

# The impact of obesity: a narrative review

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## Abstract

Obesity is a disease with a major negative impact on human health. However, people with obesity may not perceive their weight to be a significant problem and less than half of patients with obesity are advised by their physicians to lose weight. The purpose of this review is to highlight the importance of managing overweight and obesity by discussing the adverse consequences and impact of obesity. In summary, obesity is strongly related to >50 medical conditions, with many of them having evidence from Mendelian randomisation studies to support causality. The clinical, social and economic burdens of obesity are considerable, with these burdens potentially impacting future generations as well. This review highlights the adverse health and economic consequences of obesity and the importance of an urgent and concerted effort towards the prevention and management of obesity to reduce the burden of obesity.

**Keywords:** Clinical impact, economic burden, obesity

## INTRODUCTION

The prevalence of obesity has increased significantly over the last two decades worldwide, including in Singapore, a multiethnic Southeast Asian country.<sup>[1,2]</sup> Recent national health surveys of adult Singaporeans suggest a continuation of this rising trend after a brief period of stabilisation.<sup>[3]</sup> Obesity, which is characterised by excessive adiposity, is not benign.

Obesity predisposes affected individuals to a large array of diseases that are often interconnected, leading to an increased risk of simple (two comorbid diseases) and complex (four or more comorbid diseases) multimorbidity in these individuals, when compared to people with healthy weight.<sup>[4]</sup> For example, in a large Finnish cohort of 114,657 people aged 16–78 years, with a mean follow-up of 12.1 years, people with obesity were five times more likely to develop simple multimorbidity and 12 times more likely to develop complex multimorbidity, with stronger associations found in people with more severe obesity.<sup>[4]</sup> This dose–response relationship between obesity and multimorbidity is also observed in other populations, including Asian populations.<sup>[5,6]</sup> In Singapore, the proportion of

disability-adjusted life years, a composite measure of all health loss within a population, contributed by overweight and obesity, increased from 3.9% in 1990 to 6.4% in 2017, making it the fifth leading risk factor affecting health in Singapore.<sup>[7]</sup> Hence, obesity is a disease with a major negative impact on human health and has become a major global and regional health problem.

However, according to international surveys and interviews, people with obesity may not perceive their weight to be a significant problem,<sup>[8]</sup> with evidence also suggesting that less than half of patients with obesity are advised by their physicians to lose weight.<sup>[9,10]</sup> Hence, the purpose of this narrative review, as part of a series on obesity, is to highlight the importance of managing overweight and obesity by presenting and summarising the latest evidence on the adverse

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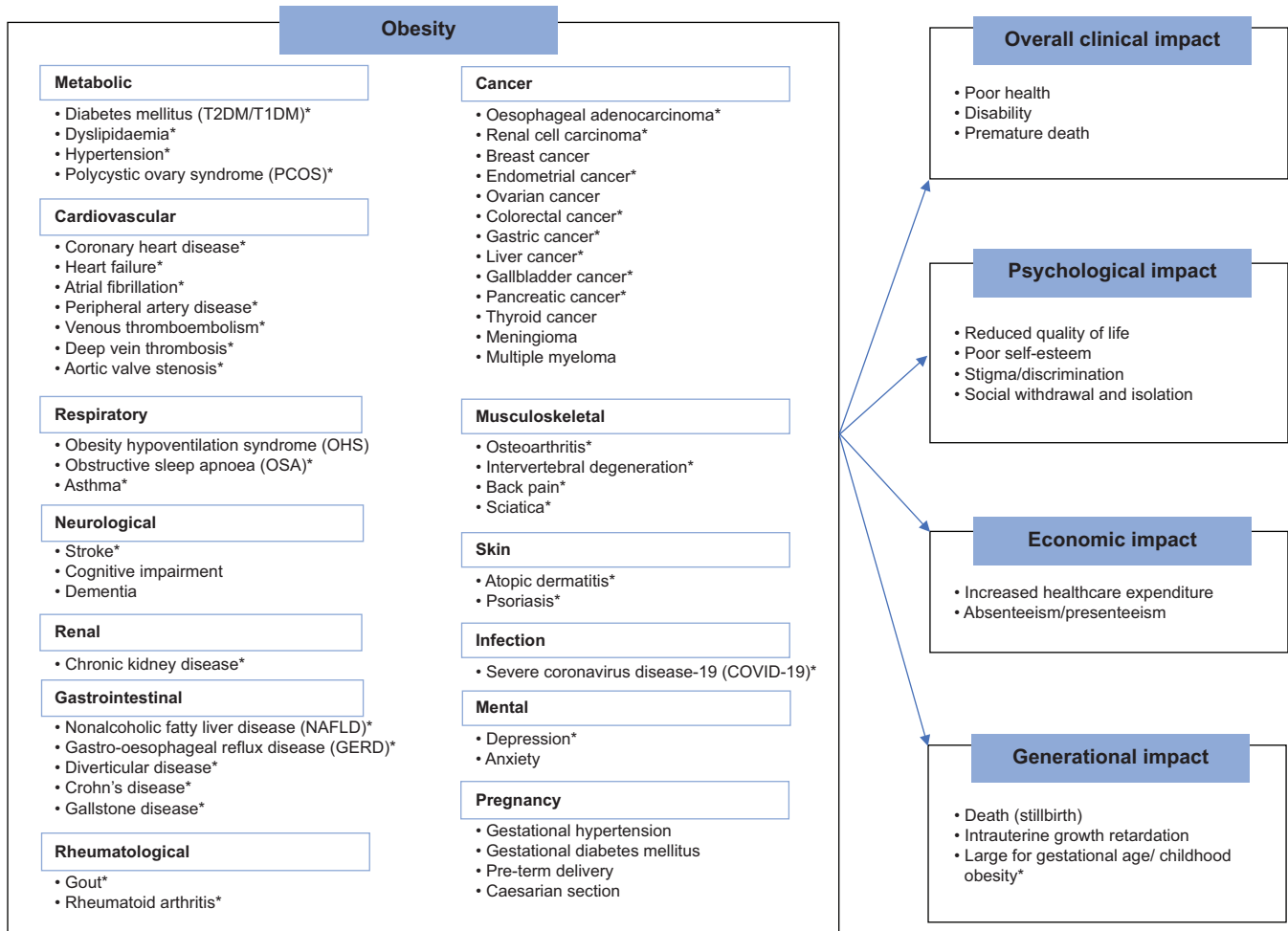
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**Figure 1:** Diagram shows a summary of the diseases and conditions associated with obesity and the potential impacts. \*Supported by mendelian randomisation studies. T1DM: type 1 diabetes mellitus, T2DM: type 2 diabetes mellitus

consequences and impact of obesity [Figure 1]. The causal role of excess adiposity on obesity-related conditions (as established by the many epidemiological evidence already described in literature) will be explored. In addition, data from Singapore, if any, will be included in the review for each section, with the review on the economic burden of overweight and obesity focusing on Singapore.

### EVIDENCE FOR CAUSAL ROLE OF EXCESS ADIPOSITY ON OBESITY-RELATED DISEASES

The hypertrophy of adipose tissue is associated with proinflammatory adipokine production and macrophage infiltration. In addition, the failure of adipose tissue to continually expand leads to lipotoxicity and ectopic fat deposition in lean tissues such as the heart, liver, pancreas and kidneys.<sup>[11,12]</sup> These phenomena contribute to a proinflammatory and insulin-resistant milieu and, together with increased mechanical stress due to increased adipose tissue mass,<sup>[11,13]</sup> are the main pathophysiological mechanisms responsible for the development of multiple medical conditions. Hence, there are reasonable pathways to link outcome to exposure (i.e.

plausibility), one of the principles useful for establishing a causal relationship.<sup>[14]</sup>

This causal role of obesity is further supported by evidence from Mendelian randomisation (MR) studies. MR is an analytical technique involving genetic variants that are associated with exposures (risk factors such as obesity) as instrumental variables to investigate the effects of these exposures on an outcome of interest (e.g. a disease).<sup>[15]</sup> Since these genetic variants are fixed, randomly allocated at conception and temporally precede the outcome, MR is less likely to be subject to bias, confounding and reverse causation, which are frequent in conventional observational studies.<sup>[15]</sup> ‘BMI’, ‘obesity’, ‘Mendelian randomisation’, ‘Mendelian randomization’ and the outcome of interest (e.g. ‘diabetes’) were used as search terms, and all studies relevant to this review were considered. These obesity-related diseases, with evidence for the causal role of obesity (plausible biological mechanisms and MR studies), and the various impacts of obesity will be discussed next.

### Diabetes mellitus, dyslipidaemia and hypertension

As highlighted, obesity leads to insulin resistance. Additionally, elevated free fatty acid from the adipose tissues and ectopic

fat deposition cause pancreatic  $\beta$ -cell dysfunction.<sup>[16,17]</sup> Hence, the various pathological mechanisms synergistically exacerbate the onset of type 2 diabetes mellitus (T2DM). In particular, visceral fat deposition plays an important role in the development of T2DM.<sup>[18]</sup> Hepatic fat worsens hepatic insulin resistance, while pancreatic fat affects insulin secretion and glucose tolerance.<sup>[18]</sup> In a meta-analysis of MR studies, genetically predicted higher body mass index (BMI) was consistently associated with T2DM, with a combined odds ratio (OR) of 2.03 (95% confidence interval [CI] 1.88–2.19) per 1 standard deviation increase in BMI.<sup>[19]</sup> In Singapore, multiple observational studies confirm the increased risk of T2DM with increasing BMI in all major ethnic groups,<sup>[20–22]</sup> although there might be ethnic-specific sensitivity to the effects of increasing adiposity.<sup>[23]</sup>

There is also increasing evidence for the role of obesity in the increased incidence of type 1 diabetes mellitus (T1DM), with studies from North America and the UK suggesting an increasing prevalence of overweight and obesity in people with T1DM.<sup>[24]</sup> It has been hypothesised that obesity-induced insulin resistance may be responsible for the accelerated loss of pancreatic  $\beta$  cells through excessive stimulation<sup>[25]</sup> and a chronic proinflammatory state.<sup>[26]</sup> This causal role is supported by MR studies, although the evidence is not as consistent (compared to obesity and T2DM), with high heterogeneity between the studies.<sup>[19]</sup>

Obesity is associated with dyslipidaemia, which is characterised by increased triglycerides (TGs) and free fatty acids, decreased high-density lipoprotein-cholesterol (HDL-C) with HDL dysfunction and increased low-density lipoprotein cholesterol (LDL-C), in particular, small dense LDL-C, which is particularly atherogenic.<sup>[27]</sup> The underlying mechanisms involve hepatic fat accumulation, insulin resistance and chronic inflammation.<sup>[27,28]</sup> In a recent MR study based on participants from the UK Biobank, genetically predicted higher BMI was significantly associated with dyslipidaemia (low HDL-C levels).<sup>[29]</sup> In Singapore, in a multiethnic sample of 4,723 adult participants, elevated TG was more common in people with obesity, with the prevalence of elevated TG increasing with higher BMI and waist-to-hip ratio (WHR),<sup>[20]</sup> consistent with the evidence.

Hypertension is more than twice as prevalent in people with obesity compared to people with normal weight.<sup>[30]</sup> The mechanisms for obesity-induced hypertension are varied (involving adipokines, cytokines, free fatty acids, insulin, the rennin–angiotensin–aldosterone system) and interconnected, with the final common pathways being endothelial dysfunction, extracellular fluid overload and sympathetic nervous system activation.<sup>[30,31]</sup> Hence, obesity is an established risk factor for hypertension, and its causal role is supported by MR studies,<sup>[19,32]</sup> particularly that of higher adiposity with a more unfavourable metabolic profile (higher

visceral and ectopic fat).<sup>[32]</sup> In Singapore, the increased prevalence of hypertension with higher BMI and WHR is consistent, especially in males.<sup>[20]</sup>

### Nonalcoholic fatty liver disease

Nonalcoholic fatty liver disease (NAFLD) is a condition in which fat accumulates in the liver in the absence of excessive alcohol consumption. Genetic variants that increase hepatic fat content have been shown to be associated with increased liver enzymes, hepatocellular damage and fibrosis, suggesting that hepatic fat accumulation mediates the development of liver fibrosis, independent of inflammation.<sup>[33]</sup> Hence, NAFLD may lead to nonalcoholic steatohepatitis (NASH), and ultimately, cirrhosis or hepatocellular carcinoma.

The prevalence of NAFLD has risen in tandem with the global epidemic of obesity, with NAFLD now being the most common cause of chronic liver disease worldwide.<sup>[34]</sup> A meta-analysis of MR studies confirms the causal effect of obesity on NAFLD,<sup>[19]</sup> with central adiposity (waist circumference) having the strongest relationship (OR 2.93, 95% CI 1.85–4.63) among the various obesity measures.<sup>[35]</sup> In Singapore, studies consistently show that participants with evidence of NAFLD have significantly higher BMI and waist circumference.<sup>[36,37]</sup>

### Cardiovascular diseases

The association between obesity and increased incidence of cardiovascular diseases such as heart failure, coronary heart disease and stroke has long been established.<sup>[38]</sup> For example, based on pooled data from 97 prospective cohort studies involving 1.8 million participants, the hazard ratio (HR) for each 5 kg/m<sup>2</sup> higher BMI was 1.27 (95% CI 1.23–1.31) for coronary heart disease and 1.18 (95% CI 1.14–1.22) for stroke after adjustment for potential confounders.<sup>[39]</sup> Additional adjustment for diabetes mellitus, hypertension and dyslipidaemia reduced the HRs to 1.15 (95% CI 1.12–1.18) and 1.04 (95% CI 1.01–1.08) for coronary heart disease and stroke, respectively, suggesting that 46% (95% CI 42%–50%) of the excess risk of BMI for coronary heart disease and 76% (95% CI 65%–91%) for stroke were mediated by these conditions,<sup>[39]</sup> which are common in people with obesity.<sup>[4,30]</sup>

Obesity itself leads to an increased risk of these cardiovascular events, likely via mechanisms such as the secretion of adipokines, proinflammatory cytokines and hypofibrinolytic factors, that together could lead to increased oxidative stress and endothelial dysfunction resulting in atherosclerosis.<sup>[40]</sup> Additionally, excessive adiposity results in haemodynamic alterations via various neurohormonal and metabolic abnormalities, causing left ventricular (LV) hypertrophy and subsequent dysfunction, leading to LV failure. LV failure, facilitated by pulmonary arterial hypertension from hypoxia due to obstructive sleep apnoea (OSA) and/or obesity hypoventilation syndrome (OHS), may subsequently lead to right ventricular failure.<sup>[41]</sup> This causal role of obesity is

supported by multiple MR studies,<sup>[19,29,32]</sup> with the strongest association between BMI and heart failure, followed by BMI and coronary artery disease, then BMI and stroke.<sup>[19,32]</sup>

Another obesity-related cardiovascular disease is atrial fibrillation (AF), with evidence suggesting that obesity is an independent risk factor for AF, even after accounting for OSA.<sup>[41]</sup> Also, studies have demonstrated a strong graded association between higher BMI and the risk of persistent AF and higher BMI, with increased risk of postablation AF.<sup>[41]</sup> The mechanisms linking obesity and AF are complex and incompletely understood, with increased left atrial and ventricular abnormalities, altered haemodynamics, increased epicardial and pericardial fat, inflammation, and metabolic and neurohormonal abnormalities being the potential causal mechanisms.<sup>[41]</sup> This causal relationship is similarly supported by MR studies which consistently show that genetically predicted BMI is associated with AF.<sup>[19,32,42]</sup>

In Singapore, a longitudinal study involving 2,605 Chinese participants found that the adjusted HR for cardiovascular and stroke mortality was highest in the group with obesity (BMI  $\geq 30$  kg/m<sup>2</sup>) among those aged  $\geq 65$  years,<sup>[43]</sup> which is consistent with the association between obesity and increased incidence of cardiovascular diseases.

### Obstructive sleep apnoea and hypoventilation syndrome

The increased intra-abdominal and intrathoracic pressure as a result of excessive adiposity impedes inflation of the lung, which can significantly affect the lung function, thereby leading to hypoventilation and ventilation–perfusion imbalance.<sup>[44]</sup> A constellation of obesity, daytime hypoventilation characterised by hypercapnia and hypoxaemia, and sleep-disordered breathing, without an alternative cause for hypoventilation, is known as OHS, with an estimated prevalence of 8%–20% in patients with obesity who were referred to sleep centres for evaluation of sleep-disordered breathing.<sup>[45]</sup>

The most common sleep-disordered breathing in such patients and people with obesity is OSA, as fat accumulation around the upper airways predisposes to the collapse of these airways.<sup>[44]</sup> About 50% of people with OSA have obesity, and approximately 40%–90% of people who are overweight suffer from OSA.<sup>[44,45]</sup> Consistent with epidemiological observations and genetic correlation (between OSA and BMI), an MR study shows that genetically predicted BMI is strongly associated with OSA, supporting the causal effect of BMI on OSA.<sup>[46]</sup> In Singapore, a study based on 587 Chinese participants reported that people with OSA had significantly higher BMI, and also BMI remained an important predictor of OSA after adjusting for hypertension and smoking,<sup>[47]</sup> in line with the overall evidence.

### Polycystic ovary syndrome

Obesity is strongly associated with polycystic ovary syndrome (PCOS),<sup>[48]</sup> which is characterised by

reproductive dysfunction (oligo-amenorrhoea, infertility), hyperandrogenism (hirsutism, acne, androgenic alopecia and biochemical hyperandrogenism) and a polycystic ovarian morphology (high antral follicle counts or increased ovarian volume).<sup>[49]</sup> Up to 88% of women with PCOS are overweight or obese,<sup>[48]</sup> with a meta-analysis showing that women with obesity had a twofold to threefold higher risk for PCOS when compared to women without obesity.<sup>[50]</sup> The pathogenesis of PCOS involves primarily insulin resistance, with the ensuing secondary hyperinsulinaemia resulting in enhanced steroidogenesis in the ovaries, particularly androgen production.<sup>[48]</sup> Hence, the insulin-resistant milieu associated with obesity can lead to the development of PCOS. This causal effect of obesity on PCOS is supported by MR studies,<sup>[32,51]</sup> with one MR study suggesting that this effect is predominantly metabolic in nature.<sup>[32]</sup> In Singapore, a study based on a multiethnic population of 389 participants reported that women with PCOS had significantly higher BMI compared to women without PCOS,<sup>[52]</sup> consistent with the evidence.

### Cognitive impact and dementia

Experimental studies have shown that cellular mechanisms such as oxidative stress and inflammation can affect the brain structure and function.<sup>[53]</sup> Obesity is an established risk factor for dementia,<sup>[54]</sup> and has been associated with cognitive impairment<sup>[55,56]</sup> and decreased grey matter volume linked with executive functioning.<sup>[53,57]</sup> However, while MR studies have found causal relationships between BMI and grey matter volumes,<sup>[58]</sup> evidence for BMI and dementia has so far not been significant.<sup>[32,58,59]</sup> In Singapore, a longitudinal analysis of 1,519 cognitively normal older persons (>55 years) of Chinese ethnicity showed that central obesity was associated with a higher risk of developing mild cognitive impairment,<sup>[60]</sup> consistent with the overall evidence that higher adiposity has a negative impact on the brain.

### Chronic kidney disease

Excess adiposity results in pathological processes such as lipotoxicity, inflammation, oxidative stress and activation of the renin–angiotensin–aldosterone system, leading to glomerular and tubular injuries (obesity-induced nephropathy).<sup>[61]</sup> Multiple MR studies have confirmed this causal relationship between obesity and kidney disease,<sup>[32,62,63]</sup> including one study conducted in an East Asian population using BMI-associated variants validated in East Asia.<sup>[63]</sup> In Singapore, longitudinal gain in adiposity was associated with progressive renal decline in a prospective multiethnic cohort with T2DM, suggesting that increasing adiposity would lead to adverse renal outcomes over time.<sup>[64]</sup>

### Cancers

Obesity is known to be associated with 13 types of cancers: oesophageal adenocarcinoma, renal cell carcinoma, postmenopausal breast cancer, endometrial cancer, colorectal cancer, meningioma, multiple myeloma, and cancer of the

gastric cardia, liver, gallbladder, pancreas, ovary and thyroid.<sup>[65]</sup> In Singapore, these obesity-associated cancers make up four out of the top five cancers affecting women (breast, colorectal, endometrial and ovarian) and two of the top five cancers affecting men (colorectal and liver).<sup>[66]</sup> Potential mechanisms of increased cancer risk in obesity include hyperinsulinaemia, chronic inflammation and oestrogen excess.<sup>[67]</sup> This causal role of obesity in cancer is supported by MR studies,<sup>[19,32]</sup> particularly for cancers of the digestive system, with all of them (oesophageal, colorectal, gastric, liver, gallbladder, pancreas) positively associated with genetically predicted BMI based on a meta-analysis of MR studies.<sup>[19]</sup>

### Depression and anxiety

The prevalence of depression is much higher among people with obesity than that in the general population.<sup>[68,69]</sup> Similarly, anxiety occurs more frequently in people who are overweight or obese compared to people with normal weight, and the relationship is stronger among those who are more severely obese.<sup>[70-72]</sup> Research findings consistently show that people with obesity frequently suffer from psychological issues ranging from stress associated with weight-related issues, perceived weight discrimination and stigmatisation to body image dissatisfaction.<sup>[68,69]</sup> Additionally, there is evidence that the dysfunctional adipose tissues present in obesity result in metabolic abnormalities, such as altered glucocorticoid, adipokine, insulin, leptin and inflammatory signalling, which either directly or indirectly impact the control of emotions and mood.<sup>[73,74]</sup> Hence, the causal relationship between obesity and depression/anxiety is likely to have both psychological and biological components. This is supported by MR studies which demonstrate the relationship between genetically predicted BMI (and fat mass) and depression,<sup>[75-77]</sup> even when using a genetic instrument that omits the metabolic consequences of higher BMI.<sup>[75]</sup>

In Singapore, a study based on 83 patients with obesity at a weight management clinic reported that the prevalence of anxiety symptoms and depressive symptoms was 28% and 11%, respectively,<sup>[78]</sup> suggesting that symptoms of depression and anxiety are highly prevalent in people with obesity in Singapore and are higher than the national prevalence of depression and anxiety,<sup>[79]</sup> consistent with international data.

### Severe coronavirus disease-19

The dysfunctional physiological milieu of obesity has been associated with altered lymphoid tissue integrity, shifts in leukocyte populations and proinflammatory profiles, such that immune responses and pathogen defence are impaired.<sup>[80]</sup> This is demonstrated in previous influenza outbreaks<sup>[81]</sup> and the current coronavirus disease 2019 (COVID-19) pandemic, where obesity (high adiposity) is a major risk factor for severe COVID-19 (death and hospitalisation), as supported by multiple epidemiological studies worldwide<sup>[82]</sup> and MR studies<sup>[83-86]</sup> using data from the COVID-19 Host

Genetics Initiative (an international collaboration that aims to uncover the genetic determinants of outcomes related to COVID-19 susceptibility and severity). In Singapore, where the COVID-19 mortality rate is low (<0.001),<sup>[87]</sup> a subgroup analysis of younger (<60 years) COVID-19 patients found that a BMI  $\geq 25$  kg/m<sup>2</sup> was significantly associated with the need for low-flow supplemental oxygen and mechanical ventilation,<sup>[88]</sup> consistent with observations internationally.

### Other diseases

Other diseases with established epidemiological and strong MR evidence include asthma,<sup>[32]</sup> gastro-oesophageal reflux disease,<sup>[19,32]</sup> diverticular disease,<sup>[19,32]</sup> gallstone disease,<sup>[19,32]</sup> Crohn's disease,<sup>[19,89]</sup> osteoarthritis,<sup>[32,90]</sup> intervertebral degeneration (including back pain and sciatica),<sup>[91,92]</sup> peripheral arterial disease,<sup>[19,32]</sup> venous thromboembolism,<sup>[19,32]</sup> deep vein thrombosis,<sup>[19,32]</sup> aortic valve stenosis,<sup>[19]</sup> atopic dermatitis,<sup>[93]</sup> psoriasis,<sup>[32]</sup> gout<sup>[32]</sup> and rheumatoid arthritis.<sup>[32]</sup>

### IMPACT ON MOTHER AND CHILD

Maternal obesity has been associated with adverse outcomes, including increased mortality, for both mother and child.<sup>[94]</sup> Mothers with obesity are more likely to develop pregnancy complications such as gestational hypertension, preeclampsia, gestational diabetes mellitus and thromboembolic disease, with a higher risk of preterm delivery, caesarian section, stillbirth, intrauterine growth retardation and foetus that is large for gestational age.<sup>[94-96]</sup> In an MR study, genetically elevated maternal BMI was associated with higher offspring birthweight, supporting a causal relationship.<sup>[97]</sup> These adverse outcomes can lead to complications and disability, with increased birth weight being associated with childhood adiposity and metabolic disorders during life.<sup>[94]</sup> Hence, the impact of obesity may extend beyond the current generation (mother) to the next generation (child). In Singapore, findings from the Growing Up in Singapore Towards Healthy Outcomes (GUSTO) study, a prospective mother-offspring birth cohort, showed that pre-pregnancy BMI and maternal obesity were associated with child size and adiposity<sup>[98]</sup> and childhood obesity,<sup>[99]</sup> respectively, confirming the generational impact of obesity.

### PSYCHOSOCIAL IMPACT

Obesity negatively impacts health-related quality of life, with greater degrees of obesity associated with greater impairments.<sup>[100-102]</sup> While most individuals often report significant difficulties with physical and occupational functioning, many also experience problems with social functioning, such as social withdrawal<sup>[103]</sup> and social isolation.<sup>[104]</sup> This could be due to perceived negative attitudes and discrimination towards people with obesity, increased self-consciousness and self-blame for being overweight.<sup>[69,104]</sup> People with obesity, especially females, are often dissatisfied with their body image, which is exacerbated by society's expectation of thinness, with the degree of dissatisfaction

positively correlated with the amount of excess weight.<sup>[102,105,106]</sup> Taken together, obesity can negatively impact an individual's self-esteem,<sup>[69]</sup> thereby affecting self-efficacy,<sup>[107]</sup> possibly resulting in a vicious circle and downward spiral.

## ECONOMIC IMPACT

There are substantially higher healthcare utilisation and medical costs among people who are overweight or obese due to treatment of medical conditions caused by excess adiposity and for direct obesity treatments, which may include weight loss surgeries and medications.<sup>[108]</sup> In addition to direct medical costs, there is also an increase in indirect costs as a result of increased absenteeism (workdays missed due to illness or injury) and presenteeism (reduced productivity while working).<sup>[109]</sup>

The economic burden of overweight and obesity has been well described and quantified in North America,<sup>[108,110]</sup> Europe,<sup>[111-114]</sup> Brazil,<sup>[115]</sup> Australia,<sup>[116,117]</sup> China<sup>[118]</sup> and Saudi Arabia,<sup>[119]</sup> with an estimated cost of 0.8%–2.4% of gross domestic product (GDP) in 2019 based on eight countries.<sup>[120]</sup> As for Singapore, a recent study has attempted to quantify the economic burden of overweight and obesity.<sup>[121]</sup> Using econometric methods and cross-sectional data from the Singapore Epidemiology of Eye Diseases (SEED) cohort, which includes measured height and weight, self-reported healthcare utilisation and absenteeism/presenteeism (based on a modified version of the Work Productivity Activity Impairment questionnaire), the incremental per capita and aggregate direct and indirect costs of excess weight among a multiethnic population of older adults (aged 40–80) were estimated.

Among Chinese, individuals who were overweight missed one additional workday per year compared to those who were of normal weight. Individuals in the obese category had SGD720 per year greater medical expenditures, but missed workdays were not statistically different from those in the normal weight category. Among Indians, differences were not significant between normal and overweight categories, but Indians in the obese category incurred an additional SGD310 per year in absenteeism costs than those of normal weight. For Malays, no significant differences by BMI category were identified.<sup>[121]</sup>

In aggregate, the predicted total medical expenditures attributable to overweight and obesity in Singapore were estimated to be SGD178 million, representing 1.6% of Singapore's total healthcare expenditures (SGD11,300 million in 2019). This figure is on the low end of published estimates, which range between 2.9% and 9.7% of the total healthcare spending.<sup>[121]</sup> Including absenteeism increases this estimate to SGD261 million, although this estimate is likely to be conservative because it does not include costs for presenteeism (reduced productivity while working), retraining, injuries or other costs resulting from excess weight in the

workplace.<sup>[121]</sup> By ethnicity, Malays are responsible for 19% of the total costs of excess weight, even though they make up only 12% of the Singapore population.<sup>[121]</sup> This disproportionate burden is consistent with the disproportionately higher rates of overweight and obesity among Malays.<sup>[3]</sup>

## LIMITATIONS OF REVIEW

First, this review discussed mainly the impact of adult obesity, with a focus on diseases that have shown a strong relationship with obesity, especially those supported by MR studies. Hence, the impact of paediatric obesity is not discussed and not all diseases have been covered. Second, not all the diseases supported by evidence from MR studies were discussed in detail. Nonetheless, they are listed in the section 'Other diseases' and included in Figure 1. Third, interventional studies which show significant weight loss-improving health outcomes were not discussed. These studies, by showing the positive impact of weight loss, would have further supported the negative impact of obesity. Lastly, while there are some MR studies based on Asian cohorts, the majority of MR studies were based on genetic data derived from individuals of European ancestry or large cohorts that were predominantly European. Hence, the inference of causality may be limited in non-European populations.

## CONCLUSION

As discussed, obesity is strongly related to more than 50 medical conditions [summarised in Figure 1], with evidence from MR studies to support causality for many of these conditions. Based on the 2017 Global Burden of Diseases study, the top four causes (cardiovascular diseases, cancers, musculoskeletal disorders and mental disorders) of disability-adjusted life years in Singapore account for more than 50% of the total burden,<sup>[7]</sup> with many of the common conditions in these four causes related to obesity. Hence, the clinical, social and economic burdens of obesity are considerable, potentially impacting future generations as well. This review, therefore, highlights the importance of an urgent and concerted effort towards the prevention and management of obesity to reduce the burden of obesity.

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## Conflicts of interest

There are no conflicts of interest.

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