Adiposity and the Menopausal Transition

Rachel P. Wildman, PhD[a,*], MaryFran R. Sowers, PhD[b,†]

KEYWORDS
• Obesity • Adiposity • Abdominal obesity • Menopause

The prevalence of obesity has reached epidemic proportions in the United States and other developed countries, and is rapidly becoming a primary public health concern in developing countries. In the United States, the frequency of obesity [body mass index (BMI) ≥30 kg/m^2) is higher among women than men; grade 2 or 3 obesity (BMI ≥35 kg/m^2 and ≥40 kg/m^2, respectively) is especially prevalent among women (17.8% in women vs 10.7% in men in recent U.S. National Health and Nutrition Examination Survey data).[1] In the United States, which is relatively far along in the obesity epidemic, obesity rates among women are stabilizing; however, there is no evidence that rates are decreasing.[1] The prevalence of abdominal obesity, the depot more strongly associated with negative health consequences, is almost double that of general obesity, at 65.5% in women aged 40 to 59 years and 73.8% in women aged 60 years or more in 2008.[1]

Weight gain among midlife women has been frequently reported, but the interrelationships between obesity, weight gain, and the menopausal transition remain incompletely understood. The purpose of this review is to summarize the published literature on this topic from 3 primary vantage points: (1) The potential influence of adiposity and weight gain on the timing and characteristics of the menopausal transition, (2) the potential influence of the menopausal transition on adiposity and weight gain, and (3) the potential modification of menopausal transition effects on health outcomes by adiposity.

WHAT DO STUDIES OF REPRODUCTIVE AGING REVEAL ABOUT POTENTIAL EFFECTS OF ADIPOSITY ON THE MENOPAUSE TRANSITION?

Adiposity and Menstrual Cycle Characteristics

Although there has been considerable research into the effects of weight and obesity on the timing of menarche and on menstrual cycle characteristics in women of

[a] Department of Epidemiology & Population Health, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Belfer Building, Room 1309, Bronx, NY 10461, USA
[b] Department of Epidemiology, Center for Integrated Approaches to Complex Diseases, University of Michigan, 1846 SPH I, 1415 Washington Heights, Ann Arbor, MI 48109-2029, USA
†Deceased.
* Corresponding author.
E-mail address: rachel.wildman@einstein.yu.edu

Obstet Gynecol Clin N Am 38 (2011) 441–454
doi:10.1016/j.ogc.2011.05.003 **obgyn.theclinics.com**
0889-8545/11/$ – see front matter

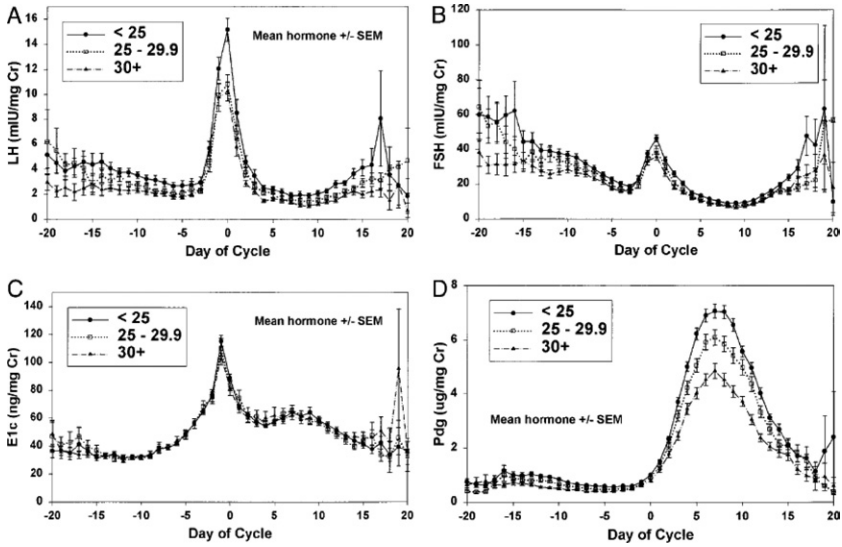

Fig. 1. Mean ± standard error of the mean daily levels of urinary hormones by BMI category (<25, 25–29.9, and ≥30 kg/m^2). All hormone values normalized for creatinine (*Cr*). Note that women with BMIs (>25 kg/m^2) are more likely to have lower LH, FSH, and progesterone metabolite pregnanediol glucuronide. (*From* Santoro N, Lasley B, McConnell D, et al. Body size and ethnicity are associated with menstrual cycle alterations in women in the early menopausal transition: The Study of Women's Health across the Nation (SWAN) Daily Hormone Study. J Clin Endocrinol Metab 2004;89:2626; with permission.)

reproductive age, a relative paucity of data exists about whether obesity contributes to menstrual cycle alterations associated with the menopause transition. Data from the Study of Women's Health Across the Nation (SWAN), a multicenter, multiethnic, prospective cohort study tracking changes in biological, psychological, and psychosocial parameters across the menopause transition, has been one of the few studies to explore the influence of obesity on diminishing ovarian function and menstrual cycle characteristics among midlife women. In addition to the annual follow-up visits conducted among the approximately 3300 SWAN enrollees, daily urinary hormones were collected on a subset of approximately 850 SWAN women for 1 complete menstrual cycle or for 50 days once per year, forming the basis of the Daily Hormone Ancillary Study. Data from the SWAN Daily Hormone Ancillary Study suggest that obese women may have fewer cycles with evidence of luteal activity than their normal weight counterparts (BMI <25 kg/m^2; 78.3% vs 84.7%, respectively).[2] SWAN data also suggest that among women with evidence of luteal activity, obesity is associated with altered menstrual cycle length and hormone patterns. Obese women tended to have longer total cycle lengths, apparently attributable to longer follicular phases and significantly shorter luteal phases.[2] Furthermore, within the single characterized menstrual cycle, obese women tended to have lower total cycle gonadotropin levels and luteal phase progesterone metabolites, as evidenced by lower values of urinary follicle-stimulating hormone (FSH), urinary luteinizing hormone, and pregnanediol glucuronide (**Fig. 1**).[2] Therefore, as the authors note, hormonal dynamics are altered by obesity even during an ovulatory cycle.[2] This finding in perimenopausal women echoes findings among younger cycling obese women,[3–5] and recent evidence

among younger ovulatory female candidates for bariatric surgery suggests that weight loss improves, although does not completely ameliorate, these hormone deficiencies.[6]

Adiposity and the Timing of Menopause

Although cycling obese women were less likely to have evidence of luteal activity and to have altered menstrual cycle lengths when there was evidence of luteal activity, it is not clear whether age at menopause is different among obese women. A number of studies have reported that obese women have a later age at menopause than nonobese women,[7–11] and cite this as consistent with higher circulating estrogen (estrone) levels arising from aromatization of androgens in expanded adipose beds in obese women. However, other studies have found a similar age at menopause among obese and nonobese women,[12–14] and 1 study has even found obese women to have an earlier age at menopause.[15] Among women in cross-sectional analyses of the SWAN study, obesity was not related to age at natural menopause, but was related to the likelihood of surgical menopause, with premenopausal obese women more likely to undergo surgical menopause.[13] This had the effect of lessening the number of obese women in the premenopausal category, whereas the percent of obese women in the perimenopausal and postmenopausal categories were similar.[13] Both SWAN and the Penn Ovarian Aging Study (POAS), a longitudinal study of midlife African-American and Caucasian women, have evaluated whether obesity influences time to menopause, apart from age at menopause. Among perimenopausal women, SWAN did not observe an association between obesity and time to the final menstrual period (FMP),[16] whereas in the POAS, there was a positive association between BMI and the odds of transitioning from premenopause to perimenopause, but no association between BMI and transition from perimenopause to postmenopause.[17] This latter finding may relate to the findings of a greater likelihood for obese women to be anovulatory and have either very short or very long cycles, which may result in their meeting definitions for early perimenopausal more readily than normal weight women, but not necessarily experiencing the FMP sooner.

Adiposity and Hormone Changes During the Transition

A number of investigations have reported the magnitude or pattern of hormone changes across the menopausal transition in obese versus nonobese women. In both SWAN and POAS, obese and nonobese women had different estradiol and FSH levels, and in the POAS, different luteinizing hormone and inhibin B levels as well.[18–21] The POAS suggested that findings were similar when measures of central adiposity, such as waist circumference and waist:hip ratio, were utilized to categorize obese and nonobese women.[17] More recently, a number of more rigorous analyses have tracked changes in hormone levels across the time before and after the FMP in obese versus nonobese women. These investigations have revealed similar differences in absolute hormone levels in obese versus nonobese women with respect to earlier investigations cited above, with lower estradiol levels in obese women before the FMP, and the reverse after the FMP (**Fig. 2**).[22] In addition, although the pattern of observed hormone changes in estradiol and FSH were similar in obese and nonobese women until approximately 2 years before the FMP, after this point there was a blunted hormone change surrounding the FMP in obese versus nonobese women. Data from the Michigan Bone Health and Metabolism Study (MBHMS), a prospective study of Caucasian midlife women living in the Detroit area, also demonstrate this blunted estradiol decline in obese women.[23] The lesser estradiol decline observed in obese women may result from enhanced aromatization rates given their excess adipose

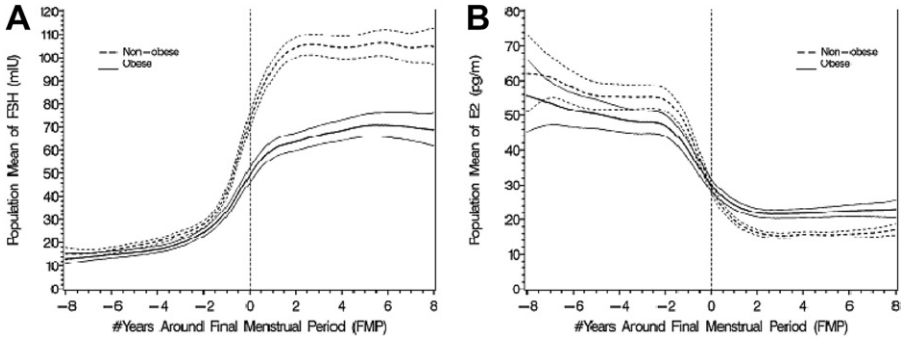

Fig. 2. Mean and 95% confidence interval for FSH and estradiol (E2) in obese versus nonobese women in relation to the FMP. (*From* Randolph JF Jr, Zheng H, Sowers MR, et al. Change in follicle-stimulating hormone and estradiol across the menopausal transition: effect of age at the final menstrual period. J Clin Endocrinol Metab 2011;96:749, with permission.)

tissue. In SWAN, the rate of estradiol decline during the critical transition period around the FMP seemed to be determined by both obesity and single nucleotide polymorphisms for aromatase and type 1 β17HSD genes (the enzyme associated with the potentially bidirectional conversion of estrone and estradiol).[24] The blunted decline observed in estradiol among obese women observed in the MBHMS and SWAN data is physiologically corroborated by a similarly blunted FSH rise surrounding the FMP in obese versus nonobese women (**Fig. 2**).[22]

Summary

The literature clearly supports that the magnitude of reproductive hormone changes experienced within individual menstrual cycles as the transition approaches, as well as during the transition itself, are altered in obese women, seeming to be blunted in comparison with nonobese women. The published literature also finds that the pattern of the difference in hormone levels between obese and nonobese women changes at some point late in the menopause transition. One mechanism likely underlying these findings relates to the change in the primary source of circulating estradiol as the menopause transition progresses; the primary source of circulating estradiol premenopausally is the ovary, whereas in postmenopause, the primary source of circulating estradiol is aromatization of androgens within adipose tissue. This change in estradiol source provides postmenopausal obese women with a nonovarian reservoir of estrogen that normal weight women do not have, which may blunt the gonadotropin rises and mitigate ovarian estrogen loss with menopause. These hormonal alterations may also blunt menopause-associated adverse health effects. What mechanisms underlie the lower estradiol levels in obese versus nonobese women premenopausally are presently unclear. Some have posited low ovarian reserve. However, this is not supported by recent ultrasound data identifying no difference in antral follicle count between obese and normal weight late reproductive-age women (40–52 years),[25] as well as the lack of evidence (cited above) suggesting that obese women have an earlier menopause. Follicular dysfunction and alterations in central nervous system regulation of hormonal levels among obese women may be factors, but additional research in this area is needed.

WHAT DO STUDIES OF REPRODUCTIVE AGING REVEAL ABOUT POTENTIAL EFFECTS OF THE MENOPAUSE TRANSITION ON ADIPOSITY?

Chronological Aging Versus the Menopause Transition

Much of the early work examining the possible link between adiposity and the menopausal transition focused on whether women gained weight during the menopausal transition. Although it is commonly thought that menopause is associated with weight gain, longitudinal analyses with careful accounting of chronologic versus ovarian aging are inconclusive. Studies using body weight suggest that weight gain in midlife among women is more consistent with a pattern of chronologic aging, and not uniquely due to the menopausal transition,[26–29] whereas a study using actual fat mass measures finds otherwise. Wing and colleagues[28] were among the first to attempt to tease this apart by following women over time and comparing weight gain among women who remained premenopausal over follow-up to weight gain among women who experienced a natural menopause by the end of follow-up. Weight gain was similar in the 2 groups, and perhaps even a bit greater among women who remained premenopausal (+2.07 vs +1.35 kg).[28] Similarly, in a comparison of premenopausal and postmenopausal women matched for age, premenopausal women actually had a higher mean body weight.[30] Weight gain during midlife may be an ambiguous measure, because it represents not only increasing fat tissue, but also potential declines in bone mass and skeletal muscle. Body composition analyses within a SWAN ancillary study demonstrated a positive, linear slope of fat mass by study year as a proxy for chronologic aging (**Fig. 3**, *bottom left*), but a curvilinear increase in fat mass was seen surrounding the FMP, whereby fat mass increased to a greater degree before menopause and thereafter leveled off (**Fig. 3**, *bottom right*), suggesting that accumulation of fat mass slowed after the FMP.[31]

Menopause Transition Effects on Body Fat Distribution

The literature also suggests that ovarian aging may influence where fat is distributed, with a central redistribution of fat. Cross-sectional analyses comparing premenopausal women with postmenopausal women have reported that adjustment for age eliminates significant differences in total body fat and subcutaneous adipose tissue, but that abdominal adiposity measures remain higher in postmenopausal women.[32,33] However, other cross-sectional analyses have failed to show differences in waist circumference between premenopausal and postmenopausal women.[30,34]

Three reports all using longitudinal analyses to track patterns of body fat distribution measures across the menopausal transition anchored by the FMP have produced inconclusive results. In a study of women aged 43 years and older at baseline, changes in body weight, percent fat mass, and abdominal subcutaneous fat seemed linear from 4 years before the start of postmenopause (12 months without a period and FSH >30 mIU/mL) through the first 2 years of postmenopause, whereas abdominal visceral adipose tissue seemed to change quickly during perimenopause, leveling off approximately at the FMP (**Fig. 4**).[35] A similar pattern was reported using waist circumference change tracked around the FMP in the SWAN body composition ancillary study among African-American and Caucasian women (**Fig. 3**, *top right*), although these results were less pronounced, perhaps because waist circumference represents changes in both subcutaneous and visceral adipose tissue.[31] However, in subsequent SWAN longitudinal analyses with longer follow-up (9 vs 6 years) and including Japanese and Chinese women, change in waist seemed to be linear in relation to the FMP (**Fig. 5**).[36]

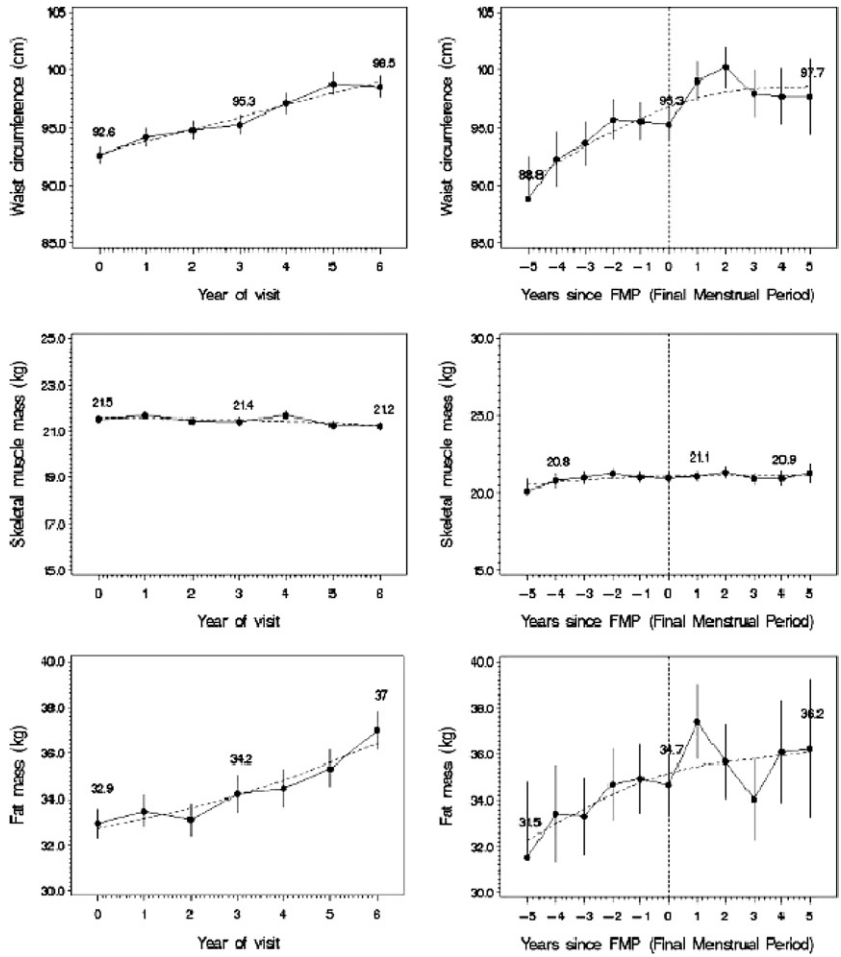

Fig. 3. Mean waist circumference and body composition values in relation to time (*left side*) and the FMP (*right side*). (*From* Sowers M, Zheng H, Tomey K, et al. Changes in body composition in women over six years at midlife: ovarian and chronological aging. J Clin Endocrinol Metab 2007;92:898; with permission.)

Reproductive Hormone Effects on Adiposity

In addition to analyses of the associations between weight or weight change and the menopause transition, the question of whether ovarian aging may cause weight gain has also been addressed from the perspective of sex hormones. In the SWAN study, neither changes in circulating estradiol nor FSH levels were associated with incident obesity or severe obesity over 9 years of follow-up.[37] Similarly, null findings were reported in relation to central adiposity in cross-sectional analyses of a SWAN ancillary study relating estradiol levels to computed tomography-determined abdominal visceral adipose tissue levels,[38] and in longitudinal analyses of the Melbourne Women's Midlife Health Project relating baseline estradiol and change in estradiol from baseline with central fat measurements 5 years later derived from dual energy x-ray absorptiometry.[39]

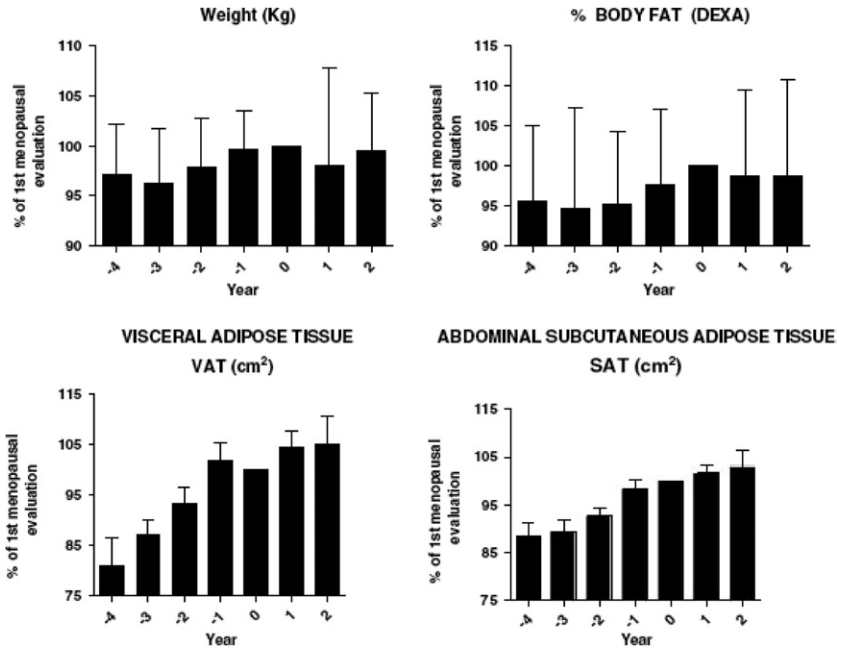

Fig. 4. Longitudinal changes in body composition and body fat distribution in relation to the FMP. (*From* Lovejoy JC, Champagne CM, de Jonge L, et al. Increased visceral fat and decreased energy expenditure during the menopausal transition. Int J Obes (Lond) 2008;32:953, with permission.)

Summary

Although the published literature is quite convincing of an effect of obesity on the magnitude of menopause-associated hormonal changes, it does not clearly support a relationship in the opposite direction, namely an effect of the menopause transition or its associated hormonal changes on either overall weight gain or central redistribution of body fat. There is some evidence that the perimenopause is associated with more rapid increases in fat mass and redistribution of fat to the abdomen, but published findings are conflicting, and additional longitudinal investigations are needed.

DOES OBESITY MODIFY THE EFFECTS OF THE MENOPAUSE TRANSITION ON THE EXPERIENCE OF MENOPAUSAL SYMPTOMS OR HEALTH OUTCOMES?

A fairly large body of literature has assessed the influence of obesity on the experience of vasomotor symptoms associated with the menopausal transition. It was initially hypothesized that obese women would experience fewer vasomotor symptoms owing to an assumption that obese women would have higher estradiol levels resulting from peripheral conversion of androgens to estrogens in the adipose tissue. As discussed, however, estradiol levels are not higher; rather, they are lower in obese women early in the transition. It is only by the late transition and postmenopause that the peripheral conversion of androgens to estrogen have an impact on circulating estradiol. Evidence suggests that obese women actually experience more vasomotor symptoms and more bothersome symptoms, at least in the relatively earlier stages of the

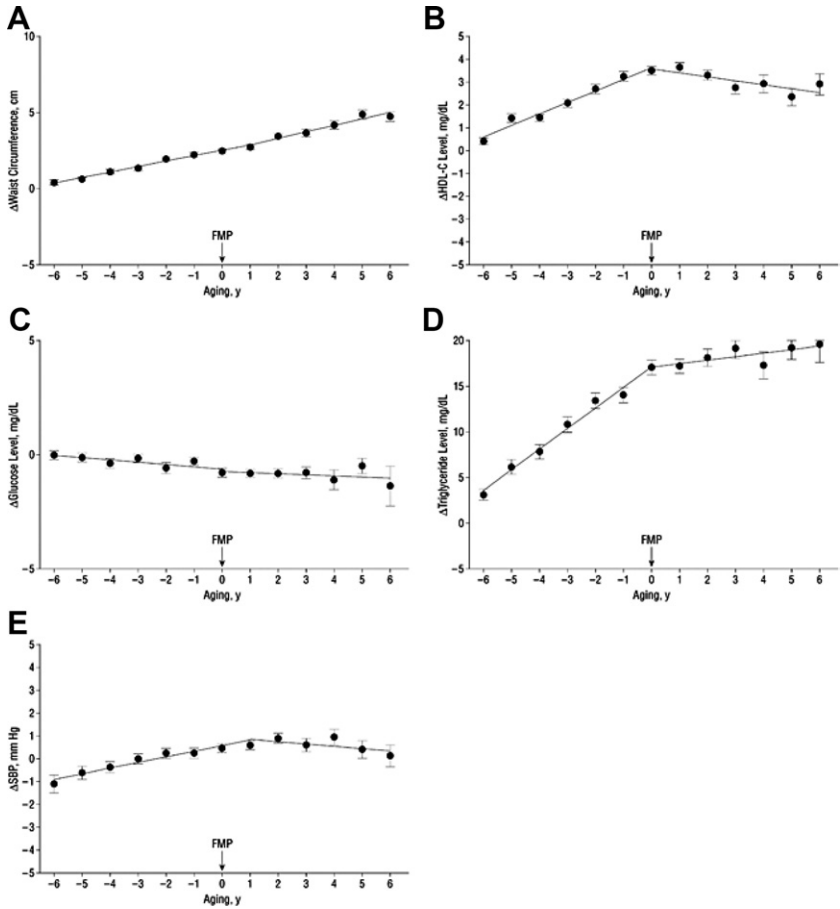

Fig. 5. Changes in metabolic syndrome components in relation to the FMP. (*From* Janssen I, Powell LH, Crawford S, Lasley B, et al. Menopause and the metabolic syndrome: the Study of Women's Health Across the Nation. Arch Intern Med 2008;168:1572; with permission.)

menopausal transition. Among SWAN enrollees, a higher percent body fat, a higher mass of abdominal subcutaneous fat, and greater weight gain are each associated with more frequent hot flashes.[40–42] Similarly, the MBHMS has reported that the bothersomeness of symptoms is greater with increasing BMI.[43] These findings have been interpreted as suggestive that adipose tissue acts as an insulator, increasing hot flashes and their intensity.[42] Although these findings were not altered by menopausal stage among SWAN participants, other studies have demonstrated that such findings are strongest earlier in the menopause transition.[44] This raises the potential that the relatively higher circulating estradiol levels in obese women later in the menopausal transition may somewhat counteract symptoms.

There has been less work examining whether obesity modifies the menopause-associated increased risks of various chronic diseases. The SWAN study was the first to examine the influence of body weight on the increases in lipids associated with the menopausal transition. Examination of lipid and lipoprotein changes across menopause status categories revealed that the gradual increase in lipids observed from

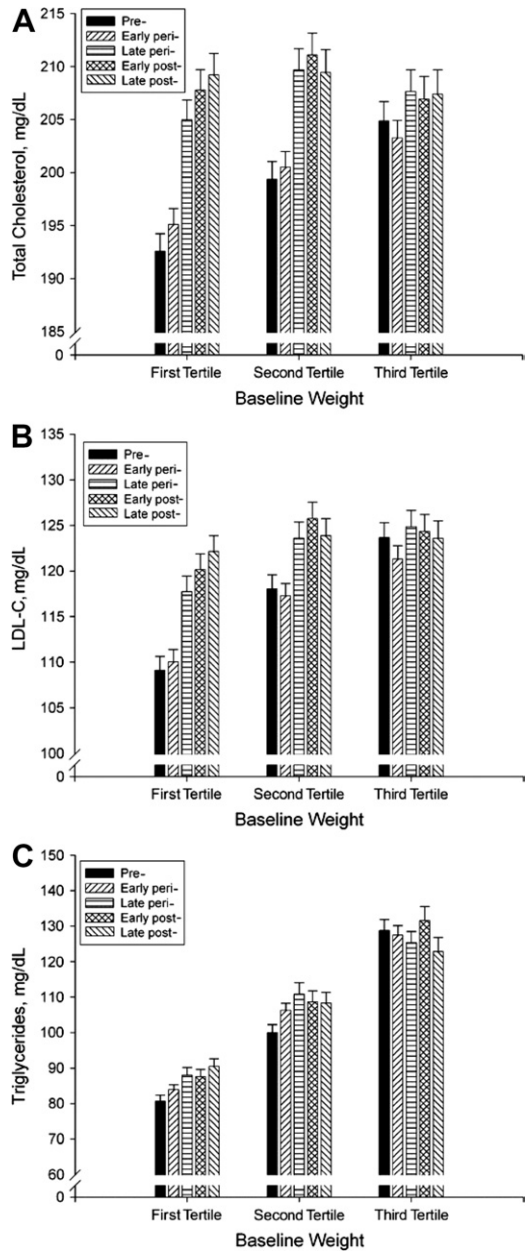

Fig. 6. Mean cardiovascular risk factors by menopausal status and baseline weight category. (*From* Derby CA, Crawford SL, Pasternak RC, et al. Lipid changes during the menopause transition in relation to age and weight: the Study of Women's Health Across the Nation. Am J Epidemiol 2009;169:1358; with permission.)

premenopause to perimenopause to postmenopause, independent of aging, was blunted in heavier women (**Fig. 6**); this effect was partially explained by the higher estradiol levels among heavier postmenopausal women.[45] Consistent with these findings, a subsequent SWAN analysis, limited to women with a natural menopause,

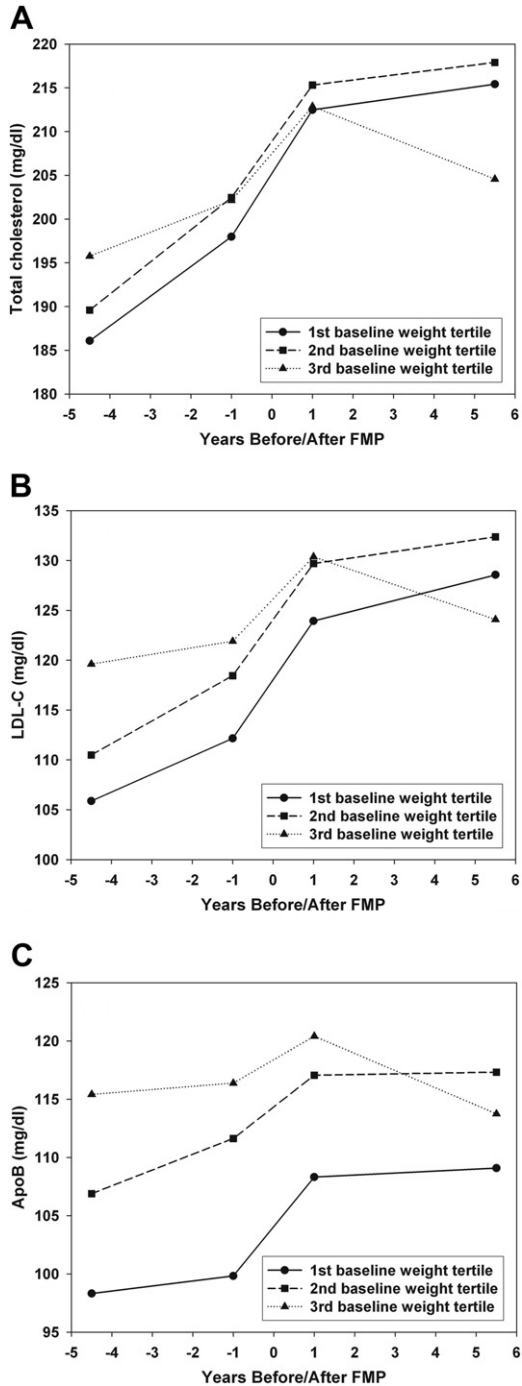

Fig. 7. Annual mean lipids in relation to the FMP by baseline weight. (*From* Matthews KA, Crawford SL, Chae CU, et al. Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? J Am Coll Cardiol 2009;54:2372; with permission.)

identified that body size did not seem to influence the pattern of lipid changes leading up to the FMP (all body weight groups experienced a sharp increase in lipids leading up to the FMP), but did seem to alter postmenopausal lipid changes (**Fig. 7**).[46] Among the heaviest women, adverse lipid and lipoprotein changes seemed to stop increasing, or even decreased slightly after the FMP, whereas in the lower weight groups the increases continued after the FMP, but were somewhat blunted (**Fig. 7**).[46]

Among midlife women in the MBHMS, similar analyses were performed in relation to bone loss surrounding the FMP, and again, a blunting of menopause associated bone resorption was observed in the obese versus nonobese women.[47] Among both obese and nonobese women, bone loss accelerated in the 4 to 5 years around the FMP.[47] However, in obese women, bone loss subsided to baseline rates after the FMP, whereas nonobese women continued to experience a somewhat greater rate of bone loss 6 to 8 years after the FMP.[47]

Summary

Mirroring the blunted gonadotropin changes observed in obese women as they traverse the menopause, obese women also display blunted menopause-associated lipid/lipoprotein and bone changes. Whether these obesity-related modifications are directly explained by the relative elevation in estradiol in obese postmenopausal women remains unclear. In contrast with the consistency of lipid/lipoprotein and bone findings with blunted gonadotropin responses across the menopause, data suggest that obese women have an exacerbated menopausal symptom response, experiencing greater numbers of hot flashes, as well as more bothersome hot flashes, likely owing to the insulating effects of adipose tissue, although this effect may be weaker later in the menopause transition because of the blunted estradiol decrease in obese women.

CONCLUSION

Although data are limited, current information suggests there are substantial effects of obesity and adiposity on the magnitude of hormone changes experienced during the transition, as well as on the risks of chronic disease resulting from the menopause transition. The ability to partition these effects into those resulting from overall adiposity versus specific fat depots or the metabolic environment generated with excess adiposity awaits additional data. The high prevalence of obesity among women across the lifespan and the particular vulnerability of menopausal women to chronic diseases underscore the importance of further study into the potentially circular relationship between adipose tissue and menopause-associated hormone changes.

REFERENCES

1. Flegal KM, Carroll MD, Ogden CL, et al. Prevalence and trends in obesity among US adults, 1999–2008. JAMA 2010;303:235–41.
2. Santoro N, Lasley B, McConnell D, et al. Body size and ethnicity are associated with menstrual cycle alterations in women in the early menopausal transition: The Study of Women's Health across the Nation (SWAN) Daily Hormone Study. J Clin Endocrinol Metab 2004;89:2622–31.
3. Rowland AS, Baird DD, Long S, et al. Influence of medical conditions and lifestyle factors on the menstrual cycle. Epidemiology 2002;13:668–74.
4. Grenman S, Ronnemaa T, Irjala K, et al. Sex steroid, gonadotropin, cortisol, and prolactin levels in healthy, massively obese women: correlation with abdominal fat cell size and effect of weight reduction. J Clin Endocrinol Metab 1986;63:1257–61.

5. Jain A, Polotsky AJ, Rochester D, et al. Pulsatile luteinizing hormone amplitude and progesterone metabolite excretion are reduced in obese women. J Clin Endocrinol Metab 2007;92:2468–73.
6. Rochester D, Jain A, Polotsky AJ, et al. Partial recovery of luteal function after bariatric surgery in obese women. Fertil Steril 2009;92:1410–5.
7. Willett W, Stampfer MJ, Bain C, et al. Cigarette smoking, relative weight, and menopause. Am J Epidemiol 1983;117:651–8.
8. Nagata C, Takatsuka N, Inaba S, et al. Association of diet and other lifestyle with onset of menopause in Japanese women. Maturitas 1998;29:105–13.
9. Sherman B, Wallace R, Bean J, et al. Relationship of body weight to menarcheal and menopausal age: implications for breast cancer risk. J Clin Endocrinol Metab 1981; 52:488–93.
10. Palmer JR, Rosenberg L, Wise LA, et al. Onset of natural menopause in African American women. Am J Public Health 2003;93:299–306.
11. Dorjgochoo T, Kallianpur A, Gao YT, et al. Dietary and lifestyle predictors of age at natural menopause and reproductive span in the Shanghai Women's Health Study. Menopause 2008;15:924–33.
12. Bromberger JT, Matthews KA, Kuller LH, et al. Prospective study of the determinants of age at menopause. Am J Epidemiol 1997;145:124–33.
13. Gold EB, Bromberger J, Crawford S, et al. Factors associated with age at natural menopause in a multiethnic sample of midlife women. Am J Epidemiol 2001;153: 865–74.
14. Amigoni S, Morelli P, Chatenoud L, et al. Cross-sectional study of determinants of menopausal age and hormone replacement therapy use in Italian women. Climacteric 2000;3:25–32.
15. Kato I, Toniolo P, Akhmedkhanov A, et al. Prospective study of factors influencing the onset of natural menopause. J Clin Epidemiol 1998;51:1271–6.
16. Santoro N, Brockwell S, Johnston J, et al. Helping midlife women predict the onset of the final menses: SWAN, the Study of Women's Health Across the Nation. Menopause 2007;14:415–24.
17. Sammel MD, Freeman EW, Liu Z, et al. Factors that influence entry into stages of the menopausal transition. Menopause 2009;16:1218–27.
18. Freeman EW, Sammel MD, Gracia CR, et al. Follicular phase hormone levels and menstrual bleeding status in the approach to menopause. Fertil Steril 2005;83: 383–92.
19. Gracia CR, Freeman EW, Sammel MD, et al. The relationship between obesity and race on inhibin B during the menopause transition. Menopause 2005;12:559–66.
20. Freeman EW, Sammel MD, Lin H, et al. Obesity and reproductive hormone levels in the transition to menopause. Menopause 2010;17:718–26.
21. Randolph JF Jr, Sowers M, Bondarenko IV, et al. Change in estradiol and follicle-stimulating hormone across the early menopausal transition: effects of ethnicity and age. J Clin Endocrinol Metab 2004;89:1555–61.
22. Randolph JF Jr, Zheng H, Sowers MR, et al. Change in follicle-stimulating hormone and estradiol across the menopausal transition: effect of age at the final menstrual period. J Clin Endocrinol Metab 2011;96:746–54.
23. Sowers MR, Zheng H, McConnell D, et al. Estradiol rates of change in relation to the final menstrual period in a population-based cohort of women. J Clin Endocrinol Metab 2008;93:3847–52.
24. Sowers M, Randolph JF Jr, Zheng H, et al. Genetic polymorphisms and obesity influence estradiol decline during the menopause. Clin Endocrinol (Oxf) 2011;74: 618–23.

25. Su HI, Sammel MD, Freeman EW, et al. Body size affects measures of ovarian reserve in late reproductive age women. Menopause 2008;15:857–61.
26. Guthrie JR, Dennerstein L, Dudley EC. Weight gain and the menopause: a 5-year prospective study. Climacteric 1999;2:205–11.
27. Davies KM, Heaney RP, Recker RR, et al. Hormones, weight change and menopause. Int J Obes Relat Metab Disord 2001;25:874–9.
28. Wing RR, Matthews KA, Kuller LH, et al. Weight gain at the time of menopause. Arch Intern Med 1991;151:97–102.
29. Crawford SL, Casey VA, Avis NE, et al. A longitudinal study of weight and the menopause transition: results from the Massachusetts Women's Health Study. Menopause 2000;7:96–104.
30. Bjorkelund C, Lissner L, Andersson S, et al. Reproductive history in relation to relative weight and fat distribution. Int J Obes Relat Metab Disord 1996;20:213–19.
31. Sowers M, Zheng H, Tomey K, et al. Changes in body composition in women over six years at midlife: ovarian and chronological aging. J Clin Endocrinol Metab 2007;92: 895–901.
32. Donato GB, Fuchs SC, Oppermann K, et al. Association between menopause status and central adiposity measured at different cutoffs of waist circumference and waist-to-hip ratio. Menopause 2006;13:280–5.
33. Toth MJ, Tchernof A, Sites CK, et al. Menopause-related changes in body fat distribution. Ann N Y Acad Sci 2000;904:502–6.
34. Pasquali R, Casimirri F, Pascal G, et al. Influence of menopause on blood cholesterol levels in women: the role of body composition, fat distribution and hormonal milieu. Virgilio Menopause Health Group. J Intern Med 1997;241:195–203.
35. Lovejoy JC, Champagne CM, de Jonge L, et al. Increased visceral fat and decreased energy expenditure during the menopausal transition. Int J Obes (Lond) 2008;32: 949–58.
36. Janssen I, Powell LH, Crawford S, et al. Menopause and the metabolic syndrome: the Study of Women's Health Across the Nation. Arch Intern Med 2008;168:1568–75.
37. Sutton-Tyrrell K, Zhao X, Santoro N, et al. Reproductive hormones and obesity: 9 years of observation from the Study of Women's Health Across the Nation. Am J Epidemiol 2010;171:1203–13.
38. Janssen I, Powell LH, Kazlauskaite R, et al. Testosterone and visceral fat in midlife women: the Study of Women's Health Across the Nation (SWAN) fat patterning study. Obesity (Silver Spring) 2010;18:604–10.
39. Guthrie JR, Dennerstein L, Taffe JR, et al. Central abdominal fat and endogenous hormones during the menopausal transition. Fertil Steril 2003;79:1335–40.
40. Thurston RC, Sowers MR, Chang Y, et al. Adiposity and reporting of vasomotor symptoms among midlife women: the study of women's health across the nation. Am J Epidemiol 2008;167:78–85.
41. Thurston RC, Sowers MR, Sutton-Tyrrell K, et al. Abdominal adiposity and hot flashes among midlife women. Menopause 2008;15:429–34.
42. Thurston RC, Sowers MR, Sternfeld B, et al. Gains in body fat and vasomotor symptom reporting over the menopausal transition: the study of women's health across the nation. Am J Epidemiol 2009;170:766–74.
43. Ford K, Sowers M, Crutchfield M, et al. A longitudinal study of the predictors of prevalence and severity of symptoms commonly associated with menopause. Menopause 2005;12:308–17.
44. Whiteman MK, Staropoli CA, Benedict JC, et al. Risk factors for hot flashes in midlife women. J Womens Health (Larchmt) 2003;12:459–72.

45. Derby CA, Crawford SL, Pasternak RC, et al. Lipid changes during the menopause transition in relation to age and weight: the Study of Women's Health Across the Nation. Am J Epidemiol 2009;169:1352–61.
46. Matthews KA, Crawford SL, Chae CU, et al. Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? J Am Coll Cardiol 2009;54:2366–73.
47. Sowers MR, Zheng H, Jannausch ML, et al. Amount of bone loss in relation to time around the FMP and follicle-stimulating hormone staging of the transmenopause. J Clin Endocrinol Metab 2010;95:2155–62.