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REVIEW

Weight Gain in Midlife Women

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Abstract

Purpose of Review To summarize the evidence and clinical implications of weight and body composition changes during midlife in women and provide an overview of weight gain prevention and management in this population.

Recent Findings Aging-related changes such as decreased energy expenditure and physical activity are important culprits for weight gain in midlife women. The hormonal changes of menopause also influence body adiposity distribution and increase central adiposity. These body changes can have health consequences including the development of cardiometabolic diseases, osteoarthritis, cancer, worsening in cognition, mental health, and menopause symptoms.

Summary Midlife women experience changes related to aging, menopause, and lifestyle which favor weight gain. Clinical practice should focus on early counseling and anticipatory guidance on the importance of dietary changes and physical activity to attenuate this phenomenon. Future research should focus on the longitudinal relationship between weight trends in midlife and health consequences and mortality.

Keywords Midlife women · Weight gain · Body composition · Metabolic rate · Lifestyle intervention

Introduction

Midlife is the period of life between early adulthood and old age, typically between the ages of 40 and 65. This period is characterized by a variety of physical, psychological, and social changes, particularly in women as it coincides with the menopause transition. Concerns about weight are common among women during midlife, with reports of weight gain and increased abdominal adiposity, occurring in isolation or together. There are several factors that can contribute to weight and body composition changes, including a decrease in physical activity, declining hormone levels (i.e., decreased estrogen and androgen levels, and estrogen to androgen ratio), and dietary changes. Weight and body composition changes in midlife may result in the development of overweight and obesity, contributing to an overall increased risk in cardiovascular disease (CVD) and mortality. In this review, we will summarize the evidence and clinical implications of weight and body composition changes during midlife in women and provide a brief overview of weight gain prevention and weight management in this population.

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Weight and Body Composition Changes

Weight gain is a common concern for midlife women and has been reported in several studies. In the Study of Women's Health Across the Nation (SWAN), midlife women ($n = 3064$; mean age 45.9 years) gained an average of 0.7 kg (1.5 pounds) per year, independent of age at baseline or menopause status [1]. Although racial and socioeconomic disparities impacted body weight at baseline (i.e., nonwhite and lower socioeconomic status are associated with higher baseline weight), in a following study, weight gain occurred in all midlife women, suggesting the uniformity of this trend [2]. Similarly, in the Nurses' Health Study (NHS), midlife women ($n = 41{,}518$; mean age 53.7 years) gained an average of 3 kg (6.8 pounds) over 8 years of follow-up, for an average of 0.4 kg (0.85 pounds) per year [3]. Comparably, women without any chronic comorbidities in the Biobehavioral Health in Diverse Midlife Women Study ($n = 232$; mean age 43.42 years) gained an average of 1.4 kg (3 pounds) over 2 years, for an average of 0.7 kg (1.5 pounds) per year [4]. In another study, almost 70% of women reported gaining weight during the menopause transition [5], and weight gain appeared to continue even postmenopause [5, 6]. However, weight gain is not limited to midlife; numerous studies have documented an average yearly weight gain of 0.5 to 1 kg (1–2 lb) in US adults [7]. In one specific US study, women aged 36–79 experienced an increase of 5.4 kg (approximately 11.9 lb) over the prior 10 years, with the age group of 36–39 years showing the highest weight gain (9 kg or 19.8 lb) [8]. Additionally, in another Australian study, women aged 18–23 years gained 8.6 kg (approximately 18.9 lb) over a 13-year period, which on average is about 0.66 kg (approximately 1.46 lb) per year [9].

Nonetheless, persistent weight gain throughout adulthood, particularly when it does not level off during midlife, can significantly contribute to the progression or onset of overweight and obesity. In 2015, the Women's Health Initiative Observational Study reported that in women aged 50 to 79 years, one-third had overweight and one-quarter had obesity at baseline [6]. Further, 36% of the participants gained clinically significant weight (> 3% of their weight) over 3 years of follow-up [6]. In the US, the prevalence of obesity has increased over the past few decades across all age groups of women; however, the prevalence of obesity among 40–60-year-old women was higher compared to women between the ages of 20 and 39: 43.3 vs. 39.7%, respectively [10].

In fact, current data may underestimate the incidence of weight gain in midlife women. This may be due to several reasons, the first of which is that some of the studies reporting on this topic included mostly women with preexisting excess adiposity, and many women who experience weight gain during this stage of their lives may still not yet have overweight or obesity [1, 2, 6, 11]. Second, some national registries do not address overweight as part of the spectrum of excess adiposity. For instance, the National Center for Health Statistics (NCHS) only reports the prevalence of obesity without addressing the equally prominent issue of overweight [10]. Third, many studies only report the change in weight in women across the menopause transition, rather than across the midlife stage [11–13]. Therefore, data regarding the average anticipated weight gain in midlife women are incomplete. Nevertheless, weight gain in midlife women is observed in clinical practice, and it predisposes midlife women to obesity and other adverse health outcomes [10].

Unlike weight gain, a more specific phenomenon to midlife women is the change in body composition [1]. There is a consistent rise in body fat mass over the years in women. However, research indicates that midlife women experience a more precipitous increase of body fat from age 45 to 75 years compared to younger and older women [14]. In addition, when stratifying women by menopause status, peri- and postmenopausal women tend to have significantly higher absolute and relative total body fat than premenopausal women [12, 13, 15]. Similarly, midlife women have an increase in central fat deposition. In the SWAN study ($n = 3064$; mean age 45.9 years), midlife women had an average increase in waist circumference of 2.2 cm (0.9 in) over a span of 3 years [1]. In contrast, the Biobehavioral Health in Diverse Midlife Women Study ($n = 232$; mean age 43.42 years) showed no statistically significant difference in waist circumference over a 2-year follow-up. It is important to note that in the SWAN study, after the 3 years of follow-up, 60.9% of the women were perimenopausal, and 13% of women were postmenopausal, while in the Biobehavioral Health in Diverse Midlife Women Study, most women (75%) were still premenopausal [1, 4]. This suggests that the change in body composition in midlife may be primarily driven by the hormonal changes that accompany the menopause transition. This theory is supported by the fact that waist circumference progressively increases through the menopause transition, from pre-, to peri-, and then to postmenopause [15]. Finally, midlife women tend to lose lean mass, and postmenopausal women tend to have significantly lower muscle mass than premenopausal women [16, 17].

Pathophysiology

It can be challenging to discern the effects of aging from the effects of menopause on weight gain in midlife women as these two life events overlap. Women are more

likely to report weight gain in midlife, but both men and women gain weight during this stage of life, suggesting the role of aging [18]. A systematic review that included 2472 women revealed that weight gain was attributed to aging rather than menopause status after evaluating different statistical models to compare the two [12]. However, menopause was a strong predictor of increased central fat deposition as waist circumference increased by 4.63 cm (1.82 inches) during the menopause transition [12]. Therefore, aging seems to be playing a key role in weight gain, although menopause alters body composition in midlife women. However, this may be an oversimplification given the various mechanisms behind weight gain in midlife women (Fig. 1).

Energy Balance

Increases in stored energy—often presenting as weight gain—results from the discordance between calorie intake and total energy expenditure (TEE). TEE is determined by the basal metabolic rate (BMR), activity energy expenditure, and dietary induced thermogenesis (DIT) [19]. BMR accounts for 60–80% of TEE, and it is used interchangeably with resting metabolic rate (RMR) in the literature [20, 21]. Both measure oxygen consumption and/or carbon dioxide production via indirect calorimetry, with the only difference being that BMR is measured under stricter conditions, i.e., in the morning after an overnight fast and after a 24-h exercise- and stress-free period [22]. In

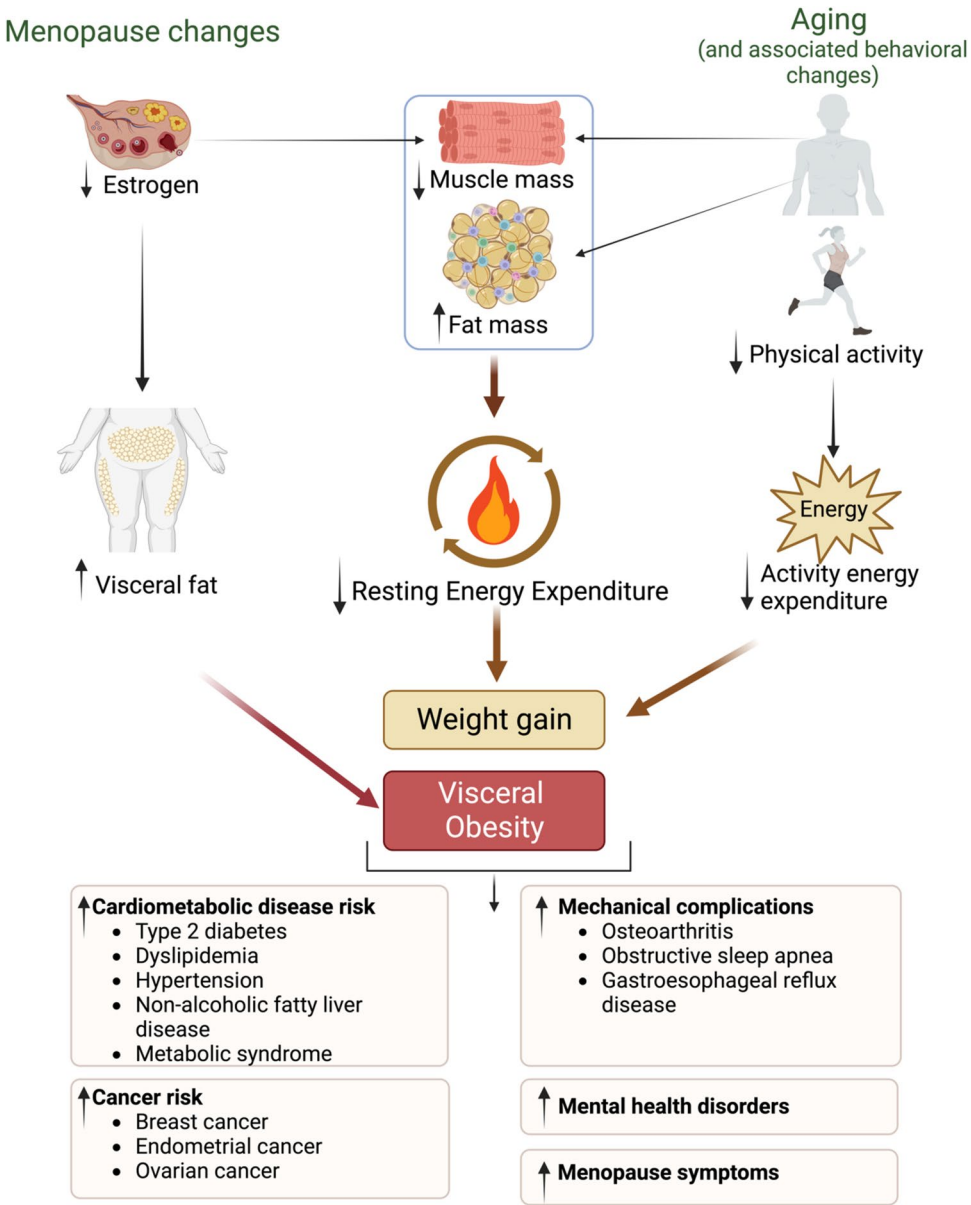

Fig. 1 Changes in weight and body composition in midlife women and clinical consequences

general, women have lower absolute BMR and RMR than men which may be explained by the differences in body composition (lower lean mass and higher fat mass) [22, 23]. On the other hand, DIT contributes to 10% of TEE, while activity-related energy expenditure encompasses a range of 15–30% of TEE.

BMR and RMR decline linearly with age, consequently resulting in a decline in TEE [20–22]. Consequently, as a woman ages, weight gain can naturally occur if dietary habits and physical activity remain unchanged. Body lean mass, i.e., muscle mass, is one of the strongest determinants of BMR and the major contributor to the decline in BMR with age. As such, age-related muscle mass loss may explain most of the decline in BMR in midlife women [19]. After the age of 30, muscle mass loss occurs at a rate of 3–8% per decade, making it more challenging to maintain muscle mass [17]. This is further exacerbated by the hormonal changes during menopause [16]. Estrogen deficit after menopause is associated with increased inflammatory markers that are associated with muscle degradation [24]. Moreover, estrogen acts directly on muscle stem cells to promote muscle maintenance, regeneration, and repair, effects that are attenuated after menopause [25]. In addition, women experience androgen loss as they age, mainly during their early reproductive years [26], with a slower decline during midlife, and no apparent additional effect of the menopause transition [27]. In women from the Melbourne Women's Midlife Health Study, testosterone levels were stable during midlife, but dehydroepiandrosterone sulfate (DHEAS) declined by 1.5% annually [27]. While the literature is mixed, there is some evidence that lower testosterone levels are associated with lower body lean mass [28] and increased risk of sarcopenia in women [29]. Therefore, androgen loss may contribute to the muscle loss in midlife women, and hence to the decrease in BMR.

Further, physical activity and resistance training play a key role in slowing muscle loss and increasing BMR and active energy expenditure. Almost 30% of adults ≥ 50 years of age in the US report no physical activity outside of work [30]. The Physical Activity Guidelines Advisory Committee recommends at least 150 min (about 2 and a half hours) a week of moderate-intensity exercise [31]. In the SWAN cohort, only 7.2% of the study population reported physical activity levels that consistently met the recommendation over their midlife span [32]. Similarly, two studies based on the SWAN population reported that 25% of midlife women who participated in the registry had decreasing physical activity over a 15-year follow-up, and that the decrease in physical activity was associated with the most weight gain, when compared to unchanged or increased level of physical activity [1, 33].

In terms of dietary changes, lower intake of dietary fiber and higher intake of dietary fat in midlife is associated with increased risk of weight gain, but longitudinal studies report a decrease rather than an increase in calorie intake in midlife women [6, 34, 35]. Moreover, weight gain in midlife women has been better explained by decreased levels of physical activity as opposed to increased caloric intake in regression models [35].

Vasomotor Symptoms and Sleep

The SWAN cohort has provided evidence that frequent VMS (hot flashes and night sweats) are associated with subsequent weight gain, higher BMI, and higher waist circumference in midlife women [36]. Both the onset of high-frequency VMS and the increase in VMS frequency over time were associated with greater weight gain during subsequent visits [37]. This is relevant as VMS are reported by up to 75% of women during the menopause transition [38]. The mechanisms behind this association have not been established. VMS have been associated with decreased exercise and overall physical activity, important risk factors for weight gain [37, 39–42]. Additionally, data support that poor sleep quality may have an impact on weight gain rather than sleep duration, as another report from the SWAN cohort revealed that sleep duration was not associated with prospective weight gain [36, 43]. In the SWAN cohort, self-reported sleep problems, defined as trouble falling asleep, waking up early, and/or waking up several times per night occurring three times or more, accounted for almost 30% of the effect of VMS on weight gain [36]. This suggests that sleep disruptions may significantly contribute to weight gain but are not the sole factor in women experiencing high-frequency VMS.

Clinical Implications

The accumulation of excess adiposity can contribute to the development of cardiometabolic diseases, mechanical complications, cancer, changes in cognition and mental health, and worse menopause symptoms. While there is robust evidence on the association between obesity (primarily based on BMI) and these disorders, there is a paucity of data on the longitudinal relationship between weight gain and the incidence of these conditions throughout women's lifespans, particularly as it relates to the midlife stage. Adiposity-associated diseases can increase with age, but as summarized below, there is a rapid increase in their prevalence during midlife in women, with research indicating a potential role of hormonal changes as women go through menopause [44].

Cardiometabolic Risk Factors

Hypertension

It is not surprising that the incidence of hypertension increases in midlife as the relationship between aging and increased blood pressure has been well established [45]. However, the incidence of hypertension varies across women's lifespans, with a precipitous rise in its prevalence in early to mid-adulthood, a rise that gradually becomes less pronounced in midlife and late adulthood [46]. In the United States, between 2017 and 2020, the prevalence of hypertension was 15% in women aged 20–34 years old, 32% in women aged 35–44 years old, 49% in women aged 45–54 years, 63% in women aged 55–64 years old, 75% in women aged 65–74 years old, and 81% in women aged ≥ 75 years old [46]. In addition to aging, weight gain is a strong predictor of hypertension. Particularly, younger age at onset of weight gain, i.e., early adulthood and extending into early midlife, is associated with a higher risk of incident hypertension, whereas late-onset weight gain is not [47, 48]. Sundstrom et al. reported that every 10 kg (22 pounds) of weight gain in women, starting at age 20 and throughout midlife, was associated with a 3.2 and 2.4 mmHg increase in systolic and diastolic blood pressures, respectively [48]. Similarly, data from the NHS revealed that every 4.5 kg (10 pounds) of weight gained during early midlife was associated with a 30% increased risk of hypertension [49]. The changes in blood pressure across the midlife period in women has been shown to be independent of menopause status [50].

Metabolic Dysfunction-Associated Steatotic Liver Disease

In women younger than 50 years old, the prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD—previously referred to as non-alcoholic fatty liver disease) tends to be stable around 10–15% and increases steadily afterwards, reaching a peak of 20–35% at the age of 60 years [51–54]. Although it could be theorized that aging could explain this upward trend, at least in part, this phenomenon is not seen in men aged 50 or older, in whom MASLD prevalence remains stable [52]. Research indicates that the menopause transition may be a major risk factor, with the prevalence of MASLD doubling in postmenopausal women compared to premenopausal women [55]. MASLD is the leading cause of chronic hepatic disease, cirrhosis, and liver cancer globally [56]. In women, MASLD is the leading indication for liver transplantation [57]. Like in the general population, weight gain and increased adiposity, particularly in the central distribution, are associated with increased risk of MASLD in midlife women. However, their effects have not been quantified in this population [58, 59].

Dysglycemia and Dyslipidemia

As with other cardiometabolic risk factors, diabetes and dyslipidemia incidence vary across women's lifespans, slowly rising in early adulthood, then rapidly increasing between the ages 40 and 55 years and slowly decreasing thereafter [60]. Consequently, compared to women aged 20–40 years, the prevalence of diabetes and dyslipidemia in midlife women increases by three- to fourfold, and compared to women aged 65 years and older, the prevalence of both diseases is slightly lower during midlife [61–64]. All published data on dysglycemia and dyslipidemia assess the effect of baseline weight or BMI rather than the longitudinal relationship between weight gain and the incidence of dysglycemia and dyslipidemia. For instance, data from the SWAN cohort has revealed that over the span of a follow-up of 16 years, the incidence of type 2 diabetes was 37% in midlife women, with women with incident diabetes having a 14% higher BMI at baseline [62]. Similarly, data from multiple cohort studies, including the SWAN, the Dutch Lifelines Cohort, and the UK Medical Research Council National Survey of Health Development, indicate that an elevated BMI during women's midlife, particularly as they approach the menopause transition, is associated with a greater increase in total cholesterol, low density lipoprotein cholesterol, and apolipoprotein A and B, independent of age [65–67].

Cardiovascular Disease

CVD is the leading cause of death among women [44]. In women, the prevalence of CVD increases with age, particularly after midlife, and it is estimated as follows: 17% in women aged 20–39 years, > 50% in women aged 40–59 years, 77% in women aged 60–79 years, and > 90 after age 80 years [46]. Evidence suggests that menopause is a major and independent risk factor for CVD, with an inverse linear association between age at menopause onset and CVD risk [68–70]. Weight gain and changes in body composition among midlife women are associated with increased risk of CVD and mortality [44]. Multiple studies have reported a strong association between obesity and central obesity (independent of BMI) and increased CVD mortality in midlife women [71, 72]. Indeed, data suggest that women with normal BMI but with central obesity may have a greater CVD risk compared to women with BMI in the obesity range and without central obesity [72]. This risk appears to be the result of a combination of midlife metabolic and cardiovascular changes which are exacerbated by the menopause transition which is now considered a female-specific CVD risk factor [44]. Throughout the menopause transition, independent of age, women experience an increase in carotid intima media thickness, carotid atherosclerosis and remodeling, arterial stiffness, and fat deposition within and outside the pericardial sac, changes that are exacerbated by excess adiposity [73, 74].

Cancer

Excess adiposity poses a risk for esophageal, gastric, colorectal, hepatic, gallbladder, pancreatic, breast, endometrial, ovarian, and kidney cancers, among others [75]. A study by Chadid et al. reported that in midlife women, weight gain of more than 0.45 kg (1 pound) per year is associated with a 30% increased risk of obesity-related cancers [76]. Furthermore, weight gain combined with metabolic dysfunction (e.g., prediabetes, type 2 diabetes, dyslipidemia, hypertension) increased this risk by 77% [76]. In this study, women transitioning from a BMI in the normal range to the overweight range during midlife had a 60% greater risk of obesity-related cancer [76]. These findings are concordant with the evidence on weight gain and breast cancer risk, the most common cancer in women. Data from the National Institutes of Health-AARP Diet and Health Study showed that in postmenopausal women not on hormone therapy (HT), weight gain of 10–19.9 kg (22–44 pounds) from age 35 to 50 increased the risk of postmenopausal breast cancer by 40%, whereas weight gain greater than 50 kg (110 pounds) more than doubled this risk [77]. Along the same lines, another study reported that every 5 kg (11 pounds) increase in weight was associated with a 39% increased risk of postmenopausal endometrial cancer, a 13% increased risk of postmenopausal ovarian cancer, and a 4% increased risk of colorectal cancer [78, 79]. In midlife women, the changes in body composition are of importance as studies have reported a strong association between central obesity, independent of BMI, and increased cancer mortality, particularly among postmenopausal women [71]. Notably, while weight gain and excess adiposity late in midlife, particularly after menopause, is associated with an increased risk of breast cancer, excess adiposity during puberty and early adulthood may confer protection against breast cancer, and specifically against hormone receptor-positive breast cancer [80, 81].

Obstructive Sleep Apnea

Excess adiposity has been identified as major risk factor for obstructive sleep apnea (OSA) across adulthood, irrespective of sex [82]. The global prevalence of OSA among women varies between 3 and 25%, and data reveal that its prevalence increases significantly in midlife women [83]. For instance, in a large population-based study, the prevalence of mild to severe OSA among women aged less than 45 was calculated at 24%, compared to 56% in women aged 45–54, and 75% in women aged between 55 and 70 [84]. The effect of weight and body composition changes that women experience in midlife on the risk of sleep apnea incidence and severity has not been studied.

Osteoarthritis

Osteoarthritis is the leading cause of chronic pain and disability in the US, affecting at least 19% of adults over the age of 45 years, with a higher prevalence among women [85–88]. Increased body adiposity is one of the early established risk factors for osteoarthritis in the scientific literature [89]. In the Melbourne Women's Midlife Health Project, BMI was one of factors contributing to the increased prevalence of osteoarthritis in otherwise healthy middle-aged women over an 11-year follow-up period [87]. Importantly, the increased mechanical joint load is not the only mechanism explaining this association given that increased adiposity has been shown to enhance the risk of arthritis in non-weight bearing joints such as hand osteoarthritis [90]. One explanation is that the increase in inflammatory cytokines from excess adipose tissue, especially visceral adipose tissue, mediates synovial inflammation [87, 91].

Cognition

Overweight and obesity during midlife have been associated with a decline in cognitive function later in life in both men and women. In one study, male and female participants who had overweight/obesity during midlife (mean age 41.6 years) had worse cognitive function with a steeper decline later in life (over a 20-year period) [92]. Similarly, in another study, overweight/obesity during late midlife (mean age 61.1 years) was associated with worse cognitive function later in life, but a steeper decline only in verbal abilities and memory [93]. The influence of weight change during midlife on cognitive function is less understood. In the latter study, weight loss rather than weight gain during midlife was associated with cognitive function decline later in life [93]. However, in this study, those who lost weight across the midlife stage had the highest BMI in early midlife. Therefore, BMI may be a generic parameter that does not accurately reflect the cardiometabolic changes taking place. In a recent cross-sectional analysis from the Kronos Early Estrogen Prevention Study (KEEPS), in 621 recently menopausal women, mean age 52.7 years, central obesity rather than overall obesity was associated with lower cognitive function measured by Modified Mini Mental Status score. These findings underscore the need for considering adiposity measures beyond BMI to assess and manage the negative consequences of excess adiposity [94].

Psychosocial Considerations

There are no data reporting on the effect of weight gain and mental health diseases in midlife women. A complex and

bidirectional interaction exists between body weight and mental health, and it is usually reciprocal. In midlife women, higher BMI may be associated with an increased prevalence of depressive symptoms and major depression diagnosis [95]. Further, midlife women with higher BMI are more likely to have lower life satisfaction and higher physical and psychological health stress such as body aches, difficulty relaxing, headaches, or feeling stressed and nervous [96].

Excess adiposity has been associated with sexual dysfunction in midlife women, which based on the NHS cohort, is reported by 50% of sexually active women [97]. In general, adiposity per se can pose physical limitations for sexual activity in women, without necessarily affecting sexual desire and satisfaction [98]. However, women with excess adiposity are more likely to experience negative body image that is in turn associated with lower arousal, sexual desire, lubrication, orgasm, and sexual satisfaction [99]. In midlife women, baseline BMI is inversely associated with frequency of intercourse but there is no association between BMI and sexual desire, arousal, and orgasm [100]. Further, longitudinal analysis over a 14-year study period showed that sexual desire, arousal, orgasm, and frequency of intercourse declined over time, and while BMI increased over time, there was no association between the changes in BMI and sexual function variables [100]. Studies assessing the effect of weight loss on sexual function suggest that lifestyle interventions, pharmacotherapy with naltrexone/bupropion, and bariatric surgery improve sexual function in women with overweight and obesity [101–103].

Menopause Symptoms

Vasomotor Symptoms

Traditionally, in women with overweight and obesity, increased estrogen production via androgen aromatization in the adipose tissue was thought to protect against VMS. Interestingly, the association between excess adiposity and VMS may vary by menopause stage. On one hand, data from several large cohort studies suggest that higher adiposity is associated with lower odds of VMS during the late menopause, and on the other hand, women with excess adiposity, particularly in the central and subcutaneous distribution, report more frequent and more severe VMS early in the menopause transition. There is no robust evidence suggesting an association between weight gain or increased abdominal adiposity and incidence, frequency, or intensity of VMS [104]. However, lifestyle changes resulting in weight loss have been shown to decrease the number and intensity of VMS [105]. The connection between excess adiposity and increased VMS is not well understood. Thermodysregulation may explain, at least in part, the connection between excess adiposity and increased VMS during early menopause. Thermodysregulation could be the result of decreased heat dissipation from excess fat accumulation and altered adipokine secretion, particularly increased leptin levels [106].

Urogenital Symptoms

Excess adiposity has been associated with increased urogenital symptoms. The genitourinary syndrome of menopause (GSM) is an umbrella term that encompasses vaginal, genital, and urinary symptoms affecting up to 85% of women in the menopause transition [107]. Compared to normal-weight women, postmenopausal women with obesity are four times more likely to have vulvovaginal itching and irritation [108]. Similarly, women with obesity have a higher prevalence of urinary incontinence and urinary urgency [40].

Weight Management in Midlife Women

Weight Gain Prevention

The US Preventive Services Task Force (USPSTF) recommends interventions for adults with overweight or obesity but provides no guidance for prevention of weight gain in adults with a BMI below 25 kg/m^2 [109]. A recent systemic review by the Women's Perspective Services Initiative (WPSI) showed that counseling women on weight loss had favorable weight outcomes with minimal adverse events [110•]. Given these data and the weight and body composition trends in midlife women, in 2022, the WPSI provided guidelines to counsel midlife women with normal or overweight BMI (18.5–29.9 kg/m^2) to maintain weight or limit weight gain to prevent obesity [111]. Counseling should be proactive and started in women in their late 30 s, while in their early 40 s, an individualized weight management intervention plan should be instituted [112]. Despite these general guidelines, there are limited data supporting specific recommendations on interventions in midlife women [113]. Based on data from the Pittsburgh Women's Healthy Life Project, a hypocaloric diet of 1300 kcal/day with reduced saturated fat and cholesterol throughout the menopause transition can prevent weight gain over a 4.5-year follow-up period [114]. Similarly, based on the Women's Health Initiative (WHI) trials, a low-fat diet paired with an increased intake of vegetables, fruits, and grains, and without purposeful caloric restriction, prevents weight gain in postmenopausal women [115]. Importantly, interventions focusing on education, coaching, motivational interviewing, and dietary changes, alone or combined with physical activity, are consistently more effective than physical activity interventions alone [114–119].

Management of Menopause Symptoms

As changes associated with the menopause transition, particularly in relation to VMS, can significantly impact multiple aspects of a woman's lifestyle and contribute to weight gain and body composition changes, special considerations should be given to this aspect. There is robust evidence supporting that HT decreases VMS and can lead to improved sleep, increased activity, and overall increased quality of life, all factors that can mitigate weight gain in midlife women [120]. As such, HT should be considered for all women with bothersome VMS [120]. If HT is contraindicated, women should be offered alternative treatment modalities. Cognitive behavioral therapy and hypnosis are effective interventions that improve the severity and frequency of VMS, respectively [121, 122]. Similarly, nonhormonal pharmacologic interventions have been shown to be effective for the management of VMS [123]. Particular attention should be paid to avoiding weight promoting medications. If weight gain is a major concern, weight neutral medications including venlafaxine, desvenlafaxine, oxybutynin, and fezolinetant are preferred, whereas gabapentin, clonidine, paroxetine, citalopram, and escitalopram should be avoided [120, 123, 124].

HT has been associated with decreased visceral adiposity, decreased total adiposity, decreased muscle mass loss, and a favorable effect on energy expenditure; however, these associations were of low magnitude [125–128]. HT use has also been associated with improved metabolic parameters, such as a reduced risk of insulin resistance and new onset diabetes [129]. While HT provides some body composition and metabolic benefits, it should not be prescribed for these indications, especially as these effects have not been proven to have any positive clinical impact on major health outcomes in women. For clinical awareness, HT is weight neutral, and while some women report weight gain after HT initiation, there is no evidence that HT increases adiposity. The reported weight gain associated with HT use may be due to the effect of estrogen and/or progestogen-mediated fluid retention [130].

Overweight and Obesity Treatment

Screening for overweight and obesity should be performed throughout a woman's lifespan. While BMI is the universal screening tool, given the changes in body composition and body fat redistribution that occur in midlife women, other measures such as waist-to-hip ratio or measurement of whole-body adiposity by dual-X-ray absorptiometry (DXA) or bioimpedance could be considered for screening and monitoring of progress [112, 113]. In women living with overweight or obesity (BMI of 25 kg/m^2 or greater, waist-to-hip ratio of 0.85 or greater, and/or body fat for greater than 30%), each visit with a health care practitioner should be considered an opportunity to assess awareness and knowledge of the disease and readiness to discuss and to start a weight management program [112]. Excess adiposity, from overweight to obesity, is a complex and multifactorial disease that can affect virtually all body systems and as such, requires an interdisciplinary approach [112].

In general, weight management in midlife women should not be different than in the general population with a few special considerations. Comprehensive lifestyle interventions remain the backbone of any treatment plan for weight gain prevention or weight loss and should include medical nutrition therapy, exercise, and behavioral interventions. A protein intake of at least 30% of total daily caloric intake or at least 1.2 g/kg of body weight has demonstrated favorable effects on body composition during a weight loss intervention in middle-aged women [131]. Exercise has a modest effect on weight loss but improves body composition by reducing visceral adiposity and protecting against excessive lean mass loss, which is of particular importance as midlife women go through the menopause transition [132, 133]. In midlife women, cognitive behavioral therapy for weight loss has not only shown to result in weight reduction but is also associated with improved restrained eating and quality of life [134].

Table 1 Guidelines for anti-obesity treatments

BMI	Intervention			
	Lifestyle	**Anti-obesity medications**	**Sleeve gastroplasty**	**Bariatric surgery**
25–26.9	Yes			
27–29.9	Yes	Yes, with adiposity-related comorbidities[a]	Yes, with adiposity-related comorbidities[a]	
30–34.9	Yes	Yes	Yes	Yes, with metabolic syndrome
35–39.9	Yes	Yes	Yes	Yes, with adiposity-related comorbidities[a]
> 40	Yes	Yes	Yes	Yes
Estimated weight loss at 1 year (%) [135]	5–7%	5–15%	15–17%	25–30%

[a]Indicated if adiposity-related comorbidities are present. These include type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, obstructive sleep apnea, gastroesophageal acid reflux, osteoarthritis, among others

Due to metabolic and behavioral adaptations in response to caloric restriction, some women may not achieve any weight loss, and among the ones who do, most will experience weight regain with lifestyle interventions. Hence, in many cases, second level therapies including anti-obesity medications, bariatric endoscopic procedures, and metabolic/bariatric surgery need to be considered in conjunction with lifestyle changes. There are established indications for the use of these tools (Table 1). As we aim to improve the treatment of overweight/obesity and its metabolic complications, it is customary practice to use multimodal approaches for treatment of this disease. There are no studies assessing the short- and long-term outcomes of these interventions in midlife women specifically. For now, when determining the appropriate intervention, factors such as the goal weight loss, co-existing health conditions, and potential complications should be considered.

Conclusions

Weight gain experienced by women during midlife is a result of declining BMR, decrease in physical activity, and changes in body composition that include muscle mass loss and increased fat mass. The weight gain and body composition change that women experience during midlife increase the risk of developing overweight or obesity and its clinical ramifications, leading to increased morbidity and mortality. As the prevalence of overweight and obesity in women rise during and after midlife, it is of utmost importance to implement strategic interventions to prevent weight gain and manage overweight and obesity in this population. Efforts should focus on behavioral and lifestyle changes, particularly decreasing caloric intake, and increasing physical activity, along with second level anti-obesity treatments when needed. While there are robust data on the effect of obesity on adiposity-related diseases in midlife women, there remains a paucity of data on the longitudinal relationship between weight trends in midlife and the incidence of cardiometabolic risk factors, CVD, and cardiovascular and overall mortality.

Author Contribution M.D.H. formulated the paper's goals and aims, wrote the first draft, and prepared Table 1. M.S. formulated the paper's goals and aims, wrote the first draft, and prepared Fig. 1. E.K. reviewed and edited the manuscript. C.L.S. reviewed and edited the manuscript. S.S.F. formulated the paper's goals and aims, supervised the writing process, and reviewed and edited the manuscript.

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Compliance with Ethical Standards

Conflict of Interest MDH: None. MS: None. EK: Ekta Kapoor has no conflicts of interest related to the subject of this manuscript. However, over the past 36 months, she has had the following conflicts of interest: She has been a consultant for Astellas and Mithra Pharmaceuticals, Scynexis, and Womaness. She receives grant support from Mithra Pharmaceuticals. She has received payment for development of educational content from Med Learning Group and Academy of Continued Healthcare Learning. She has received honoraria for CME activity from PriMed and OBG Management. CLS: None. SSF: Stephanie Faubion has no conflicts of interest related to the subject of this manuscript. However, over the past 36 months, she has received honoraria for lectures from PriMed. She is also the medical director of The Menopause Society.

Human and Animal Rights and Informed Consent This is a review article that did not involve any human or animal studies, thus ethical approval and informed consent were not applicable.

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