressive symptoms are correlated with long sleep duration (9). Moreover, both are known risk factors for weight gain and thus could provide a partial explanation of the association between long sleep duration and weight gain. If sleep duration (short or long) is a component cause, targeting an 'optimal' level without addressing the associated factors is unlikely to alter the added risk of future weight gain. In contrast, addressing extremes of sleep duration in conjunction with other component causes may potentially ameliorate the risk. Given the strict criteria that is often imposed for proving causal associations, it is understandable Marshall and colleagues take a cautious stand in their report on whether sleep duration is a potential 'cause' of obesity. At present, there is insufficient evidence to support the notion that sleep duration is an independent risk factor for obesity. Proof of causality will require a truly integrative approach that will incorporate the many of criteria proposed by Hill (10):

1. Temporal relationship (i.e., do changes in sleep duration precede changes in body weight);
2. Dose-response relationship (i.e., does the degree of habitually short or long sleep proportionally increases the risk for weight gain);
3. Consistency (i.e., can the association between sleep duration weight gain be replicated in different settings and different samples);
4. Strength of association (i.e., what is the magnitude of association between sleep duration and weight gain);
5. Biologic plausibility (i.e., is there some biological basis or underlying mechanisms that explain the link between sleep duration and obesity);
6. Experimental induction (i.e., can altering sleep duration using an appropriate experimental regimen changes body weight);
7. Alternation explanations (i.e., are there confounding factors that explicate the observed association); and
8. Coherence (i.e., does the notion that short or long sleep increases weight conflict with existing knowledge on natural history of obesity).

Unraveling the tapestry that links sleep duration and weight gain will require a concerted approach between basic and clinical researchers which will certainly improve our understanding of the overall functions of sleep. In this quest for the true essence of sleep, issues aside from the burden of proving causality need to be carefully considered. One such issue is

defining the time window during which an individual is susceptible to the adverse effects of short or long sleep duration. Defining this window or the exposure time frame is not a trivial matter. Some health exposures confer risk for adverse outcomes only during a specific time frame. For example, exposure to lead during early childhood increases the risk for poor cognitive outcomes (11). However, higher serum lead levels in adults do not have such a predisposition. If sleep duration operates only during a particular time window (e.g., increases obesity risk only during middle age) a lack of consistency across studies in different aged populations is expected. For other exposures, the effects often lag and measurement of previous exposure level is necessary to determine the risk for incident outcomes. Smoking is an example of an exposure that is associated with lagged outcomes where prior history, but not current status, predicts the risk of outcomes (e.g. lung cancer) (12). A bulk of evidence on sleep duration and weight gain is based on the concurrent assessment of the exposure (i.e. sleep duration) and outcome (i.e. body weight). If sleep duration was time invariant, simultaneous assessments of exposure and outcome would not alter the biological inferences on sleep and obesity. However, sleep duration is highly variable over time and often varies from night-to-night in the general population (13). Given its time variant nature, a single assessment of sleep duration, whether subjective or objective, provides only a 'snap shot' or a cross-section of a longitudinally evolving process. The failure to capture the overall pattern in sleep behavior can lead to misclassification of individuals across categories of habitually short, normal, and long sleep duration. Furthermore, for each category of sleep duration three types of time-varying trajectories are possible: increasing duration, decreasing duration, or stable duration. Cross-sectional or even longitudinal surveys that fail to include time-varying measurements of both sleep duration and body weight will yield limited insight into the cause-and-effect sequence and contribute little in closing the gaps of how sleep alters body weight.

Obviously, sleep is of vital importance for human life given that we spend one-third of our lifespan in this state. Thus, the question is not whether sleep is important, but rather why and what myriad of biological functions does it influence. Based on the target article by Marshall and colleagues (2) and the associated commentary by Taheri and Thomas (14), body weight may well be determined by how much or how little we sleep. Going forward, the challenge for those of us entrenched in sleep medicine will be, first, to collect unequivocal evidence on whether the sleep duration-obesity relationship reflects a causal effect or is it merely a correlation due to unmeasured factors. Research using state-of-the-art methods for assessing sleep duration is vital in this determination as is the need for coupling human and animal-based studies. Second, we need to determine whether sleep duration works alone or in concert with other causal factors to increase the risk for obesity. Third, it will be critical to establish whether acute changes in sleep duration alter this risk or does risk for obesity develop only through long-term exposure to extremes of sleep duration. Fourth, we need to clarify whether the vulnerability to weight gain with short or long sleep is present during certain time periods (e.g. childhood, old age)? Finally, and perhaps more importantly, can 'optimal' sleep duration aid in decreasing weight once it has been gained? Clearly, suggesting that short or long sleep duration is a risk factor for weight gain is an over simplification. If sleep can indeed modify body weight, it is essential that we acquire a better understanding of this link given that the obesity epidemic have become of global proportions. In the end, we may in fact find that:

Sleep that knits up the ravelled sleeve of care
 The death of each day's life, sore labour's bath
 Balm of hurt minds, great nature's second course,
 Chief nourisher in life's feast.
 ~William Shakespeare, Macbeth

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