

## Obesity Update in Women

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### Abstract

The Clinical Update series is intended to help busy providers stay up to date with important and potentially practice changing articles that have been published on topics pertinent to the care of women. The rates of obesity and the resultant morbidities are rising worldwide, making it a high-priority health issue for the medical community. Moreover, the pathophysiology and management of obesity and visceral fat accumulation in women has important nuances, distinct from those in men. It is important to consider the effect of unique female-specific influences such as reproductive stage and pregnancy. Therefore, we have chosen to review six high-impact recent studies relating to obesity and its management in women. These include guidelines for management of obesity in pregnancy, risk of nonmelanoma skin cancer in overweight/obese women, the association of vascular fat and decline in physical function in midlife women, the predictors for weight gain in premenopausal women with early-stage breast cancer, dietary patterns and obesity in postmenopausal women, and finally, normal weight obesity and mortality risk in postmenopausal women.

**Keywords:** obesity, pregnancy, menopause, mortality

### Introduction

**T**HE CLINICAL UPDATE series is intended to help busy providers stay up to date with important and potentially practice changing articles that have been published on topics pertinent to the care of women. The rates of obesity and the resultant morbidities are rising worldwide,<sup>1</sup> making it a high-priority health issue for the medical community. Moreover, the pathophysiology and management of obesity and visceral fat accumulation in women has important nuances, distinct from those in men. It is important to consider the effect of unique female-specific influences such as reproductive stage and pregnancy. Therefore, we have chosen to review six high-impact recent studies relating to obesity and its management in women. These include guidelines for management of obesity in pregnancy, risk of nonmelanoma skin cancer in overweight/obese women, the association of vascular fat and decline in physical function in midlife women, the predictors for weight gain in premenopausal women with early-stage breast cancer, relationship between dietary patterns and obesity in postmenopausal women, and finally, normal weight obesity and mortality risk in postmenopausal women.

### Guidelines for Management of Obesity in Pregnancy

Vitner D, Harris K, Maxwell C, Farine D. Obesity in pregnancy guidelines. *J Matern Fetal Neonatal Med* 2019;32:2580–2590.

#### *What we know*

With millions of women of reproductive age worldwide being identified as obese,<sup>1</sup> not surprisingly the rates of obesity in pregnancy have climbed as well.<sup>2,3</sup> Obesity in pregnancy poses a risk to both the mother and the fetus, including a higher risk of gestational diabetes mellitus, venous thromboembolism, postpartum hemorrhage, gestational hypertension, cesarean delivery, and maternal death.<sup>4,5</sup> Multiple organizations have provided guidelines for screening and treatment of obesity in pregnancy. In this article, the recent guidelines from four international organizations were compared: American College of Obstetricians and Gynecologists (ACOG),<sup>6</sup> Royal Australian and New Zealand College of Obstetricians and Gynecologists (RANZCOG),<sup>7</sup> Royal College of Obstetrics and Gynecology (RCOG),<sup>8</sup> and the Society of Obstetrics and Gynecologists of Canada (SOGC).<sup>9</sup>

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### Study results

The review summarizes similarities and differences between the guidelines, providing a comprehensive table with information for providers as well as recommendations for future study in this area. Overall, the guidelines have many similarities. All define obesity as a body mass index (BMI)  $\geq 30 \text{ kg/m}^2$  and emphasize the importance of recognizing women who are overweight and obese before pregnancy to allow time for counseling regarding exercise and nutrition. Also, the guidelines have similar recommendations regarding counseling of the risks associated with obesity during pregnancy and emphasize the importance of having resources available in clinics specific to obese women. Screening for gestational diabetes is discussed in the guidelines, but specific information about how to screen is not uniformly addressed. ACOG and RANZCOG recommend early screening for women with a high BMI with repeat screening at 24–28 weeks, whereas RCOG recommends a 2 hour 75 g glucose tolerance test at 24–28 weeks for a BMI  $\geq 30 \text{ kg/m}^2$  and SOGC does not make any specific recommendation. Differences between the guidelines are seen with regard to recommendations for folic acid and vitamin D supplementation, aspirin use to prevent preeclampsia, and antenatal thromboprophylaxis. In some areas, the guidelines use different calculations to evaluate outcomes such as fetal neonatal complications, making comparisons difficult. The authors recommend taking a more standardized approach to management of pregnant obese women with regard to third trimester ultrasound and operative considerations, as well as developing a more cohesive or uniform recommendation for patient care management.

### What this changes or adds

This review highlights the increasing recognition of the importance of addressing obesity before and during pregnancy. There is considerable consistency among the different guidelines regarding identification and counseling of women about their risks before and during pregnancy, an important take-home message for practitioners. Still, there remains opportunity for improvement in standardization of the recommendations in future guidelines. Although all guidelines acknowledge the risk of preeclampsia in obese women, only RCOG recommends low-dose aspirin usage for prevention of hypertensive disorders. Macrosomia is more common in obese women, so it is possible that a standardized third trimester ultrasound would be beneficial to estimate fetal weight. Lastly, Cesarean sections occur at higher rates in obese women. Given that surgeries may be more complex in women with higher BMI, standardized preparation, and surgical approaches such as those suggested in the ACOG statement may improve outcomes.

### Measures of Weight and Skin Cancer

Chan AA, Noguti J, Pak Y, et al. Interaction of body mass index or waist-to-hip ratio and sun exposure associated with nonmelanoma skin cancer: A prospective study from the Women's Health Initiative. *Cancer* 2019;125:1133–1142.

### What we know

Nonmelanoma skin cancers (NMSC) are common and their incidence is rising.<sup>10,11</sup> It has been well documented

that ultraviolet radiation exposure is a risk factor for the development of NMSC,<sup>12,13</sup> but other factors may also influence the risk of development of these cancers. Although an inverse correlation between obesity and the risk of NMSC has been reported,<sup>14–16</sup> the interaction between measures of obesity (such as BMI and waist-to-hip ratio, WHR) and sun exposure has not been studied. Also, these relationships have not specifically been evaluated in postmenopausal women.

### Study results

A total of 71,745 postmenopausal women from the Women's Health Initiative observational study were studied at baseline and for a mean follow-up of 11.93 years. The ultraviolet radiation sun exposure was assessed in watts ( $\text{J/S/m}^2$ ) or langley (g  $\text{cal/cm}^2$ ) based on the locations of the 40 clinical centers at enrollment. Anthropometric measures were measured at baseline, and included WHR and BMI ( $\text{kg/m}^2$ ), where overweight was defined as a BMI  $\geq 25$  (59.0% of participants) or a WHR  $\geq 0.80$  (49.2% of participants). There were a total of 13,351 incidents of NMSC. Associated hazard ratios (HRs) of NMSC were lower for women with a BMI  $\geq 25$  or WHR  $\geq 0.80$  (HR for BMI, 0.78; 95% confidence interval [CI], 0.72–0.85; HR for WHR, 0.89; 95% CI, 0.82–0.96). However, an association between sun exposure and NMSC was seen such that at higher levels of sun exposure, there was a higher risk of NMSC for women with a BMI  $\geq 25$  or WHR  $\geq 0.80$  compared with those with a normal weight ( $p$  for interaction for BMI  $< 0.001$ ,  $p$  for interaction for WHR = 0.022). However, the effect size was age dependent ( $p$  for interaction  $< 0.001$ ), and was greatest in women aged 50–59 years, less in women 60–69 years, and lost significance in women  $\geq 70$  years. Therefore, although obesity has been shown to have an inverse relationship between NMSC risk and BMI (with higher BMI being protective), with increasing age and greater sun exposure this protective effect appears to decrease, and the risk may be higher in overweight/obese women with greater sun exposure compared with normal weight women.

### What this changes or adds

These findings demonstrate the complex interaction among sun exposure, BMI and NMSC risk. All women should be counseled about sun avoidance to decrease NMSC risk. This may be even more important for overweight/obese women, who may be at greater risk than their normal weight counterparts with increasing levels of sun exposure and age. The study has important limitations that reduce its generalizability. These include an exclusively white study population, and sun exposure outcomes based on self-report and ambient exposure at baseline only.

### Midlife Vascular Fat and Physical Function in Later Life

El Khoudary SR, Chen X, Nasr A, et al. Greater periaortic fat volume at midlife is associated with slower gait speed later in life in women: The SWAN cardiovascular fat ancillary study. *J Gerontol A Biol Sci Med Sci* 2019. Epub 12 April, 2019.

*What we know*

The menopause transition is associated with changes in body composition, specifically with changes in fat distribution, with a trend toward central fat deposition.<sup>17</sup> Furthermore, menopause is also associated with declining rates of physical function.<sup>18,19</sup> However, the association between fat distribution changes and physical function after menopause has not been well studied.

*Study results*

Results from the Study of Women's Health Across the Nation (SWAN) cardiovascular fat ancillary study included 276 midlife women in whom perivascular adipose tissue (PVAT) was assessed and compared with gait speed measured on average 10 years later. PVAT, defined as fat around the descending aorta, was quantified with electron beam computed tomography. Gait speed, known to be a reliable and valid measure of physical functioning in older adults, was assessed by asking participants to walk at their usual speed for a distance of 4 m and using an average of two test results reported in meters per second. The investigators found that higher volume of PVAT in midlife correlated with significantly slower gait speed in later life ( $p=0.03$ ), even after adjustment for multiple factors, including race, education level, menopausal status, and length of descending aorta (used to estimate PVAT volume), and factors such as age, BMI, smoking status, overall health, and difficulty paying for basics (a social determinate of health) at the time gait speed was assessed.

*What this changes or adds*

Although this study has limitations, including the cross-sectional design, small sample size, and the absence of repeated measures of PVAT and gait speed that preclude determination of causality and temporality, it adds to the growing body of evidence supporting the multiple adverse consequences of visceral fat accumulation. Although the association between visceral fat and cardiovascular disease is well recognized, the relationship between midlife body fat distribution changes and physical function decline is a novel finding. Attention to dietary choices and physical activity is critically important in midlife women to attenuate or prevent weight gain and the central redistribution of body fat, which are associated with multiple adverse health consequences.

**Weight Gain in Women Treated for Breast Cancer**

Gandhi A, Copson E, Eccles D, et al. Predictors of weight gain in a cohort of premenopausal early breast cancer patients receiving chemotherapy. *Breast* 2019;45:1–6.

*What we know*

Weight gain is common in breast cancer survivors after chemotherapy.<sup>20,21</sup> In addition to the usual complications of overweight/obesity, the additional potential risk in breast cancer survivors is that of cancer recurrence.<sup>22</sup> Therefore, recognizing and managing the causes of weight gain in this population is crucial. Weight gain in breast cancer survivors is thought to result from a variety of factors, including but not limited to the treatment modalities used (chemotherapy

and endocrine therapy) and patient-related factors. Previous studies evaluating the association between chemotherapy use and weight gain have not analyzed the effect of menopausal status<sup>23</sup> and the type of chemotherapy regimen used.<sup>24</sup> Recent evidence suggests that historically used chemotherapeutic regimens (based on cyclophosphamide, methotrexate, and 5-fluorouracil) led to a greater weight gain (more than twofold higher) than contemporary chemotherapy.<sup>25</sup>

*Study results*

In this substudy of the Prospective Outcomes in Sporadic versus Hereditary (POSH) breast cancer study,<sup>26</sup> Gandhi et al. enrolled 523 premenopausal women with early breast cancer who received taxanes/anthracycline-based adjuvant chemotherapy for early breast cancer and assessed the prevalence of significant weight gain (>5% pretreatment weight) 12-months after chemotherapy. Relevant data were available from 380 participants. The mean pretreatment BMI was  $26.3 \pm 5.6 \text{ kg/m}^2$ . Thirty percent of the women gained significant weight during the study period. Interestingly, a lower BMI at diagnosis was associated with greater weight gain after chemotherapy (4.3% relative weight gain for those in the lowest BMI quartile versus 0.8% for those in the highest quartile;  $r^2_{1/4} 0.22$ ;  $p < 0.001$ ). Weight gain was not associated with the chemotherapy regimen used, parity, smoking, or chemotherapy-induced amenorrhea.

*What this changes or adds*

The study is limited by its small sample size and the lack of information on body composition changes after chemotherapy. Nevertheless, it highlights the fact that weight gain is an important complication of chemotherapy for breast cancer survivors, although the risk may be lower with contemporary chemotherapeutic regimens compared with those used in the past. All women receiving chemotherapy, even those with a normal BMI, require diligent counseling regarding the anticipated weight gain and interventions to prevent it.

**Dietary Patterns and Obesity in Postmenopausal Women**

Papavagelis C, Avgeraki E, Augoulea A, Stamatelopoulos K, Lambrinouadaki I, Yannakoulia M. Dietary patterns, Mediterranean diet and obesity in postmenopausal women. *Maturitas* 2018;110:79–85.

*What we know*

Weight gain in midlife is a common yet challenging concern for women, and lifestyle modification is the mainstay of treatment.<sup>17</sup> Two *a priori* dietary patterns, the Dietary Approach to Stop Hypertension (DASH) and the Mediterranean diet, have been associated with lower BMI in postmenopausal women.<sup>27</sup> However, robust data regarding the association between dietary patterns and measures of obesity in midlife women are lacking.

*Study results*

This cross-sectional study from Greece involved a convenience sample of 481 women recruited from a menopause clinic at a public hospital, mean age  $57.7 \pm 7.4$  years, 39.5%

of whom were overweight and 29.1% obese. Diet was assessed using a validated food frequency questionnaire; dietary patterns were identified using a posteriori principal component analysis, and the Mediterranean dietary score was used to assess adherence to an *a priori* Mediterranean dietary pattern. Physical activity was self-reported using a questionnaire validated in the Greek population. After controlling for potential confounders, including age, years since onset of menopause, and physical activity, a diet high in unrefined cereals and legumes and low in refined cereals was negatively associated with BMI (beta = -0.104,  $p = 0.057$ ), waist circumference (beta = -0.120,  $p = 0.019$ ), and waist-to-height ratio (beta = -0.105,  $p = 0.038$ ). In contrast, a diet high in red meat and potatoes and low in nuts, coffee and tea was positively associated with BMI (beta = 0.191,  $p < 0.001$ ), waist circumference (beta = 0.225,  $p < 0.001$ ) and waist-to-height ratio (beta = 0.237,  $p < 0.001$ ). Adherence to a Mediterranean diet was negatively associated with BMI, waist circumference, and waist-to-height ratio, but after adjustment for physical activity and exclusion of implausible energy intake reports (<500 kcal/day or  $\geq 3500$  kcal/day), the findings were no longer significant.

#### *What this changes or adds*

This study highlights the association of a dietary pattern high in red meat and potatoes and low in nuts, coffee, and tea (typical of an American diet) with measures of adiposity in postmenopausal women, and the association of a diet high in unrefined cereals and legumes and low in refined cereals with lower measures of body weight and central adiposity in postmenopausal women. Although the strengths of the associations were low to moderate, likely because there are a multitude of factors associated with anthropometric indices, these findings reinforce the concept that the content and quality of dietary intake in postmenopausal women has an impact on weight gain, obesity, and ultimately, on development of obesity-related diseases.

#### **Normal Weight Central Obesity and Mortality Risk in Postmenopausal Women**

Sun Y, Liu B, Snetselaar LG, et al. Association of normal-weight central obesity with all-cause and cause-specific mortality among postmenopausal women. *JAMA Netw Open* 2019;2:e197337.

#### *What we know*

BMI is considered the standard, and often the sole measurement for obesity in clinical practice and health care guidelines.<sup>28</sup> However, BMI does not provide any information regarding body fat distribution, which is equally, if not more important than the BMI as a metabolic risk factor.<sup>29</sup> Central or abdominal obesity, characterized by increased visceral fat, is very well recognized as a predictor of cardiovascular risk and mortality, irrespective of the BMI.<sup>30</sup> This is particularly important for midlife women who commonly experience an increase in central body fat distribution after menopause.<sup>17</sup> Although presence of abdominal obesity is considered significant in overweight or obese individuals, clinical and health care guidelines do not typically recommend assessment and management of abdominal obesity in normal weight individuals.

#### *Study results*

This prospective cohort study was conducted in 156,624 postmenopausal women (mean age  $63.2 \pm 7.2$  years) enrolled in the Women's Health Initiative randomized controlled trials and observational study, between 1993 and 1998, and followed through February 2017. The women were classified as being normal weight (BMI 18.5–24.9 kg/m<sup>2</sup>), overweight (BMI 25–29.9 kg/m<sup>2</sup>), and obese (BMI  $\geq 30$  kg/m<sup>2</sup>), and as having abdominal obesity if they had a high waist circumference (>88 cm). After adjustment for demographic factors, socioeconomic status, lifestyle factors, and hormone therapy use, the risk for all-cause mortality was similar in the obese women with central obesity and normal weight women with central obesity. In comparison with normal weight women with no central obesity, the HR for all-cause mortality was 1.31 (95% CI, 1.20–1.42) in women with normal weight and central obesity, 1.30 (95% CI, 1.27–1.34) in women with obesity and central obesity, 1.16 (95% CI, 1.13–1.20) in women with overweight and central obesity, 0.93 (95% CI, 0.89–0.94) in women with obesity and no central obesity, and 0.91 (95% CI, 0.89–0.94) in women with overweight and no central obesity. The women with normal weight central obesity also had a higher risk of cardiovascular disease (HR, 1.24; 95% CI, 1.05–1.46) and cancer mortality (HR, 1.20; 95% CI, 1.01–1.43) compared with normal weight women without central obesity.

#### *What this study adds*

In postmenopausal women, normal-weight central obesity may pose a mortality risk comparable with that conferred by central obesity in the presence of obesity. Therefore, reliance on BMI alone to estimate a woman's risk for cardiovascular disease and mortality may lead to underestimation of the risk. Medical providers need to pay attention to assessment and management of abdominal obesity, even in normal weight individuals. This is particularly important for postmenopausal women, who characteristically exhibit body fat redistribution changes marked by an increase in abdominal fat.

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