Can treatment of obesity reduce depression or vice versa?

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Both obesity and depression are widespread problems with major health and socioeconomic implications. The number of individuals who are overweight or obese has increased dramatically over the last 25 years. Globally, 39% of adults aged 18 and older were overweight and 13% obese, and more than 264 million people of all ages suffer from depression. Both illnesses are risk factors for a number of chronic diseases, including cardiovascular disease, and a bidirectional link between risk of depression and obesity in individuals has been proposed. Given that obesity is on the rise in many countries, an increasingly large proportion of the population is at risk for depression. Vulnerability to depression among people with obesity suggests that there may be mechanistic links underlying these disorders, although the biological mechanisms remain poorly understood. This editorial discusses the evidence for the link between obesity and depression and the neurobiological mechanisms that may underlie this vulnerability (Figure 1). This has the potential to inform clinical evaluation and identify research questions in this area to help further define treatments.

Epidemiological and observational studies assessing an association between obesity and depression have reported mixed findings. Some studies purport a positive association, whereas others indicate no association or a U-shaped association whereby both underweight and obesity are associated with depression. A meta-analysis examining longitudinal studies determined that individuals with obesity were 55% more likely to become depressed, and individuals with depression were 58% more likely to become obese. Notably, associations between higher body mass index (BMI) and higher odds of depression are stronger in women than men, with a U-shaped association in men. Thus, obesity increases the risk of depression and, conversely, depressive disorders are predictive of developing obesity. While these studies identify the relative odds of co-occurrence of these disorders, determining if BMI causally influences depression is challenging without a mechanistic understanding of the vulnerabilities.

People with depression and/or anxiety commonly experience a symptom profile that influences appetite, energy and motivation. As a result, presentation of major depressive disorder (MDD) is often consistent with a phenotype that increases vulnerability toward weight gain. Individuals with atypical depression may be particularly prone to obesity, as this subtype of MDD is characterized by overeating, over-sleeping and fatigue. This can be exacerbated by iatrogenic effects of treatment of MDD. The most commonly used atypical antipsychotics, mood stabilizers and antidepressants result in some degree of weight gain. For example, atypical antipsychotics, such as olanzepine, induce substantial weight gain. This can be somewhat mitigated by switching to other medications, such as clozapine; however, this is also known to increase body weight. Obesity is also positively associated with anxiety. Internalization of negative weight stereotypes may influence this association, as this stigma is associated with negative health consequences. For example, obesity is associated with stigma leading to interpersonal distress, which can lead to depression. Depression, especially atypical depression, can then result in reduced physical activity, emotional eating, increased alcohol consumption and further development of obesity. While these psychosocial factors underlie the association between obesity and depression, there are several other neurobiological and metabolic factors that may causally underlie vulnerability to these disorders.

Cortisol

The most common biological perturbation associated with depression is an increase in cortisol. Chronic activation of the hypothalamic–pituitary–adrenal (HPA) axis is associated with chronically stressful or traumatic experiences; immunosuppression; and alteration in monoaminergic pathways, including noradrenaline, dopamine and serotonin. Glucocorticoids are normally anabolic, causing increased gluconeogenesis and increased glucose release. High cortisol levels can lead to impaired glucose homeostasis, insulin resistance and visceral fat deposition. While these features do not always occur in MDD as they might with Cushing disease, patients with depression showed an elevation in cortisol during a social stress test and
higher baseline cortisol levels than control participants.26 A possible outcome of higher baseline cortisol is impaired cognitive function. Changes in short-term memory and attention have been reported in individuals with MDD.27–29 Increased cortisol may also underlie increased visceral fat in individuals with depression. In a small sample of women with MDD, there was a 2-times-greater difference in intra-abdominal fat measured with computed tomography compared with the control group matched for body weight, total body fat and BMI.30 This effect was positively correlated with baseline cortisol levels.30 Consistent with this, patients with depression and high cortisol levels have increased visceral fat and insulin resistance compared with those with depression and normal cortisol levels.31 While only about half of patients with depression have elevated cortisol, those with increased cortisol may be susceptible to greater visceral fat deposition and associated metabolic consequences, such as insulin resistance.32 Metyrapone, a cortisol synthesis inhibitor, has shown limited efficacy in patients with treatment-resistant depression.32 However, this broad sample did not specifically identify those with hypercortisolism or those with risk factors for metabolic syndrome. Hair cortisol measurements may be a relatively simple method to identify risk for weight gain in patients with depression and may lead to better implementation of cortisol-lowering therapies.33 Furthermore, use of metformin in individuals with type 2 diabetes to reduce hepatic glucose output and increase insulin sensitivity shows promising effects on improving cognitive function and outcomes in patients with depression and type 2 diabetes.34 Thus, while cortisol-lowering agents or metformin may have limited effects in a broader MDD population, they may be useful for targeting those with subtypes of depression with high cortisol or high risk for metabolic disorders.

**Adipokines and inflammation**

Another primary neurobiological factor underlying both obesity and depression is increased inflammation. Increased adipocyte size in people with obesity produces local inflammation through increased secretion of cytokines and chemokines.35 Leptin, adiponectin and resistin are termed “adipokines” as they are exclusively released from adipose tissue. Leptin is a cytokine released from adipocytes, and levels circulate in proportion to body fat.36 Leptin acts in the hypothalamus to convey satiety. In people with obesity, leptin receptors can be desensitized, leading to a reduction in negative feedback on both satiety signalling and leptin secretion.36 Leptin resistance also can occur in individuals with atypical MDD, leading to impaired negative feedback and higher leptin levels.15 Leptin...
treatments in individuals with obesity have generally failed owing to the presence of higher circulating levels of leptin and leptin resistance, a fate that could apply if used for treatment of MDD. Adiponectin is another protein released from adipocytes and regulates glucose levels and fatty acid breakdown. Adiponectin exerts insulin-sensitizing effects and is inversely associated with obesity and type 2 diabetes. Some studies have identified decreased plasma adiponectin associated with MDD, although a meta-analysis showed no significant differences in adiponectin peripheral levels between individuals with MDD and healthy controls. However, they noted that sex and MDD severity were strong moderating factors, whereby women have significantly higher adiponectin levels and the difference in adiponectin between individuals with MDD and controls was positively associated with depression severity. Resistin is an adipokine involved in insulin sensitivity and glucose homeostasis. While resistin has been implicated in obesity and insulin resistance, it is not yet fully elucidated how resistin plays a role in metabolic dysfunction. An exploratory meta-analysis showed that resistin levels are lower in participants with MDD than in healthy controls, although the effect size of this difference was small. Adipokines may make promising drug targets for both obesity and MDD. While adipokine antagonists are in preclinical development, human data validating adipokines as novel drugs or drug targets are lacking. However, adipokines may prove to be good biomarkers for MDD with an inflammatory or metabolic component, or to help distinguish subtypes of MDD or MDD from bipolar disorder.

Proinflammatory cytokines, such as C-reactive protein, tumour necrosis factor-α (TNF-α), interleukin (IL)-1, IL-2 and IL-10, are also increased in individuals with mood disorder symptoms such as anhedonia, depressed mood and lethargy, and this is also one of the fundamental characteristics of obesity. Obesity status was associated with higher gene expression for inflammatory markers in visceral and subcutaneous adipose tissue, whereas mRNA for inflammatory markers was higher in the visceral adipose tissue of patients who were not obese but not in patients who were obese. That study suggests that the visceral adipose tissue may be more sensitive to changes in inflammatory response linked to mood disorders, as has been suggested by others. Proinflammatory cytokines released peripherally gain access to the brain through humoral, neural and cellular roots and can influence activity of microglia cells in the hypothalamus and other regions. This normally exerts a protective action whereby the immune response activates the HPA axis as well as a variety of behaviours, including fatigue, psychomotor slowing, anhedonia and sleep alterations, in efforts to promote reduced exertion during recovery. However, chronic activation of microglia and induction of proinflammatory cytokines can have negative effects on neural circuits by influencing plasticity and altering expression of neurotransmitters and their receptors. For example, chronic interferon-α treatment downregulates expression of serotonin 1a (5HT1a) and glucocorticoid receptors. Given that novel immune therapeutics can produce antidepressant effects in individuals with MDD, it will be interesting to determine whether this also improves mood outcomes in individuals with obesity.

Peripheral cytokines can potentially infiltrate brain parenchyma through a leaky blood–brain barrier in individuals with depression. In postmortem tissue from humans with depression, there is a decrease in gene expression of CLDN5, for the tight junction protein, claudin 5. In the chronic social defeat stress mouse model, targeted suppression of this tight junction protein promoted infiltration of the peripheral cytokine IL-6 into the nucleus accumbens. Decreased blood–brain barrier function was associated with depression-like behaviours in mice, but not in stress-resistant mice, because of epigenetic mechanisms that support claudin 5 expression in the blood–brain barrier of the nucleus accumbens. Thus, factors that influence blood–brain barrier permeability to peripheral inflammatory cytokines could also be considered as potential biomarkers for MDD.

**Dysregulated mesolimbic system**

A dysregulated mesolimbic system may also be implicated in obesity and MDD. Mesolimbic dopamine neurons encode the salience or motivational value of rewards. Individuals with obesity have lower striatal dopamine D2/3 receptor availability and less striatal responsivity to high calorie beverage taste. While decreased D2/3 receptor availability is mainly observed in individuals with severe obesity, increased dopamine with increasing BMI has been observed in individuals with mild obesity, suggesting that increased dopamine with BMI may reflect a risk factor for obesity and may precede a downregulation of D2/3 receptors with substantial weight gain. Rodent studies indicate that obesity is associated with reduced D2 receptor sensitivity and alterations in dopamine turnover in the nucleus accumbens. Similarly, anhedonia in rodents is marked by impaired phasic firing of dopaminergic projections to the nucleus accumbens. Deep brain stimulation in the nucleus accumbens can reduce anhedonia severity in humans, and pramipexole, the high-affinity D2/3 receptor agonist appears to be efficacious at treating individuals with MDD, with prominent anhedonia. Consistent with this, individuals with depression who had lower D2/3 receptor availability and lower dopamine levels responded best to pramipexole treatment. However, while pramipexole has not been tested for efficacy in people with obesity, it has been noted that in treatment of Parkinson disease, pramipexole and other dopaminergic agonists can induce impulse-control disorders, including binge eating, limiting their potential efficacy in the treatment of obesity. Thus, both MDD and obesity have associated impairments in dopamine signalling in the mesolimbic circuit. This may influence reward learning and goal-directed behaviour and might have implications for behavioural therapy.

**Sleep**

Sleep disturbances are also significant in both MDD and obesity. Sleep loss can contribute to the maintenance and/or exacerbation of anxiety and depression. Notably, disruption of sleep associated with MDD is a significant factor in weight...
Several neurobiological factors may underly the association of sleep disruption with weight gain. Reduction in sleep duration decreases the satiety signal, leptin. A potential mechanism behind decreased leptin release is sleep-restriction-induced increased sympathetic activity, an effect known to suppress leptin release. Sleep disturbances are also associated with increased ghrelin levels. The enteric hormone ghrelin stimulates appetite and is associated with increased food intake. It is possible that increased ghrelin levels during sleep deprivation may be due to increased energy demands during wakefulness. Ghrelin synthesis inhibitors, inverse agonists, and receptor antagonists have demonstrated some efficacy in animal models of obesity. In contrast, increasing ghrelin induces antidepressant-like responses in chronic social defeat stress in mice. However, this has not yet been translated to humans. Sleep disruption also influences glucose homeostasis, resulting in a decrease in insulin sensitivity. Chronic elevation of glucocorticoids also leads to insulin resistance through a variety of factors. Given that chronic sleep loss can increase HPA activation and cortisol, this may be another mechanism by which sleep disturbances are associated with increased risk for type 2 diabetes. Major depressive disorder is also associated with HPA axis dysregulation, elevated cortisol, disrupted insulin, leptin and ghrelin signalling. Thus, it is possible that the metabolic effects associated with sleep disruption may be additive with obesity-induced hormonal dysregulation on risk and outcomes for individuals with MDD. Sleep disturbances are also associated with increased systemic inflammation, an effect that may be activated by adrenergic signalling. Given that increased inflammation occurs with obesity and MDD, sleep-loss-induced inflammation may be another moderating factor that underlies the association between obesity and MDD. Suvorexant is a non-benzodiazepine sleep aid that is a competitive antagonist of orexin 1 and 2 receptors. Given that orexin neuropeptides play a central role in the regulation of the sleep-wake cycle, appetite, motivation and affect, this treatment strategy may be useful in patients with sleep disruption co-occurring with obesity and depression. Indeed, suvorexant significantly increases sleep efficiency and decreases glucose levels in individuals with insomnia symptoms and type 2 diabetes. Furthermore, a similar drug, seltorexant, can improve sleep efficiency and duration in patients with MDD and persistent insomnia who are being treated with antidepressants. Future studies should examine if orexin receptor antagonists also decrease inflammation associated with sleep disruption or obesity.

**Conclusion**

Obesity is a challenging and complex chronic disease. So far, the current tools available for treating obesity are lifestyle modifications and medications, including the lipase inhibitor orlistat (which decreases intestinal fat absorption), phentermine-topiramate and naltrexone-bupropion. Notably, bupropion is a dopamine and norepinephrine reuptake inhibitor antidepressant. Recently, a GLP-1 receptor agonist, semaglutide in combination with behavioural therapy, showed a significant reduction in body weight compared with controls in a double-blind randomized clinical trial. This is an encouraging trial, although future assessments should assess if mental health comorbidities are also improved with this treatment. Furthermore, it will be interesting to assess if clinical trials using anti-inflammatories for MDD are effective in weight management. Future trials on existing and novel treatments for obesity should explore the extent to which controlling obesity is sufficient for benefit in individuals with depression. Understanding the link between depression and obesity has not only the potential to inform clinical evaluation, but also to identify novel research questions in this area to help further define treatments. Early identification and management of depression can optimize outcomes and other comorbidities among individuals with obesity. Mental health considerations should be a key factor in behavioural methods of weight control. Furthermore, when initiating pharmacotherapeutic treatment for mental illness, avoid medications with higher metabolic risk. Patients with obesity and comorbid mental illness should be supported with behavioural therapy as part of a multimodal intervention to manage weight.

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**References**

1. Obesity and overweight. Geneva: World Health Organization. Available: www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (accessed 2021 Feb. 23).

2. Depression. Geneva: World Health Organization. Available: www.who.int/news-room/fact-sheets/detail/depression (accessed 2021 Feb. 23).

3. Penninx BW, Beekman AT, Honig A, et al. Depression and cardiac mortality: results from a community-based longitudinal study. Arch Gen Psychiatry 2001;58:221-7.

4. GBD 2015 Obesity Collaborators, Afshin A, Forouzanfar MH, et al. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med 2017;377:23–37.

5. Luppino FS, de Wit LM, Bouvy PF, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatry 2010;67:220-9.

6. de Wit LM, van Straten A, van Herten M, et al. Depression and body mass index, a u-shaped association. BMC Public Health 2009;9:1–4.

7. Simon GE, Von Korff M, Saunders K, et al. Association between obesity and psychiatric disorders in the US adult population. Arch Gen Psychiatry 2006;63:824-30.

8. Roberts RE, Deleger S, Strawbridge WJ, et al. Prospective association between obesity and depression: evidence from the Alameda County Study. Int J Obes Relat Metab Disord 2003;27:314-21.
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10. Herva A, Laitinen J, Miettunen J, et al. Obesity and depression: results from the longitudinal Northern Finland 1966 Birth Cohort Study. Int J Obes (Lond) 2006;30:520-7.

11. Bjerkeset O, Romundstad P, Evans J, et al. Association of adult body mass index and height with anxiety, depression, and suicide in the general population: the HUNT study. Am J Epidemiol 2008;167:193-202.

12. Kasen S, Cohen P, Chen H, et al. Obesity and psychopathology in women: a three decade prospective study. Int J Obes (Lond) 2008;32:558-66.

13. van Gool CH, Kempen GJIM, Bosma H, et al. Associations between lifestyle and depressed mood: longitudinal results from the Maastricht Aging Study. Am J Public Health 2007;97:887-94.

14. McCreA RL, Berger YG, King MB. Body mass index and common mental disorders: exploring the shape of the association and its moderation by age, gender, and education. Int J Obes (Lond) 2012;36:414-21.

15. Pae C-U, Tharwani H, Marks DM, et al. Atypical depression: a comprehensive review. CNS Drugs 2009;23:1023-37.

16. Brown ES, Varghese FP, McEwen BS. Association of depression with left amygdala volume: a meta-analysis. Brain Behav Immun 2015;100:3529-38.

17. Serretti A, Mandelli L. Antidepressants and body weight: a comprehensive review and meta-analysis. J Clin Psychiatry 2010;71:1299-72.

18. Nihalani N, Schwartz TL, Siddiqui UA, et al. Obesity and psycho-tropics. CNS Neuropsy Ch 2012;18:57-63.

19. Allinson DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999;156:1686-96.

20. Gariepy G, Nitka D, Schmitz N. The association between obesity and anxiety disorders in the population: a systematic review and meta-analysis. Int J Obes (Lond) 2010;34:407-19.

21. Pearl RL, Puhl RM. Weight bias internalization and health: a systematic review. Obes Rev 2018;19:1141-63.

22. Sachar EJ, Hellman L, Fukushima DK, et al. CRH and cortisol production in obesity. J Psychiatr Res 2000;34:227-38.

23. Rush AJ, Gilea DJ, Schlesser MA, et al. The dexamethasone suppression test in patients with mood disorders. J Clin Psychiatry 1996;57:470-84.

24. Di Dalmazi G, Fanelli F, Mezzullo M, et al. Steroid profiling by LC-MS/MS in nonsecreting and subclinical cortisol-secreting adreno-cortical adenomas. J Clin Endocrinol Metab 2015;100:3529-38.

25. Brown ES, Varghese FP, McEwen BS. Association of depression with left amygdala volume: a meta-analysis. Brain Behav Immun 2015;100:3529-38.

26. Williams RA, Hagerty BM, Cimprich B, et al. Changes in directed back sensitivity and depression in patients with hepatitis C virus. Physiol Behav 2016;166:14-21.

27. Guo M, Mi J, Jiang Q-M, et al. Metformin may produce antidepressant effects through improvement of cognitive function among depressed patients with diabetes mellitus. Clin Exp Pharmacol Physiol 2014;41:650-6.

28. Bays HE, Gonzalez-Campoy JM, Bray GA, et al. Pathogenic potential of adipose tissue and metabolic consequences of adipocyte hypertrophy and increased visceral adiposity. Expert Rev Cardiovasc Ther 2008;6:343-68.

29. Izquierdo AG, Cunqueiros AB, Casanueva FF, et al. Leptin, obesity, and leptin resistance: Where are we 25 years later? Nutrients 2019;11:2704.

30. Young EA, Lopez JF, Murphy-Weinberg V, et al. Hormonal evidence for a mechanism connecting obesity and depression. Bio Psychiatry 2017;81:807-14.

31. Serretti A, Mandelli L. Antidepressants and body weight: a comprehensive review and meta-analysis. J Clin Psychiatry 2010;71:1299-72.

32. Nihalani N, Schwartz TL, Siddiqui UA, et al. Obesity and psychotropics. CNS Neuropsy Ch 2012;18:57-63.

33. Allinson DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999;156:1686-96.

34. Gariepy G, Nitka D, Schmitz N. The association between obesity and anxiety disorders in the population: a systematic review and meta-analysis. Int J Obes (Lond) 2010;34:407-19.

35. Pearl RL, Puhl RM. Weight bias internalization and health: a systematic review. Obes Rev 2018;19:1141-63.

36. Sachar EJ, Hellman L, Fukushima DK, et al. Cortexol production in depressive illness. A clinical and biochemical clarification. Arch Gen Psychiatry 1970;23:289-98.

37. Carpenter WT, Bunney WE. Adrenal cortical activity in depressive illness. Am J Psychiatry 1971;128:31-40.

38. Rush AJ, Gilea DJ, Schlesser MA, et al. The dexamethasone suppression test in patients with mood disorders. J Clin Psychiatry 1996;57:470-84.

39. Di Dalmazi G, Fanelli F, Mezzullo M, et al. Steroid profiling by LC-MS/MS in nonsecreting and subclinical cortisol-secreting adreno-cortical adenomas. J Clin Endocrinol Metab 2015;100:3529-38.

40. Brown ES, Varghese FP, McEwen BS. Association of depression with medical illness: Does cortisol play a role? Biol Psychiatry 2004;55:1-9.

41. Williams RA, Hagerty BM, Cimprich B, et al. Changes in directed attention and short-term memory in depression. J Psychiatr Res 2000;34:227-38.

42. Ilsley JE, Moffoot APR, O’Carroll RE. An analysis of memory dysfunctions in major depression with atypical features: evidence for a mechanism connecting obesity and depression. Biol Psychiatry 2017;81:807-14.

43. Serretti A, Mandelli L. Antidepressants and body weight: a comprehensive review and meta-analysis. J Clin Psychiatry 2010;71:1299-72.

44. Nihalani N, Schwartz TL, Siddiqui UA, et al. Obesity and psychotropics. CNS Neuropsy Ch 2012;18:57-63.

45. Allinson DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999;156:1686-96.

46. Gariepy G, Nitka D, Schmitz N. The association between obesity and anxiety disorders in the population: a systematic review and meta-analysis. Int J Obes (Lond) 2010;34:407-19.

47. Young EA, Lopez JF, Murphy-Weinberg V, et al. Hormonal evidence for altered responsiveness to social stress in major depression. Neuropsychopharmacology 2000;23:411-8.

48. Williams RA, Hagerty BM, Cimprich B, et al. Changes in directed attention and short-term memory in depression. J Psychiatr Res 2000;34:227-38.

49. Ilsley JE, Moffoot APR, O’Carroll RE. An analysis of memory dysfunctions in major depression. J Affect Disord 1995;35:1-9.

50. Pelosi L, Slade T, Blümhardt LD, et al. Working memory dysfunction in major depression: an event-related potential study. Clin Neurophysiol 2000;111:1531-43.

51. Thakore JH, Richards PJ, Reznek RH, et al. Increased intra-abdominal fat deposition in patients with major depressive illness as measured by computed tomography. Biol Psychiatry 1997;41:1140-2.

52. Weber-Hamann B, Hentschel F, Kriest A, et al. Hypercortisolismic depression is associated with increased intra-abdominal fat. Psychosom Med 2002;64:29-34.

53. McAllister-Williams RH, Anderson IM, Finkelmaneyer A, et al. Antidepressant augmentation with methyrapone for treatment-resistant depression (the ADD study): a double-blind, randomised, placebo-controlled trial. Lancet Psychiatry 2016;3:117-27.

54. Jackson SE, Kirschbaum C, Steptoe A. Perceived weight discrimination and chronic biochemical stress: a population-based study using cortisol in scalp hair. Obesity (Silver Spring) 2016;24:2515-21.
57. Wittenberg GM, Stylianou A, Zhang Y, et al. Effects of immuno-modulatory drugs on depressive symptoms: a meta-analysis of randomized, placebo-controlled clinical trials in inflammatory disorders. Mol Psychiatry 2020;25:1275-85.

58. Menard C, Pau ML, Hodes GE, et al. Social stress induces neurovascular pathology promoting depression. Nat Neurosci 2017;20:1752-60.

59. Dudek KA, Dion-Albert L, Lebel M, et al. Molecular adaptations of the blood-brain barrier promote stress resilience vs. depression. J Neurosci 2020;39:12869-96.

60. Berridge KC. “Liking” and “wanting” food rewards: brain substrates and roles in eating disorders. Physiol Behav 2009;97:537-50.

61. Salamone JD, Correa M, Mingote S, et al. Nucleus accumbens dopamine and the regulation of effort in food-seeking behavior: implications for studies of natural motivation, psychiatry, and drug abuse. J Pharmacol Exp Ther 2003;305:1-8.

62. de Weijer BA, van de Giessen E, van Amelsvoort TA, et al. Lower striatal dopamine D2/3 receptor availability in obese compared with non-obese subjects. EJNMMI Res 2011;1:37.

63. Kessler RM, Zald DH, Ansari MS, et al. Changes in dopamine release and dopamine D2/3 receptor levels with the development of mild obesity. Synapse 2014;68:317-20.

64. Volkow ND, Wang G-J, Telang F, et al. Low dopamine striatal D2 receptors are associated with prefrontal metabolism in obese subjects: possible contributing factors. Neuronimage 2008;42:1537-43.

65. Stice E, Spoor S, Bohon C, et al. Relation of reward from food intake and anticipated food intake to obesity: a functional magnetic resonance imaging study. J Abnorm Psychol 2008;117:924-35.

66. Wang GJ, Volkow ND, Logan J, et al. Brain dopamine and obesity. Lancet 2001;357:354-7.

67. Stice E, Yokum S, Burger KS, et al. Youth at risk for obesity show greater activation of striatal and somatosensory regions to food. J Neurosci 2013;31:4360-6.

68. Johnson PM, Kenny PJ. Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. Nat Neurosci 2010;13:635-41.

69. Fordahl SC, Jones SR. High-fat-diet-induced deficits in dopamine terminal function are reversed by restoring insulin signaling. ACS Chem Neurosci 2017;8:290-9.

70. Geiger BM, Haburcak M, Avena NM, et al. Deficits of mesolimbic dopamine neurotransmission in rat dietary obesity. Neuroscience 2009;159:1193-9.

71. Chaudhury D, Walsh JJ, Friedman AK, et al. Rapid regulation of depression-related behaviours by control of midbrain dopamine neurons. Nature 2013;493:532-6.

72. Bewernick BH, Hullemann R, Matusch A, et al. Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. Biol Psychiatry 2010;67:110-6.

73. Goldberg JF, Burdick KE, Endick CJ. Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. Am J Psychiatry 2004;161:564-6.

74. Fawcett J, Rush AJ, Vukelich J, et al. Clinical experience with high-dosage pramipexole in patients with treatment-resistant depressive episodes in unipolar and bipolar depression. Am J Psychiatry 2016;173:107-11.

75. Whitton AE, Reinen JM, Slišťin M, et al. Baseline reward processing and ventrostriatal dopamine function are associated with pramipexole response in depression. Brain 2020;143:701-10.

76. Moore TJ, GlennenJ, Mattison DR. Reports of pathological gambling, hypersexuality, and compulsive shopping associated with dopamine receptor agonist drugs. JAMA Intern Med 2014;174:1930-3.

77. Goldstein AN, Greer SM, Salentin JM, et al. Tired and apprehensive: anxiety amplifies the impact of sleep loss on aversive brain anticipation. J Neurosci 2013;33:10607-15.

78. Pires GN, Bezerra AG, Tufik S, et al. Effects of acute sleep deprivation on state anxiety levels: a systematic review and meta-analysis. Sleep Med 2016;24:109-18.

79. Zhai L, Zhang H, Zhang D. Sleep duration and depression among adults: a meta-analysis of prospective studies. Depress Anxiety 2015;32:664-70.

80. Watanabe M, Kikuchi H, Tanaka K, et al. Association of short sleep duration with weight gain and obesity at 1-year follow-up: a large-scale prospective study. Sleep 2010;33:161-7.

81. Patel SR, Malhotra A, White DP, et al. Association between reduced sleep and sleep weight in women. Am J Epidemiol 2006;164:947-54.

82. Gangwisch JE, Malaspina D, Boden-Albala B, et al. Inadequate sleep as a risk factor for obesity: analyses of the NHANES I. Sleep 2005;28:1289-96.

83. Taberi S, Lin L, Austin D, et al. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. PLoS Med 2004;1:e62.

84. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. Lancet 1999;354:1435-9.

85. Spiegel K, Tasali E, Penev P, et al. Brief communication: sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. Ann Intern Med 2004;141:846-50.

86. Spiegel K, Leproult R, L’hermite-Balériaux M, et al. Leptin levels are dependent on sleep duration: relationships with sympathetic-gal balance, carbohydrate regulation, cortisol, and thyrotropin. J Clin Endocrinol Metab 2004;89:5762-71.

87. Rayner DV, Drayhurn P. Regulation of leptin production: sympathetic nervous system interactions. J Mol Med (Berl) 2001;79:8-20.

88. Müller TD, Nogueiras R, Andermann ML, et al. Ghrelin. Mol Metab 2015;4:437-60.

89. Schalla MA, Stengel A. Pharmacological modulation of ghrelin to induce weight loss: successes and challenges. Curr Diab Rep 2019;19:102.

90. Lutter M, Sakata I, Osborne-Lawrence S, et al. The orexigenic hormone ghrelin defends against depressive symptoms of chronic stress. Nat Neurosci 2008;11:752-3.

91. Zhu B, Shi C, Park CG, et al. Effects of sleep restriction on metabolism-related parameters in healthy adults: a comprehensive review and meta-analysis of randomized controlled trials. Sleep Med Rev 2019;45:18-30.

92. Geer EB, Islam J, Buettner C. Mechanisms of glucocorticoid-induced insulin resistance. Endocrinol Metab Clin North Am 2014;43:75-102.

93. Vgontzas AN, Chrousos GP. Sleep, the hypothalamic-pituitary-adrenal axis, and cytokines: multiple interactions and disturbances in sleep disorders. Endocrinol Metab Clin North Am 2002;31:15-36.

94. Balbo M, Leproult R, Van Cauter E. Impact of sleep and its disturbances on hypothalamic-pituitary-adrenal axis activity. Int J Endocrinol 2010;2010:759234.

95. Shan Z, Ma H, Xie M, et al. Sleep duration and risk of type 2 diabetes: a meta-analysis of prospective studies. Diabetes Care 2015;38:529-37.

96. Subba R, Sandhir R, Singh SP, et al. Pathophysiology linking depression and type 2 diabetes: a meta-analysis of prospective studies. Sleep 2015;38:529-37.

97. Irwin MR, Opp MR. Sleep health: reciprocal regulation of sleep and innate immunity. Neuropecho pharmacology 2017;42:129-55.

98. Sheridan C. Insomnia gets new mechanism sleep drug Belsomra. Nat Biotechnol 2014;32:968.

99. Thompson JL, Borgland SL. A role for hypocretin/orexin in motivation. Behav Brain Res 2011;217:446-53.

100. Toi N, Inaba M, Kurajoh M, et al. Improvement of glycemic control by treatment for insomnia with suvorexant in type 2 diabetes mellitus. J Clin Transl Endocrinol 2018;15:37-44.

101. Brooks S, Jacobs GE, de Boer P, et al. The selective orexin-2 receptor antagonist selortorexant improves sleep: an exploratory double-blind, placebo controlled, crossover study in antidepressant-treated major depressive disorder patients with persistent insomnia. J Psychopharmacol 2019;33:202-9.

102. Wilding JFP, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med 2021;384:989.