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What is the disease burden from childhood and adolescent obesity?: a narrative review

Eun Byoul Lee

Department of Pediatrics, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin, Korea

The prevalence of childhood and adolescent obesity has increased and exacerbated during the coronavirus disease 2019 pandemic, both in Korea and globally. Childhood and adolescent obesity poses significant risks for premature morbidity and mortality. The development of serious comorbidities depends not only on the duration of obesity but also on the age of onset. Obesity in children and adolescents affects almost all organ systems, including the endocrine, cardiovascular, gastrointestinal, reproductive, nervous, and immune systems. Obesity in children and adolescents affects growth, cognitive function, and psychosocial interactions during development, in addition to aggravating known adult comorbidities such as type 2 diabetes mellitus, hypertension, dyslipidemia, nonalcoholic fatty liver disease, obstructive sleep apnea, and cancer. Childhood and adolescent obesity are highly associated with increased cardiometabolic risk factors and prevalence of metabolic syndrome. The risk of cardiovascular and metabolic diseases in later life can be considerably decreased by even a small weight loss before the onset of puberty. Childhood and adolescent obesity is a disease that requires treatment and is associated with many comorbidities and disease burdens. Therefore, early detection and therapeutic intervention are crucial.

Keywords: Adolescent; Child; Comorbidity; Pediatric obesity

Introduction

Obesity is characterized by excessive accumulation of body fat caused by an imbalance in energy intake and expenditure [1]. Overweight is defined as a body mass index (BMI) between the 85th and 95th percentiles in children and adolescents, and obesity is defined as a BMI equal to or greater than the 95th percentiles for age and sex. Over the past few decades, the prevalence of childhood and adolescent obesity has increased [2], and the coronavirus disease 2019 (COVID-19) pandemic has made it worse in Korea and worldwide [3,4]. According to the Obesity Fact Sheet published in 2023 by the Korean Society for the Study of Obesity, the prevalence of obesity among children and adolescents has increased in both boys and girls over the past decade [5]. Between 2012 and 2021, the prevalence of obesity has increased approximately 2.5 times in boys (from 10.4% to 25.9%) and 1.4 times in girls (from 8.8% to 12.3%). This indicates a trend of a greater increase in obesity prevalence among children and adolescents than among adults during the same periods, where the obesity rate increased from 30.2% to 38.4% [6]. Obesity in early life is associated with obesity in adulthood [7]. Compared to children and adolescents who are not obese, individuals who are obese have an approximately five-fold increased risk of being obese in adulthood [8].

Childhood and adolescent obesity affects almost all organ systems, including the endocrine, cardiovascular, gastrointestinal, re-

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Corresponding author: Eun Byoul Lee, MD
Department of Pediatrics, Yongin Severance Hospital, Yonsei University College of Medicine, 363 Dongbaekjukjeon-daero, Giheung-gu, Yongin 16995, Korea
Tel: +82-31-5189-8485 • Fax: +82-31-5189-8567 • E-mail: eblee@yuhs.ac

productive, nervous, and immune systems (Table 1) [9]. The development of serious comorbidities depends not only on the duration of obesity but also on the age of onset [10]. Cardiometabolic comorbidities are common in many adolescents with obesity and often start around the onset of puberty [11]. Childhood and adolescent obesity often persists into adulthood, leading to lifelong obesity and impacting not only various physical complications but also the psychosocial development of children [9]. Childhood and adolescent obesity increases the major cardiometabolic morbidity and mortality in young adults under 45 years of age, which may manifest before the age of 30 years in both sexes [12].

This article aimed to comprehensively review the associated comorbidities and complications of childhood and adolescent obesity, emphasizing the significant disease burden it poses and the importance of early therapeutic interventions.

Endocrine and metabolic complications

Adipose tissue is an endocrine organ that regulates energy homeostasis. Numerous adipokines and lipokines have been discovered [13,14]. The secretion of proinflammatory adipokines such as leptin, resistin, and retinol-binding protein 4 is increased under metabolic inflammatory conditions, whereas that of anti-inflammatory adipokines such as adiponectin and omentin is decreased [13]. Chronic mild inflammation in adipose tissue is an important risk factor for the development of insulin resistance and type 2 diabetes mellitus (T2DM) in individuals who are obese [15]. The age at which diabetes mellitus (DM) develops and the degree of obesity have an inverse linear relationship, and the prevalence of T2DM among adolescents increases as obesity severity increases [12,16]. Chronic overnutrition triggers uncontrolled inflammatory responses, leading to metabolic problems such as insulin resistance [14].

Apart from adipocyte inflammation, it has been reported that adipocyte hypertrophy itself is very important for insulin resistance in obesity. Hypertrophic adipocytes with large unilocular lipid droplets exhibit impaired insulin-dependent glucose uptake, which is linked to defects in glucose transporter type 4 trafficking to the plasma membrane [17].

Hyperinsulinemia and abnormalities in glycemic homeostasis are major characteristics of obesity. In obesity, hyperinsulinemia is typically interpreted as a compensatory increase in insulin necessary to achieve biological effects on glucose uptake and maintain normal blood glucose levels [9].

In Korean adolescents aged 10 to 18 years, the prevalence of impaired fasting glucose (IFG, fasting glucose > 100 mg/dL and < 125 mg/dL) or DM (DM fasting blood glucose [DMFBG] ≥ 126 mg/dL) was estimated from the fourth (2007–2009), fifth (2010–2012), sixth (2013–2015), and seventh (2016–2018) Korea National Health and Nutrition Examination Survey (KNHANES). The age-adjusted prevalence of IFG and DMFBG in the overweight and obesity group (≥ 85th percentile or BMI ≥ 25.0 kg/m^2) increased in these years to 8.13, 8.81, 12.75, and 14.75 per 100 persons, respectively. These values were higher than those in the normal-weight group (4.73, 3.83, 9.20, and 10.65 per 100 persons, respectively) [18].

In obesity, elevated thyroid-stimulating hormone (TSH) and normal thyroid hormone levels are regularly observed as signs of disturbed thyroid function [19], and TSH levels normalize when weight is lost [9]. Increased TSH levels in children with obesity are linked to cardiometabolic markers in childhood and later to coronary heart disease (CHD) [20]. Hypothyroidism causes weight gain together with a decrease in basal metabolic rate and thermogenesis [21].

Table 1. Comorbidities and complications of childhood and adolescent obesity

Organ system	Diseases and affected conditions
Endocrine and metabolic complications	Insulin resistance
	Type 2 diabetes mellitus
	Thyroid dysfunction
Cardiovascular comorbidities	Hypertension
	Dyslipidemia
Gastrointestinal comorbidities	Nonalcoholic fatty liver disease
	Gallstones
Growth and puberty (reproductive) disturbances	Early puberty
	Polycystic ovary syndrome
	Gynecomastia
	Low fertility
Nervous and psychological comorbidities	Cognitive impairment
	Psychosocial interaction
	Depression and anxiety
	Attention-deficit/hyperactivity disorder
Respiratory comorbidities	Asthma
	Obstructive sleep apnea
Skeletal comorbidities	Abnormal bone content
	Fractures
	Vitamin D deficiency
Immunologic and autoimmune diseases	Chronic low-intensity inflammation
	Type 1 diabetes mellitus
	Multiple sclerosis
	Psoriasis
Cancer	Leukemia
	Thyroid cancer

Cardiovascular comorbidities

An increase in CHD is linked to higher BMI during childhood

[22]. Global increases in the prevalence of childhood and adolescent overweight and obesity coincide with increases in the prevalence of childhood hypertension and early atherosclerosis [23,24]. Few longitudinal studies have directly evaluated the relationship between childhood obesity and adult cardiovascular disease (CVD) because long observation periods are required [25]. However, there is growing evidence that childhood obesity and associated metabolic issues can accelerate atherosclerosis, a major cause of CVD [3]. Blood pressure and body weight are strongly correlated, and hypertension is an additional factor contributing to the clustering of cardiovascular risk factors for obesity [23]. The risk of cardiovascular and metabolic diseases in later life can be considerably decreased by even a small weight loss before the onset of puberty [22,26]. Midlife CHD risk is significantly elevated if obesity begins early in life and continues through early childhood until adolescence [11]. The early diagnosis of hypertension and initiation of treatment, are critical because the duration of hypertension influences the risk of end-organ damage [23].

In Korean children and adolescents aged 10 to 18 years (data from KNHANES 2007–2018), obesity was associated with a significantly higher prevalence of metabolic syndrome and cardiometabolic risk factors [27]. The prevalence of hypertension (blood pressure ≥ 95th percentile for sex, age, and height) in normal weight (BMI < 85th percentile), overweight (BMI ≥ 85th percentile and < 95th percentile), class I obesity (BMI ≥ 95th percentile and < 120% of 95th percentile), and class II (BMI ≥ 120% of 95th percentile and < 140% of 95th percentile, or BMI ≥ 30.0 kg/m^2 and < 35 kg/m^2) or III (BMI ≥ 140% of 95th percentile or BMI ≥ 35.0 kg/m^2) obesity was 4.88%, 10.55%, 13.80%, and 29.68%, respectively. The prevalence of low high-density lipoprotein cholesterol (HDL-C) levels (< 40 mg/dL) was 9.54%, 19.29%, 26.13%, and 41.44%, respectively, and that of high triglyceride (TG) levels (≥ 150 mg/dL) was 6.10%, 15.48%, 21.20%, and 27.80%, respectively.

After analyzing the four cohorts, the International Childhood Cardiovascular Cohort Consortium discovered that children who were overweight or obese and continued to be obese as adults had a higher chance of developing T2DM, hypertension, carotid atherosclerosis, low HDL-C levels, and high TG levels [26]. Similarly, data from KNHANES 2011–2019 showed that among Korean youths who were metabolically unhealthy and overweight/obese, dysglycemia (48.8%) was the most prevalent cardiometabolic risk factor, followed by hypertension (41.5%), low HDL-C levels (35.0%), and high TG levels (29.7%) [28]. A high proportion of adolescents with metabolic syndrome had elevated waist circumference, BMI, and fasting blood glucose levels [29].

Gastrointestinal comorbidities

When combined with obesity, nonalcoholic fatty liver disease (NAFLD) in children and adolescents is estimated to have a prevalence of 36.1% [30]. This condition persists into adulthood and causes significant hepatic and extrahepatic morbidities [31]. Early-onset chronic diseases such as T2DM and NAFLD have been observed in children and adolescents who are obese [3,31]. In the pediatric population, children and adolescents with obesity who have NAFLD are more likely to develop T2DM [9]. According to data from KNHANES 2018–2020, during the COVID-19 outbreak, the proportion of participants with abdominal obesity and NAFLD increased in the obese group (from 1.68% to 57.82%, $p = 0.032$) but decreased in the normal BMI group (from 0.07% to 0.00%, $p < 0.032$) [32]. Recently, it was proposed that the condition should be renamed and redefined because alcohol consumption is usually not an underlying contributor in children. Metabolic dysfunction-associated fatty liver disease has been proposed with age-appropriate definitions based on age percentile and sex [33].

The prevalence of gallstone disease is higher in adolescents with obesity, and the association between obesity and gallstone disease is stronger in girls than in boys [34].

Growth and puberty (reproductive) disturbances

The linear growth patterns of children with obesity are associated with increased linear growth in early childhood, resulting in accelerated maturation of the epiphyseal growth plate (EGP) [35]. Adipose tissue secretes many hormones that can directly influence the linear growth of the EGP, as well as indirectly through the growth hormone-insulin-like growth factor 1 axis. Peak BMI during childhood is inversely correlated with pubertal height gain during adolescence [36]. Neuroendocrine processes leading to puberty onset may be initiated by the degree of body fat. Children and adolescents who are obese are at risk of early puberty and accelerated linear growth, which could compromise their potential adult height [35].

Although excess adiposity during childhood may cause girls to reach puberty earlier, this is controversial for boys [37,38]. Studies have suggested puberty development in boys with obesity might be delayed [39,40], and a meta-analysis indicated no association between precocious puberty and an increased risk of obesity in boys [41]. However, a recent large-scale cohort study in Denmark reported that obesity in boys was associated with early puberty [42]. Reduced insulin induction of sex hormone-bound globulin, which increases the bioavailability of sex steroids, including estradi-

ol, is linked to peripubertal obesity. Aromatase, which can create estrogen from adrenal androgen precursors (e.g., androstenedione) is abundant in adipose tissue. In boys who are obese, pubertal development may be delayed rather than advanced. Peripubertal girls who are obese may also have hyperandrogenemia and a high risk of adolescent polycystic ovary syndrome [38].

Gynecomastia is common among pubertal boys who are obese. The increased aromatization of testosterone to estrogen in adipose tissue is thought to cause gynecomastia [9].

Obesity reduces fertility in both males and females. The effectiveness of weight loss interventions in weight reduction and improvements in reproductive outcomes has been reported in women and men who are overweight or obese, and experiencing infertility [43].

Nervous and psychological comorbidities

Children with obesity achieved lower educational levels than their normal-weight peers, independently of their parents' socioeconomic status [44]. Childhood obesity also adversely affects processing speed, memory, and other cognitive abilities [9]. Some of these effects are reversible. Effective treatment of obesity may enhance academic performance [44] and bariatric surgery in adults, which leads to significant weight loss, may enhance cognitive abilities [45].

The stigma associated with weight toward children and adolescents with obesity can negatively impact their quality of life and contribute to unhealthy behaviors that can exacerbate obesity, such as reduced physical activity, social distancing, and skipping healthcare services. Stigma and weight bias can lead to bullying and weight-related teasing, which can have detrimental psychological effects on children, including depression, attitude problems such as social isolation, eating disorders, reduced their motivation to make changes, and reduced physical activities [9,46].

Depression and obesity are significantly associated; however, contradictory results have been reported [47,48]. A systematic review and meta-analysis of longitudinal studies found that 40% of adolescents with obesity had a higher risk of depression and 70% of adolescents with depression had a higher risk of obesity [49]. According to a meta-analysis involving 51,272 participants, children and adolescents with obesity have a higher risk of depression and depressive symptoms [50]. A recent systematic review and meta-analysis showed a positive correlation between childhood and adolescent obesity and the risk of body dissatisfaction and low self-esteem. However, no correlation was found between overweight/obesity and the risk of depression or anxiety [51].

There are similar neural pathways between obesity and attention-deficit/hyperactivity disorder (ADHD), including the hypothalamic, executive, and reward centers [52]. The prevalence of ADHD was significantly higher in children who were overweight or obese than in those who were normal weight or underweight [53]. Affected executive functions, including impulsivity and decreased capacity for self-monitoring, concentration, and attention span, are characteristics of ADHD. This may lead to the development of obesity in an obesogenic environment [9].

Respiratory comorbidities and sleep disturbance

Obesity increases the risk of developing asthma by 2.5 times regardless of the presence of allergens, and it changes the clinical manifestation toward a difficult-to-control phenotype; asthma patients with obesity have considerably lower expiratory reserve volumes and are more likely to experience hyperinflation during bronchoconstriction. Obesity is associated with different types of inflammation and a decreased response to corticosteroid treatment. Systemic asthma treatment should be avoided as it exacerbates obesity [54].

Obstructive sleep apnea (OSA) is a common consequence that affects up to 60% of children and adolescents with obesity. OSA is a mechanical complication that forms part of the clinical spectrum of sleep-disordered breathing. Periodic upper airway collapse during sleep partially (hypopnea) or completely (apnea) disrupts ventilation, resulting in oxyhemoglobin desaturation, sleep fragmentation, and sleep quality disruption [55].

There is a reciprocal relationship between sleep and obesity. Sleep deprivation is associated with difficulty in appetite control and can lead to obesity. Overweight and obesity increase the risk of sleep disorders such as OSA [56,57]. Short sleep duration, low sleep quality, and sleep discrepancies are associated with adolescent obesity [58]. A nationwide cross-sectional study of Korean adolescents found a negative dose-dependent association between obesity and catch-up sleep on weekends. Even if adolescents sleep less on weekdays, getting more sleep on weekends may lower their risk of obesity [59].

Skeletal comorbidities

Children's body weight and bone mass are positively correlated, and data suggests that children with obesity have higher bone mineral content than their normal-weight peers [60]. However, excess adiposity during childhood may affect bone development, which could eventually result in bone frailty. According to a systematic review of six articles, children with obesity are 25% more likely to de-

velop extremity fractures than those who are normal weight [61]. Disrupted bone synthesis may result from low vitamin D levels, poor eating habits, low physical activity levels, chronic low-grade inflammation, and insulin resistance in obesity [62].

Children and adolescents with obesity are more likely to have vitamin D deficiency [63]. Vitamin D deficiency in childhood and adolescence has been associated with multiple sclerosis (MS) and prediabetes, which are also linked to obesity [9,29]. Adolescent boys with low serum 25-hydroxyvitamin D levels were more likely to be obese and have an increased risk of atherogenic events [64]. The mechanisms underlying low levels of vitamin D are unclear. Reduced vitamin D synthesis in the liver and adipose tissue, sequestration in adipose tissue, volumetric dilution, and limited sunlight exposure are the pathogenetic mechanisms underlying low vitamin D levels in obesity [65]. Lifestyles that can be associated with obesity, such as indoor lifestyle and poor eating habits, can contribute to low vitamin D levels [9].

Immunologic and autoimmune diseases

1. Chronic low-grade inflammation

Obesity affects the immune system both directly through immunological effects on adipose tissue and indirectly through changes in endocrinology. These immune system alterations contribute to the development of long-term obesity-associated comorbidities [9].

As a major metabolic organ, adipose tissue secretes various hormones, cytokines, and metabolites that control peripheral tissue metabolism and appetitive signals from the central nervous system. Adipokine secretion, adipocyte death, local hypoxia, and fatty acid flux are affected by changes in the quantity and size of adipocytes in the microenvironment of expanded fat tissues [14]. In obesity, pathologic high-fat accumulation in the adipose tissue leads to pathological immune activation, resulting in low-grade chronic inflammation characterized by increased infiltration and activation of innate and adaptive immune cells. Adipocyte-secreted cytokines as well as a rise in macrophages, lymphocytes, and other immunologically active cells contribute. The secretion of proinflammatory cytokines is increased, whereas that of anti-inflammatory cytokines is reduced [9].

Leptin is involved in appetite regulation in the central nervous system and puberty development and has multiple proinflammatory effects, such as stimulation of the release of interleukin 6 and tumor necrosis factor-alpha [66]. Adipokines also interact with muscle and liver tissue cytokines [67]. Macrophages, the most prevalent innate immune cell type, comprise as much as 40% of all adipose cells in obesity. Similar to macrophages, adipocytes establish a connection between the innate and adaptive immune systems by secreting adipokines and cytokines and releasing lipids, hormones, and microRNAs from exosomes [15,68]. Preschool children who are overweight or obese already show indicators of chronic inflammation, such as elevated C-reactive protein levels [9].

2. Autoimmune disease

A systematic literature review of clinical, experimental, and pathophysiological data suggested that the risk of rheumatoid arthritis (RA), MS, psoriasis, and psoriatic arthritis is increased in obesity [69]. Since MS is a chronic inflammatory disease of the central nervous system, it is thought to be associated with childhood obesity. Early prevention and treatment of obesity can decrease the prevalence of MS. However, if the prevalence of childhood obesity increases without treatment, childhood and adolescent obesity is expected to contribute to an increased risk of MS [9]. There is also evidence of an increased risk of thyroid autoimmunity, type 1 DM (T1DM), and inflammatory bowel disease (IBD). Furthermore, obesity aggravates RA, IBD, systemic lupus erythematosus, psoriasis, and psoriatic arthritis and decreases the effectiveness of treatment for these conditions [69]. In a meta-analysis, childhood obesity was investigated as a potential risk factor for T1DM [70]. Despite heterogeneous data, there was a positive correlation between childhood obesity and a higher risk of T1DM, with a calculated pooled odds ratio of 2.03 [69]. The severity of inflammation in autoimmune diseases was positively correlated with adiponectin levels, indicating a potential function of adiponectin in the proinflammatory response [71].

Cancer

According to recent data, there is a strong correlation between a higher BMI during adolescence and an increased risk of leukemia, Hodgkin disease, colorectal cancer, breast cancer, and other malignancies in adulthood [11]. Although the exact mechanisms are unknown, several oncogenes have been associated with inflammation and cancer development, and several types of tumors require an inflammatory milieu for malignant transformation. An inflammatory milieu appears to encourage angiogenesis, as well as the growth and survival of malignant cells. Natural killer cells are crucial for this process [72].

Overweight and obesity in adolescence were linked to an increased risk of papillary thyroid cancer in adulthood in a large-scale case-control study conducted in Korea [73].

Conclusion

The increasing prevalence of childhood and adolescent obesity is threatening public health because of its comorbidities and complications. In addition to the exacerbation of comorbidities previously observed in the adult population, such as T2DM, hypertension, dyslipidemia, NAFLD, OSA, and cancer, obesity in children and adolescents affects growth, cognitive function, and psychosocial interaction during development. The risk of cardiovascular and metabolic diseases in later life can be considerably decreased by even a small weight loss before the onset of puberty. Childhood and adolescent obesity require treatment and are associated with numerous comorbidities and disease burdens, highlighting the importance of early detection and intervention.

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ORCID

Eun Byoul Lee, https://orcid.org/0009-0000-4981-2446

References

1. Lustig RH, Collier D, Kassotis C, Roepke TA, Kim MJ, Blanc E, et al. Obesity I: overview and molecular and biochemical mechanisms. Biochem Pharmacol 2022;199:115012.
2. Kim JH, Moon JS. Secular trends in pediatric overweight and obesity in Korea. J Obes Metab Syndr 2020;29:12–7.
3. Park H, Choi JE, Jun S, Lee H, Kim HS, Lee HA, et al. Metabolic complications of obesity in children and adolescents. Clin Exp Pediatr 2024;67:347–55.
4. Takaya J, Higashino H, Takaya R, Sakaguchi H, Tanoue J, Higashide T, et al. Effect of the COVID-19 pandemic lockdown on the physique of school-age children in Japan. Ann Pediatr Endocrinol Metab 2023;28:124–30.
5. Jeong SM, Jung JH, Yang YS, Kim W, Cho IY, Lee YB, et al. 2023 Obesity Fact Sheet: prevalence of obesity and abdominal obesity in adults, adolescents, and children in Korea from 2012 to 2021. J Obes Metab Syndr 2024;33:27–35.
6. Hong YH. Suggestions for the management of pediatric obesity in Korea. J Korean Med Assoc 2024;67:306–11.
7. Freedman DS, Khan LK, Serdula MK, Dietz WH, Srinivasan SR, Berenson GS. The relation of childhood BMI to adult adiposity: the Bogalusa Heart Study. Pediatrics 2005;115:22–7.
8. Simmonds M, Llewellyn A, Owen CG, Woolacott N. Predicting adult obesity from childhood obesity: a systematic review and meta-analysis. Obes Rev 2016;17:95–107.
9. Marcus C, Danielsson P, Hagman E. Pediatric obesity-Long-term consequences and effect of weight loss. J Intern Med 2022;292:870–91.
10. Malhotra S, Sivasubramanian R, Singhal V. Adult obesity and its complications: a pediatric disease? Curr Opin Endocrinol Diabetes Obes 2021;28:46–54.
11. Weihrauch-Blüher S, Schwarz P, Klusmann JH. Childhood obesity: increased risk for cardiometabolic disease and cancer in adulthood. Metabolism 2019;92:147–52.
12. Horesh A, Tsur AM, Bardugo A, Twig G. Adolescent and childhood obesity and excess morbidity and mortality in young adulthood: a systematic review. Curr Obes Rep 2021;10:301–10.
13. Galic S, Oakhill JS, Steinberg GR. Adipose tissue as an endocrine organ. Mol Cell Endocrinol 2010;316:129–39.
14. Choe SS, Huh JY, Hwang IJ, Kim JI, Kim JB. Adipose tissue remodeling: its role in energy metabolism and metabolic disorders. Front Endocrinol (Lausanne) 2016;7:30.
15. Zatterale F, Longo M, Naderi J, Raciti GA, Desiderio A, Miele C, et al. Chronic adipose tissue inflammation linking obesity to insulin resistance and type 2 diabetes. Front Physiol 2019;10:1607.
16. Skinner AC, Perrin EM, Moss LA, Skelton JA. Cardiometabolic risks and severity of obesity in children and young adults. N Engl J Med 2015;373:1307–17.
17. Kim JI, Huh JY, Sohn JH, Choe SS, Lee YS, Lim CY, et al. Lipid-overloaded enlarged adipocytes provoke insulin resistance independent of inflammation. Mol Cell Biol 2015;35:1686–99.
18. Yoo SE, Lee JH, Lee JW, Park HS, Lee HA, Kim HS. Increasing prevalence of fasting hyperglycemia in adolescents aged 10-18 years and its relationship with metabolic indicators: the Korea National Health and Nutrition Examination Study (KNHANES), 2007-2018. Ann Pediatr Endocrinol Metab 2022;27:60–8.
19. Vigone MC, Capalbo D, Weber G, Salerno M. Mild hypothyroidism in childhood: who, when, and how should be treated? J Endocr Soc 2018;2:1024–39.
20. Lundbäck V, Ekbom K, Hagman E, Dahlman I, Marcus C. Thyroid-stimulating hormone, degree of obesity, and metabolic risk markers in a cohort of swedish children with obesity. Horm Res Paediatr 2017;88:140–6.

21. Rotondi M, Leporati P, La Manna A, Pirali B, Mondello T, Fonte R, et al. Raised serum TSH levels in patients with morbid obesity: is it enough to diagnose subclinical hypothyroidism? Eur J Endocrinol 2009;160:403–8.
22. Baker JL, Olsen LW, Sørensen TI. Childhood body-mass index and the risk of coronary heart disease in adulthood. N Engl J Med 2007;357:2329–37.
23. Wühl E. Hypertension in childhood obesity. Acta Paediatr 2019;108:37–43.
24. McPhee PG, Singh S, Morrison KM. Childhood obesity and cardiovascular disease risk: working toward solutions. Can J Cardiol 2020;36:1352–61.
25. Nadeau KJ, Maahs DM, Daniels SR, Eckel RH. Childhood obesity and cardiovascular disease: links and prevention strategies. Nat Rev Cardiol 2011;8:513–25.
26. Juonala M, Magnussen CG, Berenson GS, Venn A, Burns TL, Sabin MA, et al. Childhood adiposity, adult adiposity, and cardiovascular risk factors. N Engl J Med 2011;365:1876–85.
27. Kim M, Kim J. Cardiometabolic risk factors and metabolic syndrome based on severity of obesity in Korean children and adolescents: data from the Korea National Health and Nutrition Examination Survey 2007-2018. Ann Pediatr Endocrinol Metab 2022;27:289–99.
28. Kim HY, Kim JH. Temporal trends in the prevalence of metabolically healthy overweight and obesity in Korean youth: data from the Korea National Health and Nutrition Examination Survey 2011-2019. Ann Pediatr Endocrinol Metab 2022;27:134–41.
29. Shulhai AM, Pavlyshyn H, Oleksandra S, Furdela V. The association between vitamin D deficiency and metabolic syndrome in Ukrainian adolescents with overweight and obesity. Ann Pediatr Endocrinol Metab 2022;27:113–20.
30. Anderson EL, Howe LD, Jones HE, Higgins JP, Lawlor DA, Fraser A. The prevalence of non-alcoholic fatty liver disease in children and adolescents: a systematic review and meta-analysis. PLoS One 2015;10:e0140908.
31. Shaunak M, Byrne CD, Davis N, Afolabi P, Faust SN, Davies JH. Non-alcoholic fatty liver disease and childhood obesity. Arch Dis Child 2021;106:3–8.
32. Song K, Yang J, Lee HS, Kim SJ, Lee M, Suh J, et al. Changes in the prevalences of obesity, abdominal obesity, and non-alcoholic fatty liver disease among Korean children during the COVID-19 outbreak. Yonsei Med J 2023;64:269–77.
33. Eslam M, Alkhouri N, Vajro P, Baumann U, Weiss R, Socha P, et al. Defining paediatric metabolic (dysfunction)-associated fatty liver disease: an international expert consensus statement. Lancet Gastroenterol Hepatol 2021;6:864–73.
34. Koebnick C, Smith N, Black MH, Porter AH, Richie BA, Hudson S, et al. Pediatric obesity and gallstone disease. J Pediatr Gastroenterol Nutr 2012;55:328–33.
35. Shalitin S, Gat-Yablonski G. Associations of obesity with linear growth and puberty. Horm Res Paediatr 2022;95:120–36.
36. Holmgren A, Niklasson A, Nierop AF, Gelander L, Aronson AS, Sjöberg A, et al. Pubertal height gain is inversely related to peak BMI in childhood. Pediatr Res 2017;81:448–54.
37. Kim SJ, Kim JH, Hong YH, Chung IH, Lee EB, Kang E, et al. 2022 Clinical practice guidelines for central precocious puberty of Korean children and adolescents. Ann Pediatr Endocrinol Metab 2023;28:168–77.
38. Burt Solorzano CM, McCartney CR. Obesity and the pubertal transition in girls and boys. Reproduction 2010;140:399–410.
39. Lee JM, Kaciroti N, Appugliese D, Corwyn RF, Bradley RH, Lumeng JC. Body mass index and timing of pubertal initiation in boys. Arch Pediatr Adolesc Med 2010;164:139–44.
40. Wang Y. Is obesity associated with early sexual maturation? A comparison of the association in American boys versus girls. Pediatrics 2002;110:903–10.
41. Song Y, Kong Y, Xie X, Wang Y, Wang N. Association between precocious puberty and obesity risk in children: a systematic review and meta-analysis. Front Pediatr 2023;11:1226933.
42. Brix N, Ernst A, Lauridsen LL, Parner ET, Arah OA, Olsen J, et al. Childhood overweight and obesity and timing of puberty in boys and girls: cohort and sibling-matched analyses. Int J Epidemiol 2020;49:834–44.
43. Hunter E, Avenell A, Maheshwari A, Stadler G, Best D. The effectiveness of weight-loss lifestyle interventions for improving fertility in women and men with overweight or obesity and infertility: a systematic review update of evidence from randomized controlled trials. Obes Rev 2021;22:e13325.
44. Lindberg L, Persson M, Danielsson P, Hagman E, Marcus C. Obesity in childhood, socioeconomic status, and completion of 12 or more school years: a prospective cohort study. BMJ Open 2021;11:e040432.
45. Alosco ML, Spitznagel MB, Strain G, Devlin M, Cohen R, Paul R, et al. Improved memory function two years after bariatric surgery. Obesity (Silver Spring) 2014;22:32–8.
46. Smith JD, Fu E, Kobayashi MA. Prevention and management of childhood obesity and its psychological and health comorbidities. Annu Rev Clin Psychol 2020;16:351–78.
47. Blasco BV, García-Jiménez J, Bodoano I, Gutiérrez-Rojas L. Obesity and depression: its prevalence and influence as a prognostic factor: a systematic review. Psychiatry Investig 2020;17:715–24.
48. Kang NR, Kwack YS. An update on mental health problems and

cognitive behavioral therapy in pediatric obesity. Pediatr Gastroenterol Hepatol Nutr 2020;23:15–25.
49. Mannan M, Mamun A, Doi S, Clavarino A. Prospective associations between depression and obesity for adolescent males and females: a systematic review and meta-analysis of longitudinal studies. PLoS One 2016;11:e0157240.
50. Quek YH, Tam WW, Zhang MW, Ho RC. Exploring the association between childhood and adolescent obesity and depression: a meta-analysis. Obes Rev 2017;18:742–54.
51. Moradi M, Mozaffari H, Askari M, Azadbakht L. Association between overweight/obesity with depression, anxiety, low self-esteem, and body dissatisfaction in children and adolescents: a systematic review and meta-analysis of observational studies. Crit Rev Food Sci Nutr 2022;62:555–70.
52. O'Hara VM, Curran JL, Browne NT. The co-occurrence of pediatric obesity and ADHD: an understanding of shared pathophysiology and implications for collaborative management. Curr Obes Rep 2020;9:451–61.
53. Erhart M, Herpertz-Dahlmann B, Wille N, Sawitzky-Rose B, Hölling H, Ravens-Sieberer U. Examining the relationship between attention-deficit/hyperactivity disorder and overweight in children and adolescents. Eur Child Adolesc Psychiatry 2012;21:39–49.
54. Carpaij OA, van den Berge M. The asthma-obesity relationship: underlying mechanisms and treatment implications. Curr Opin Pulm Med 2018;24:42–9.
55. Ng NB, Lim CY, Tan SC, Foo YW, Tok CL, Lim YY, et al. Screening for obstructive sleep apnea (OSA) in children and adolescents with obesity: a scoping review of national and international pediatric obesity and pediatric OSA management guidelines. Obes Rev 2024;25:e13712.
56. Lee JH, Cho J. Sleep and obesity. Sleep Med Clin 2022;17:111–6.
57. Seo SH, Shim YS. Association of sleep duration with obesity and cardiometabolic risk factors in children and adolescents: a population-based study. Sci Rep 2019;9:9463.
58. Kwon A, Choi Y, Kim S, Song K, Suh J, Chae HW, et al. Characteristic sleep patterns and associated obesity in adolescents. Life (Basel) 2022;12:1316.
59. Choi Y, Kim S, Lee M, Lee HI, Song K, Suh J, et al. Effect of catch-up sleep on obesity in Korean adolescents: a nationwide cross-sectional study. Front Pediatr 2023;11:1213558.
60. Fintini D, Cianfarani S, Cofini M, Andreoletti A, Ubertini GM, Cappa M, et al. The bones of children with obesity. Front Endocrinol (Lausanne) 2020;11:200.
61. Kim SJ, Ahn J, Kim HK, Kim JH. Obese children experience more extremity fractures than nonobese children and are significantly more likely to die from traumatic injuries. Acta Paediatr 2016;105:1152–7.
62. Pollock NK. Childhood obesity, bone development, and cardiometabolic risk factors. Mol Cell Endocrinol 2015;410:52–63.
63. Fiamenghi VI, Mello ED. Vitamin D deficiency in children and adolescents with obesity: a meta-analysis. J Pediatr (Rio J) 2021;97:273–9.
64. Naganuma J, Koyama S, Arisaka O, Yoshihara S. Low serum 25-hydroxyvitamin D level is associated with obesity and atherogenesis in adolescent boys. Ann Pediatr Endocrinol Metab 2022;27:30–6.
65. Karampela I, Sakelliou A, Vallianou N, Christodoulatos GS, Magkos F, Dalamaga M. Vitamin D and obesity: current evidence and controversies. Curr Obes Rep 2021;10:162–80.
66. Francisco V, Pino J, Campos-Cabaleiro V, Ruiz-Fernández C, Mera A, Gonzalez-Gay MA, et al. Obesity, fat mass and immune system: role for leptin. Front Physiol 2018;9:640.
67. de Oliveira Dos Santos AR, de Oliveira Zanuso B, Miola VF, Barbalho SM, Santos Bueno PC, Flato UA, et al. Adipokines, myokines, and hepatokines: crosstalk and metabolic repercussions. Int J Mol Sci 2021;22:2639.
68. Blaszczak AM, Jalilvand A, Hsueh WA. Adipocytes, innate immunity and obesity: a mini-review. Front Immunol 2021;12:650768.
69. Versini M, Jeandel PY, Rosenthal E, Shoenfeld Y. Obesity in autoimmune diseases: not a passive bystander. Autoimmun Rev 2014;13:981–1000.
70. Knerr I, Wolf J, Reinehr T, Stachow R, Grabert M, Schober E, et al. The 'accelerator hypothesis': relationship between weight, height, body mass index and age at diagnosis in a large cohort of 9,248 German and Austrian children with type 1 diabetes mellitus. Diabetologia 2005;48:2501–4.
71. Choi HM, Doss HM, Kim KS. Multifaceted physiological roles of adiponectin in inflammation and diseases. Int J Mol Sci 2020;21:1219.
72. Weihe P, Spielmann J, Kielstein H, Henning-Klusmann J, Weihrauch-Blüher S. Childhood obesity and cancer risk in adulthood. Curr Obes Rep 2020;9:204–12.
73. Kim KN, Hwang Y, Kim KH, Lee KE, Park YJ, Kim SJ, et al. Adolescent overweight and obesity and the risk of papillary thyroid cancer in adulthood: a large-scale case-control study. Sci Rep 2020;10:5000.