Opinion Article

Effects of sleep deprivation on sarcopenia and obesity: A narrative review of randomized controlled and crossover trials

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Abstract

Shortened and fragmented sleeping patterns occupying modern industrialized societies may promote metabolic disturbances accompanied by increased risk of weight gain and skeletal muscle degradation. Short-term sleep restriction may alter energy homeostasis by modifying dopamine brain receptor signaling, leading to hyperpalatable food consumption and risk of increased adiposity. Concomitantly, the metabolic damage caused by lower testosterone and higher cortisol levels may stimulate systemic inflammation, insulin resistance, and suppress pathways involved in muscle protein synthesis. These changes may lead to dysregulated energy balance and skeletal muscle metabolism, increasing the risk of sarcopenic obesity, an additional public health burden. Future trials controlling for food intake and exploring further the influence of sleep deprivation on anabolic and catabolic signaling, and gut peptide interaction with energy balance are warranted.

Keywords: Cortisol, Energy balance, Sarcopenia, Sleep restriction, Testosterone

Introduction

Entering our fifth decade, it is estimated that approximately 1-2% of muscle mass and strength decline annually, which are exacerbated during older age1,2. Age-induced skeletal muscle dysregulation characterized as sarcopenia is defined by progressive loss of grip strength, gait speed, balance, and muscle mass, leading to higher risk of falls, fractures, moving difficulties, institutionalization, and lower lifestyle quality3-5. Considering that population increase over the age of 60 is expected to globally reach 2.1 billion by 2050, shaping the fastest growing age group6, metabolic disturbances during ageing may vary among different ethnicities7 and their elevated frequency may impose great economic and public health burden8. Metabolic syndrome is accompanied by abdominal obesity and skeletal muscle insulin resistance, which may predispose increased adiposity and dysregulated skeletal muscle function9,10. Incidence of sarcopenia may concomitantly occur in obese patients, leading to additional poor health outcomes and the novel state of sarcopenic obesity. However, clear consensus is presently lacking due to uncertain ranges of fat-free fat index (fat-free mass/height2) between obese and lean groups11.

Risk of sarcopenia and obesity are driven by multiple parameters, including chronic pro-inflammatory cytokine secretion, increased oxidative stress, physical inactivity, malnutrition12, and sleep disorders13. Modern societies have established an association between metabolic disorders and chronic sleep deprivation14 through excessive blue-light exposure from social media and computer screening, late social activities, and shift work15-17. Considering that older individuals are at great risk of obstructive sleep apnea, restless legs syndrome, anxiety disorders, dementia, and psychostimulants, which may trigger insomnia and further disturb sleeping patterns18,19, sleep disorders may be

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### Table 1. Randomized controlled and crossover trials investigating the changes in body composition, appetite hormones, and energy intake, following sleep restriction.

| Study Design/Subjects                                                                 | Intervention                                                                 | Outcomes                                                                                                                                                                                                 | Study |
|--------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|
| RCT n=36; age 45±6 y BMI 25-40 kg/m²                                                 | CR (n=15) (29-43% of RMR) vs. C+SR (n=21) (169±75 min/wk) for 8 weeks       | Fat mass lost ↑ in CR vs. C+SR Leptin ↓ in C+SR vs. CR                                                                                                                                            | 32    |
| Randomized Crossover Trial n=30; age 36.7±10.8 y BMI 20.4-40.7 kg/m²                 | 4-days of 6 hr sleep ↓ 1-week washout ↓ 4-days of 9 hr sleep                | ↑ food cue response in right inferior frontal gyrus & ventral medial prefrontal cortex in short vs. normal sleep                                                                               | 43    |
| Randomized Crossover Trial n=9; age 23.1±2 y BMI 22.2±3.0 kg/m²                       | 3-days of 3.5 hr vs. 7 hr sleep followed by a 7 hr recovery sleep night      | PYY & Fullness ↓ Hunger ↑ After 3.5-hr sleep vs. 7-hr sleep                                                                                                                                  | 44    |
| Randomized Crossover Trial n=19; aged 23.5±0.7 y BMI 23.1±0.4 kg/m²                 | 4-days of 8.5 hr sleep ↓ 4-week washout ↓ 4-days of 4.5 hr sleep            | Snacks and Sweets (total kcal) ↑ Ghrelin ↑ in short vs. normal sleep                                                                                                                           | 36    |
| Randomized Crossover Trial n=31; aged 14-17 y BMI <30 kg/m²                          | 5-days of 6.5 hr sleep ↓ 2-day washout ↓ 5-days of 10 hr sleep              | Kcal (11%) & Sweets (52%) ↑ in short vs. normal sleep                                                                                                                                          | 47    |
| RCT n=25; aged 34.7±4.7 y BMI 23.6±1.3 kg/m²                                         | 5-days of 4 hr sleep vs. 5-days of 9 hr sleep                              | Superior & middle temporal & frontal gyri ↑ Left inferior parietal lobule ↑ Orbitofrontal Cortex ↑ Right Insula ↑ after viewing unhealthy foods in short vs. normal sleep | 42    |
| Randomized Crossover Trial n=41; aged 14-16 y BMI <30 kg/m²                          | 5-days of 6.5 hr sleep ↓ 2-day washout ↓ 5-days of 10 hr sleep              | Desserts & sweets ↑ in short vs. normal sleep                                                                                                                                             | 33    |
| Randomized Controlled Trial Sleep-deprived n=8; aged 24.1±4.5 y vs. Control n=9; aged 25±4.7 y BMI 18.5±24.9 kg/m² | 8-days of 5.2 hr sleep vs. 8-days of 7 hr sleep                            | E1 ↑ in short sleep (559 kcal/d) E1 ↓ in normal sleep (118 kcal/d) Leptin ↔ Ghrelin ↔ between groups                                                                                       | 35    |
| Randomized Crossover Trial n=15; aged 22.4±4.8 y BMI 22.9±2.4 kg/m²                  | 3-days of 9 hr sleep ↓ 5-days of 5 hr sleep ↓ 3-days of 9 hr sleep         | EE ↑ (-5%) E1 ↑ Weight Gain ↑ (0.82±0.47 kg) in short vs. normal sleep                                                                                                                       | 51    |
| Randomized Crossover Trial n=7; aged 23.7±3.8 y BMI 22.8±1.6 kg/m²                   | 4-days of 4.5 hr sleep or 4-days of 8.5 hr sleep                           | Body-weight ↔ pAkt 30% ↓ in short vs. normal sleep                                                                                                                                        | 49    |
| Randomized Crossover Trial n=11; aged 23±2 y BMI (24.2±2.6 kg/m²) and n=10; aged 60±5 y BMI (23.3±1.9 kg/m²) | 3-wk of 10 hr sleep ↓ 3-wk of 5.6 hr sleep & circadian disruption ↓ 9-days of recovery sleep | RMR ↓ (8%) Postprandial Glucose ↑ Insulin ↓ in short vs. normal sleep                                                                                                                        | 50    |
| Randomized Crossover Trial n=27; aged 35.3±5.2 y BMI 23.5±1.1 kg/m²                  | 5-days of 4 hr sleep ↓ 3-week washout ↓ 5-days of 9 hr sleep               | RMR ↓ Hunger ↑ Appetite for Sweet ↑ in short vs. normal sleep                                                                                                                              | 45    |
| Randomized Crossover Trial n=26; aged 35.1±5.1 y BMI 23.6±1.3 kg/m²                  | 5-days of 4 hr sleep ↓ 3-week washout ↓ 5-days of 9 hr sleep               | Food stimuli response in Putamen ↑ Nucleus Accumbens ↑ Thalamus ↑ Insula ↑ Prefrontal Cortex ↑ in short vs. normal sleep                                                                    | 41    |
| Randomized Crossover Trial n=27; aged 30-45 y BMI 22-26 kg/m²                         | 5-days of 4 hr sleep ↓ 3-week washout ↓ 5-days of 9 hr sleep               | Ghrelin ↑ in men during short vs. normal sleep Insulin ↓ in women during short vs. normal sleep                                                                                               | 37    |
| Randomized Crossover Trial n=30; aged 30-49 y BMI 22-26 kg/m²                         | 5-days of 4 hr sleep and 5-days of 9 hr sleep                              | RMR ↔ EE ↔ E1 ↑ in short vs. normal sleep                                                                                                                                             | 46    |
| Randomized Crossover Trial n=11; aged 39±5 y BMI 26.5±1.5 kg/m²                       | 14-days of 5.5 hr sleep ↓ 3-month washout ↓ 14-days of 8.5 hr sleep        | Leptin ↔ Ghrelin ↔ Snacks ↑ (11087±541 vs. 866±365 kcal/d) in short vs. normal sleep                                                                                                       | 34    |

↑, increased between groups; ↓, decreased between groups; ↔, no changes between groups; BMI, body mass index; C+SR, caloric and sleep restriction group; CR, caloric restriction group; EE, energy expenditure; EI, energy intake; pAkt, phosphorylated Akt; PYY, Peptide YY; RCT, randomized controlled trial; RMR, resting metabolic rate.

accumulated in the future and perpetuate metabolic health problems. Shortened and fragmented sleep may affect food cravings and appetite regulation through gut-brain axis disruption, which may alter energy balance and lead to weight gain. Additionally, sleep restriction may interfere with steroid hormone production, increasing muscle mass and strength declines and enhance sarcopenia risk. The aim of this narrative review is to highlight the
physiological impact of sleep restriction through randomized controlled and crossover studies, focusing on how hypothalamic and steroid hormone dysfunction may impair adipose tissue and skeletal muscle, and increase the risk of obesity and sarcopenia.

The impact of sleep restriction on energy balance and food intake: Findings from experimental trials

Sleep duration is a major contributor to hormone signaling in the stomach (ghrelin) and adipose tissue (leptin), affecting food choice and energy balance. A recent experimental study demonstrated decreased leptin concentrations following sustained sleep restriction, however mean sleep loss was ~3 hr/wk, which may be deemed insignificant throughout 7-day periods. Multiple randomized crossover trials have failed to detect statistically significant changes of leptin during short-term sleep deprivation against habitual sleep duration. Likewise, experimental research around ghrelin levels is equivocal. Studies measuring ghrelin concentrations have not displayed differences between shortened sleep and normal sleep groups, although other short-term crossover studies have shown increased ghrelin levels during 4.5 hr/d sleep compared to 8.5-9 hr of daily bed rest, respectively. In addition, decreased PYY levels and perception of fullness have been demonstrated after 3 days of reduced sleep (3.5 hr/d) compared to 7 hr of sleep/night. However, experimental studies in older individuals are lacking and longer-term experimental trials, measuring appetite hormones and controlling for energy intake may be required.

Moreover, it is suggested that the nucleus accumbens is a precursor of increased food intake driven by motivational stimuli, which activates dopamine receptor subtypes through orexin neurons. Therefore, increased appetite may be stimulated by hyperpalatable food viewing, hence, obese populations may be predisposed to food overconsumption due to higher motivation to eat. Interestingly, research has advocated for increased energy intake via sweets and snacks through several brain regions being involved in food response stimulation following periods of sleep deprivation. A 5-day sleep restriction (4 hr/d) protocol may trigger dopamine receptors in hypothalamic regions to a greater extent vs. habitual sleep (9 hr/d) and these effects may be sustained following longer sleep durations, although suboptimal (6 hr/d). These results are compatible with experimental trials demonstrating increased hunger, sweet cravings, and energy intake via snack consumption in the form of sweets and desserts, highlighting a positive relationship between sleep loss and higher food intake. This may lead to gradual weight gain and further disrupt insulin and glucose signaling, alleviating the effectiveness of weight loss strategies through lesser body fat mass loss. Finally, brain responses related to food stimuli in lean vs. obese subjects may differ and should be taken into account when relevant clinical trials are conducted. Experimental studies exploring how energy balance is affected by reduced sleep duration are shown in Table 1.

Effects of sleep deprivation on testosterone and cortisol release: An increased risk of skeletal muscle degradation

Sleep deprivation is associated with decreased testosterone and increased cortisol levels. Testosterone triggers the protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway and its downstream targets. S6 kinase 1 (S6K1) and eukaryotic translation initiation factor 4-E binding protein 1 (4EBP1) via activation of insulin growth-factor-1 (IGF-1), which are precursors of muscle protein synthesis (MPS). Recently, Saner et al (2020) investigated the effects of short-term (5 days)

| Study Design/Subjects | Intervention | Outcomes | Study |
|-----------------------|--------------|----------|-------|
| RCT n=14, aged 36.6±5.6 y BMI 24.1±1.1 kg/m² | 5-days of 4 hr sleep vs. 5-days of 9 hr sleep | Testosterone ↑ in normal vs. short sleep group | 60 |
| Randomized Crossover Trial n=15, aged 27.1±1.3 y BMI 22.9±0.3 kg/m² | 2-days of 4hr sleep ↓ 6-week washout ↓ 2-days of 8 hr sleep | Morning Testosterone & Prolactin ↓ in short vs. normal sleep | 61 |
| n=10, aged 24.3±4.3 y BMI 23.5±2.4 kg/m² | 7-days of 8 hr sleep ↓ 3-days of 10 hr sleep ↓ 8-days of 5 hr sleep | Testosterone (10-15%) ↓ in short vs. normal sleep durations Cortisol ↔ | 62 |
| n=16, aged 21-26 | (n=10) went on a 1-day 24 hr sleep fragmentation (7 min asleep, 1 min awake for 72 times) vs. (n=6) 1-day of 9 hr sleep | Nocturnal Testosterone ↑ in those with REM episodes vs. fragmented sleep group | 63 |

Table 2. Randomized controlled and crossover trials exploring the changes in testosterone levels following sleep restriction.
sleep deprivation (4 hr/d) on MPS and muscle protein breakdown (MPB) markers, and the influence of high-intensity exercise following sleep restriction. Participants displayed no differences in FOXO 1/3, mTOR, Akt, and 4EBP1 pathways between short and habitual sleep groups, however, subjects undergoing solely sleep deprivation demonstrated low myofibrillar protein synthesis, which was normalized following exercise. This should be taken into account, considering that older and frail individuals may be unable to perform high-intensity exercise and offset short sleep-induced physiological consequences given their limited physical abilities. Furthermore, randomized controlled and crossover studies (Table 2) have reported lower testosterone levels during short periods (2-8 days) of sleep restriction (4-5 hr/d) compared to habitual sleep duration (8-10 hr/d)61-63. Interestingly, sleep quality is another critical component of sleeping patterns. A fragmented sleep schedule consisted of 7 min sleep/13 min awake cycles, 72 times within 24 hours, showed reduced nocturnal testosterone due to dysregulated REM states vs. participants following habitual night sleep64. More experimental trials with greater power may be necessary to establish further conclusions and provide information regarding the physiological impact of disruptive sleep length and stages on testosterone and MPS.

Disruptive sleep phases leading to shorter REM sleep may elucidate complications in the hypothalamic-pituitary-adrenal (HPA) axis, which is linked to higher cortisol levels65. Prolonged cortisol release inhibits IGF-1/Akt/PI3K pathways and represses mTOR activation through upregulation of ubiquitin-proteasome system66, regulated in development and DNA damage responses 1 (REDD1), FOXO 1/3 transcription factors, and Muscle RING-finger protein-1 (MuRF-1) expression, potentiating anabolic resistance68.

Furthermore, highly activated HPA axis leading to sustained abnormal cortisol secretion may induce glucocorticoid receptor resistance in immune cells, which may lead to systemic inflammation through pro-inflammatory cytokine secretion (i.e. TNF-α, IL-1, IL-6)67. Experimental studies have demonstrated that acute and partial sleep deprivation may induce greater proinflammatory cytokine expression68 compared to uninterrupted sleep69-71. Multiple crossover trials have explored the relationship between sleep deprivation and cortisol levels (Table 3). Acute62,73 and partial (4 hr/night) sleep deprivation in the short-term (2-5 days) may increase adrenocorticotropic hormone and cortisol secretion compared to habitual sleep74,75. However, a recent RCT indicated no differences in cortisol levels between groups undergoing 5 days of 4 hr vs. 8 hr sleep duration76. According to the aforementioned, the interrelationship between testosterone and cortisol levels following insufficient sleep may promote glucose intolerance, insulin resistance and decreased MPS/MPB levels, aggravating the risk of sarcopenia and increased adiposity. More experimental trials investigating the impact of longer fragmented sleep periods on cortisol release and its potential implications on MPS are required to elicit more conclusive data.

The overall impact of restricted sleep is highlighted in Figure 1.

### Table 3. Randomized controlled and crossover trials exploring the changes in cortisol levels following sleep restriction.

| Study Design/Subjects | Intervention | Outcomes | Study |
|-----------------------|--------------|----------|-------|
| Randomized Crossover Trial n=10, aged 24.5±2.9 y BMI 22.7±2.3 kg/m² | ET & 48 hr total sleep deprivation, then 12 hr normal sleep ↓ 4-week washout ↓ ET & 3 days of regular sleep | IL-6 ↑ Cortisol: Testosterone ↑ in short vs. normal sleep | 71 |
| RCT n=23; aged 23.1±2.5 y | 5-days of 4 hr sleep vs. 5-days of 8 hr sleep | Cortisol ↔ NPY ↔ | 75 |
| Randomized Crossover Trial n=14; aged 27±5 y BMI 24.1±1.4 kg/m² | 5-days of 4 hr sleep ↓ 4-10 week washout ↓ 5-days of 8 hr sleep | Whole-body insulin sensitivity (25%) ↓ Cortisol ↑ in sleep restriction vs. normal sleep | 73 |
| RCT n=26; aged 22-49 y | 1-day of 0 hr sleep vs. 1-day of 9 hr sleep | Cortisol ↑ in acute sleep deprivation vs. normal sleep group | 72 |
| Randomized Crossover Trial n=13; aged 20-23 y BMI 24.6 kg/m² | 2-days of 4 hr sleep ↓ 6-week washout ↓ 2-days of 10 hr sleep | ACTH & Cortisol ↑ in short vs. normal sleep | 74 |
| Randomized Crossover Trial n=13; aged 24.3±2.5 y BMI: 23.6±1.7 kg/m² | 3 light-entrained circadian cycles (21h; 7 hr slept-14 hr awake) ↓ 4-week washout ↓ 3 light-entrained circadian cycles (27h; 9 hr slept-18 hr awake) | Cortisol ↑ in participants with increased advanced phase and shortened REM sleep | 64 |
| n=14; aged 27.4±3.8 y BMI 23.5±2.9 kg/m² | 5-days of 4 hr sleep & 1-day 10 hr sleep recovery | Cortisol ↑ following sleep restriction | 76 |

↑, increased between groups; ↓, decreased between groups; ↔, no changes between groups; ACTH, adrenocorticotropic hormone; BMI, body mass index; ET, eccentric training; IL-6, interleukin-6; NPY, neuropeptide Y; RCT, randomized controlled trial; REM, rapid eye movement.
Conclusions

The interference of modern lifestyle with sleeping patterns has proposed several metabolic health ramifications, including greater risk of weight gain and muscle loss. Numerous randomized controlled and crossover studies have identified increased cortisol/testosterone levels and pro-inflammatory cytokine activation, reduced insulin sensitivity, and enhanced activity of dopamine receptors linked to hyperpalatable food consumption, which may increase the risk of sarcopenia and obesity.

At present, the majority of experimental trials have been performed on young and healthy individuals through short-term sleep protocols, suggesting that chronic sleep restriction in older age may be physiologically more detrimental. More clinical trials controlling for energy intake and investigating the impact of sleep deprivation on muscle protein synthesis and gut hormones would provide greater insight regarding the direct effects of prolonged sleep loss on muscle mass and appetite regulation.

Disclaimer

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