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Detrimental Changes in Health during Menopause: The Role of Physical Activity

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Abstract

Midlife women experience changes in cardiometabolic, physical, and psychosocial health during menopause that negatively impacts their overall quality of life. Factors that contribute to these increases in cardiometabolic risk include weight gain as well as increases in fat mass (particularly abdominal adiposity), insulin resistance, and vascular dysfunction. Other deleterious changes in physical health (e. g. reduced sleep health, bone density, and balance) as well as changes in psychosocial health (e. g. mood, anxiety, and depression) often coincide and are linked to these increases in cardiometabolic risk. Physical activity and exercise are important lifestyle components that have been demonstrated to improve cardiometabolic, physical, and psychosocial health, yet physical activity and exercise is known to decline during perimenopause and into the post-menopausal years. In this narrative review, we summarize these changes in overall health during menopause as well as how declining physical activity contributes to these changes. Additionally, we discuss how incorporating physical activity and exercise during menopause can potentially ameliorate health declines. We conclude that there exists a significant, positive impact of physical activity on cardiometabolic, physical, and psychological health among midlife women, particularly if undertaken during the perimenopausal and postmenopausal years.

Keywords

menopause; physical activity; exercise; metabolism; adiposity; insulin resistance

Introduction

Menopause is a significant turning point where women experience accelerated cardiometabolic risk, as well as declines in physical and psychosocial health [1]. During

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the menopause transition, women experience dramatic decreases in circulating estrogens-particularly estradiol (E_2)-and increases in the gonadotropin, follicle-stimulating hormone [2]. These hormonal changes are associated with increases in body weight and fat mass (mainly abdominal adiposity), as well as other cardiometabolic risk factors including dyslipidemia, hypertension, vascular dysfunction, insulin resistance, and type 2 diabetes [1, 3–5]. Additionally, declines in physical health (e. g. reduced sleep health, bone density, and balance) and psychosocial health (e. g. increased mood swings, anxiety, and depressive episodes) also become more prevalent with the menopause transition [6–8].

It is well recognized that physical activity (PA) and planned exercise can improve cardiometabolic, physical, and psychosocial health in humans. As a result, PA and exercise promotion during menopause would appear to improve cardiovascular health, accelerate metabolism, minimize weight gain, preserve bone density and balance, as well as improve mood and reduce depressive symptoms across the lifespan (Fig. 1). As a result, PA arguably becomes *most important* during the menopause transition and into the post-menopausal years. This narrative review details how menopause is associated with reductions in PA and the negative implications that reduced PA has on overall health. We also discuss the degree to which PA and exercise promotion can improve cardiometabolic, physical, and psychosocial health during menopause [9].

The Menopause Transition – A Brief Overview

The menopause transition (or perimenopause) is characterized by an increased rate of attrition of ovarian follicles, thereby causing reduced inhibin-B release from the ovaries and signals the anterior pituitary to upregulate follicle-stimulating hormone (FSH) secretion. This increased secretion of FSH works to stimulate the production of E_2 from the ovaries, with FSH continuously increasing as ovarian function declines. As women transition through perimenopause (from *early* to *late perimenopause* [10]), the ovarian follicle supply becomes critically low whereby the ovary can no longer produce E_2 in respond to the increased FSH. Once E_2 production ceases, only a steady-state of high FSH remains – thereby becoming an important diagnostic tool when differentiating between early versus late phase perimenopause [10]. *Early perimenopause* is marked by increases in menstrual cycle length of ≥ 7 days with some women reporting small but noticeable increases in hallmark menopausal symptoms, such as vasomotor symptoms (e. g. hot flashes and night sweats). *Late perimenopause* is characterized by intervals of amenorrhea for > 60 days and the hallmark elevation of FSH > 25 mIU/mL paired with increased prevalence of menopausal symptoms. *Natural menopause* is defined by 12 months of amenorrhea in women traditionally aged 45 or older [11]. Furthermore, the median age of natural menopause is approximately 51 to 52 years, with an approximate 95 % confidence interval of 45 to 55 years [12, 13]. While the length of the menopause transition typically ranges from 4 to 5 years, the length of the transition is highly variable and can last from < 1 to 10 years or longer [14].

Changes in Cardiometabolic Health and the Relationship with Physical Activity

In this section, we detail how deleterious changes in cardiometabolic health – particularly weight gain, and changes in body composition, insulin sensitivity, and vascular health – are associated with the declines in PA during menopause. Furthermore, we detail how PA interventions positively impact cardiometabolic health in menopausal women.

Weight gain and body composition

Weight gain and the accrual of abdominal adiposity are two of the most common frustrations reported by women during the menopause transition [3, 15–17]. Data from the 4-year Healthy Transitions study [3], the ongoing SWAN longitudinal study [15], the 6-year Pizarra Study [16], and the 8-year Australian Longitudinal Study on Women's Health [17] reveal that detrimental changes in body composition (i. e. increased fat mass, decreased fat-free mass, and decreased bone density) occur and exacerbate cardiometabolic risk. These menopause-related changes in body composition coincide with significant declines in PA [3, 18, 19]. Longitudinal data from the SWAN study also revealed that higher levels of vigorous PA were independently associated with lower percent body fat and smaller waist circumference, particularly among White women [20].

Experimental studies investigating the benefits of PA and exercise on weight loss and body composition tend to focus predominantly on postmenopausal women rather than also including perimenopausal women who are currently navigating the transition [9]. Data from a randomized control trial in 173 overweight, post-menopausal women revealed a significant dose-response relationship between exercise duration (i. e. treadmill walking or stationary bicycling for at least 45-min of moderate-intensity sessions, 5 days/week for 12 months) and losses in total body weight, fat mass, and intra-abdominal fat [21]. Other studies in postmenopausal women have examined whether exercise and/or caloric restriction is most effective at eliciting weight loss, particularly in the abdominal depot. The Sex Hormones and Physical Exercise (SHAPE)-2 study investigated differences in weight loss among overweight, postmenopausal women randomized to either calorie restriction plus exercise, calorie restriction alone, or control [22]. In this trial, the exercise program included both aerobic and resistance training 4 hours/week with a target of 350 kcal/day in exercise energy expenditure. Data from SHAPE-2 revealed that subcutaneous fat loss was larger in the calorie restriction plus exercise group with no differences in intra-abdominal fat loss [22]. In the Diet, Exercise, and Metabolism for Older Women Study, 60 overweight, postmenopausal women aged 45 to 80 years were randomized to either a reduced calorie diet or a reduced calorie diet plus aerobic exercise for 6 months [23]. While both groups lost similar amounts of weight (~8 %) with similar losses in subcutaneous abdominal and gluteal fat, only those women in the reduced calorie diet plus aerobic exercise maintained fat-free (muscle) mass (FFM) [23]. In a separate study, it appeared that postmenopausal women are equally capable of losing weight and reducing android fat when participating in a 3-month high-intensity exercise training program compared to premenopausal women [24]. Furthermore, data from the Women's Healthy Lifestyle Project, a 4.5-year randomized clinical trial using long-term, dietary restriction (1,300 kcal/day) and increased PA (1,000

to 1,500 kcal/week) in menopausal women revealed that waist circumference and fat mass were reduced, yet FFM was maintained [25]. Nonetheless, while habitual PA and exercise indeed have positive effects on preventing body weight and fat mass gain during menopause, regular PA does not completely ameliorate the changes in body composition that occur [26, 27]. While not detailed extensively in this narrative review, habitual PA and exercise have a significant and positive effect on cardiorespiratory fitness and muscle strength [28], which both decline with menopause progression [29]. In summary, adding PA or exercise to any reduced calorie diet or weight loss program during menopause appears to preserve FFM or reduce the amount of FFM that is lost [30], thereby helping preserve both resting (basal) and 24-h metabolic rate [31, 32].

Insulin sensitivity

In premenopausal women, estrogens (particularly E_2) exemplify a cardioprotective effect by promoting both insulin sensitivity, as well as peripheral (versus central) fat distribution [33–35]. The loss of E_2 across the menopause transition places women at greater risk of developing type 2 diabetes. This is due, in part, to the E_2-mediated interaction of abdominal (central) adiposity and insulin resistance. Indeed, postmenopausal women taking estrogen-based hormone therapy are less likely to develop insulin resistance and type 2 diabetes [36, 37].

Chronic exercise training and higher levels of PA are well-established lifestyle behaviors that improve insulin sensitivity and systemic glucose metabolism [38–40]. In adults with obesity and type 2 diabetes, exercise training (both aerobic and resistance) enhances the actions of insulin and non-insulin glucose transportation into the skeletal muscle [41–43]. In one cross-sectional study, postmenopausal women who regularly engaged in high levels of exercise had significantly higher insulin sensitivity compared to postmenopausal women who are sedentary, regardless of hormone therapy status (none, estrogen plus progesterone, or estrogen only) [44]. Data from this study also revealed that hormone therapy usage may be associated with lower plasma insulin concentrations, but an attenuation in improved insulin sensitivity [44]. The reason for this paradoxical attenuated improvement in insulin sensitivity is still not well understood.

Data from randomized controlled trials in postmenopausal women reveal reduced fasting insulin concentrations and HOMA-IR (a surrogate measure of insulin resistance) following 3 to 4 months of an aerobic exercise intervention [45, 46]. Longer interventions (6–12 months) do not appear to demonstrate the same degree of efficacy when there is no additional weight loss intervention (e. g. calorie restriction) [47, 48]. Combining aerobic and resistance exercise to a training program does appear to yield the most improvement in insulin sensitivity in menopausal women. Specifically, a 6-month exercise trial that introduced aerobic, resistance, and/or combined (aerobic plus resistance) exercise training to perimenopausal and postmenopausal women with overweight and obesity demonstrated improvements in insulin sensitivity with combined aerobic and resistance or aerobic exercise alone but not resistance exercise alone [49]. In both the combined and the aerobic only exercise group, but not the resistance group, improvements in body composition (reduced fat mass, increased FFM) were also observed [49]. Combined aerobic and resistance training

for 9 months also reduced HbA1c in older menopausal aged women more than aerobic or resistance training alone [50].

Vascular health

The aging vascular system is associated with the expansion of the extracellular matrix (increased fibrosis), and immune cell infiltration into the endothelium [51]. These biochemical and molecular changes increase arterial stiffness and cause endothelial dysfunction. In premenopausal women, estrogen abundance increases nitric oxide (NO) production via multiple mechanisms [52, 53]. Estrogen increases gene expression of endothelial nitric oxide synthase (eNOS) and prevents smooth muscle proliferation and inhibits fibrosis while increasing elastin, resulting in vascular compliance [54, 55]. These mechanistic animal studies demonstrate the importance of estrogen in NO bioavailability and the implications of the loss of estrogen (or E_2). This work also translates to human menopause as the loss of estrogen coincides with similarly lower levels of endothelial nitric oxide production (detected by reduced flow-mediated dilation, FMD) [54, 56]. Previous data has demonstrated that a decline in FMD, as well as decreased carotid artery compliance (detected by increased pulse wave velocity) accelerates during perimenopause and progressively worsens into the postmenopausal years [57]. Chronic vascular dysfunction can also lead to pathophysiological changes to the heart. For example, arterial stiffening can increase both systolic and pulse pressures, as well as create aortic impedance (via increased resistance on left ventricular ejection, thereby causing increased afterload and left ventricular hypertrophy) [58]. Evidence supporting the importance of estrogens comes from studies of OVX mice that develop left ventricular hypertrophy, which was rescued with E_2 replacement [59, 60]. Furthermore, women in heart failure are more likely to have heart failure with preserved ejection fraction (HFpEF) than men, which often has better outcomes than heart failure with reduced ejection fraction (HFrEF) [61, 62]. In experimental models of postmenopausal heart failure, estrogen treatment appears to increase NO bioavailability and improve vascular health [63].

Aerobic exercise can increase NO bioavailability and FMD [64]. As expected, exercise interventions in postmenopausal women with overweight and obesity improved endothelial function [65, 66], and these improvements occur across multiple exercise intensities [67]. However, some studies among older postmenopausal women undergoing aerobic exercise training do not find these same improvements in vascular function (FMD and microvascular blood flow) [68, 69]. Whether the prevalence of women taking estrogen-based hormone therapy in the comparator (control) groups mediated this lack of significant improvement in endothelial health in the aerobic exercise groups remains unclear [68, 69]. Given menopause is associated with increased oxidative stress, which promotes eNOS uncoupling and reduced NO bioavailability, it is possible that the loss of exercise-mediated benefit in endothelial function is primarily the result of E_2-deficiency in the postmenopausal state. Indeed, elegant studies from Moreau et al. highlight estrogen therapy as a positive regulator of exercise adaptions to the vascular endothelium [70]. Unfortunately, exercise intolerance and reduced cardiorespiratory fitness is a hallmark of HFpEF, thereby limiting the ability of menopausal women to engage in PA in the first place [71].

Changes in Physical Health and the Relationship with Physical Activity

Here, we summarize how changes in sleep health and bone health are related to PA level during menopause. Specifically, poor sleep health and reduced bone density are two of the most common physical changes during menopause that women experience and that can impact overall health.

Sleep health

Sleep disturbances (i. e. trouble falling asleep, early morning waking, interrupted sleep) become more prevalent in women around the menopause transition and coincide particularly with the decline of E_2 and progesterone [6]. Women experiencing vasomotor symptoms (e. g. hot flashes and night sweats) – arguably the most common menopausal symptom – tend to report higher levels of sleep disturbances and are at the greatest risk for clinical insomnia [72]. Poor sleep is linked to reduced overall quality of life, as well as increased dietary intake and consumption of high-fat and high-sugar foods, reduced PA, weight gain, and obesity risk [73]. It is also well recognized that insufficient or poor sleep quality can lead to lower levels of PA the following day [74]. Given more than 50 % of perimenopausal and postmenopausal women report sleep disturbances regardless of vasomotor symptom presence [75], reduced PA following a night of poor sleep and resulting fatigue is often inevitable.

Data from the SWAN longitudinal study revealed that women aged 54 to 63 years who had greater levels of habitual and recreational PA reported having more favorable sleep characteristics, including better sleep quality and fewer nightly awakenings [76, 77]. Cross-sectional studies in physically active menopausal aged women (45 + years) also report better sleep quality and fewer sleep disturbances [78]. Indeed, the association between increased PA and better sleep health has been largely confirmed by randomized controlled trials. Data from the Dose-Response to Exercise in Post-menopausal Women (DREW) study revealed that postmenopausal women randomized to all three designated exercise groups (meeting 50 %, 100 %, or 150 % of the National Institutes of Health (NIH) physical activity recommendations) had dose-response improvements in sleep quality compared to postmenopausal control [79]. Data from a 6-month Finnish study [80], as well as the 3-month Menopause Strategies: Finding Lasting Answers for Symptoms and Health (MsFLASH) trials [81, 82] further demonstrated that moderate-intensity aerobic exercise and/or yoga also improved sleep quality. Even walking can improve sleep health in women aged 45 to 65 years, as demonstrated by significant improvements in sleep symptoms after partaking in a 24-week home-based moderate intensity walking program (compared to women of similar age who did not undertake the walking program) [83]. In summary, the link between sleep and PA appears bidirectional in nature given that poor sleep can result in reduced PA and, conversely, that increased relative PA is linked to better sleep quality.

Bone health

The SWAN longitudinal study has significantly contributed to our understanding about alterations in bone health across the menopause transition. These data demonstrate that bone mineral density declines at the greatest rate beginning 1-year before the final menstrual

period and decelerates 2 years after the final menstrual period at both the lumbar spine and femoral neck sites [7]. A separate longitudinal study conducted found that bone loss began slightly earlier (~2 to 3 years before the final menstrual period) and decelerated later (ended 3 to 4 years afterwards), with spine, total body bone mineral, and femoral neck declining by 10.5, 7.7, and 5.3 %, respectively [84]. There are racial and ethnic differences in bone size, geometry, and fracture rates during the menopause transition (discussed in more detail here [85]). Indeed, preventing bone loss during menopause is inherently critical given the declines in E_2 contribute to bone fractures [86] and that history of fracture is associated with higher subsequent fractures, morbidity, and mortality [87].

The evidence that weight-bearing PA (including aerobic walking and running, as well as resistance training) improves bone health comes from a large number of meta-analyses in older women demonstrating improvements in lumbar spine bone density rather than femoral neck bone density [88–91]. Another meta-analysis of walking for preservation of bone density in postmenopausal women looked at randomized and non-randomized controlled trials and concluded that regular walking had no significant effect on preservation of bone density at the spine in postmenopausal women, while significant positive effects were evident at the femoral neck [92]. Increased PA is important for bone health during menopause, but caution is needed when recommending increased PA and/or structured exercise-especially among women with already compromised bone health. Indeed, midlife women undertaking a dietary weight loss program may experience an accelerated loss of bone strength and bone density [93, 94]; therefore, adding in PA or exercise to any weight loss program is important [95]. Medical professionals should consider prescribing resistance training exercises (versus endurance only) alongside any dietary weight loss program to limit reductions in bone density and bone strength [93, 95].

One component of physical fitness that is often overlooked among older adults but that could reduce the risk of bone fractures is the promotion of balance-related activities into activities of daily living. Cross-sectional data during the menopause transition reveal clear declines in postural stability/balance, as well as declines in other functional performance tests (which inherently require balance) [96, 97] that coincide with reduced bone health. Indeed, loss of balance is also associated with concurrent loss of muscle and bone mass, increased fat mass, and other physiological changes that commonly occur during the menopausal transition [15, 98–100]. Regular engagement in balance activities (e. g. yoga, tai chi, and Pilates [101]) is a core component of meeting United States PA Guidelines for American among older adults (especially postmenopausal women) [102]. Participating in these balance activities have the potential to improve physical function and reduce the risk of bone fractures, as indicated by previous lifestyle interventions [103].

Changes in Psychosocial Health and the Relationship with Physical Activity

Data from the SWAN longitudinal study has provided important insight into changes in mood and mental health around the menopause transition. In the SWAN Mental Health ancillary study, perimenopausal and postmenopausal women tended to experience higher levels of psychological stress, depression, and anxiety compared to premenopausal women [8]. Data from SWAN also suggest that women with the greatest increases in depressive

symptoms across the menopause transition had lower levels of PA, increased sleep disturbances, and a decrease in social support [104]. Furthermore, Black women appear to be less likely, whereas Hispanic women are more likely, to experience depressive symptoms over midlife [104]. Various external factors, such stressful life events, financial strain, low social support, sleep problems, and low PA, are all important contributors to depressive symptoms and anxiety in midlife women; however, these factors may also be somewhat independent of the menopause transition itself [75, 105].

A significant, positive impact of PA on psychological symptoms was consistently observed across studies in midlife women [78]. In SWAN, midlife women meeting guidelines for moderate-intensity exercise had lower odds of clinically significant depressive symptoms, and the finding persisted over ten years [106]. Other longitudinal studies, including the Harvard Study of Moods and Cycles [107], the Seattle Midlife Women's Health Study [108], and the Penn Ovarian Aging Study [109], also examined the relationship between menopausal status and depressive symptoms and consistently found that risk for depression (symptoms or disorder) increased during the perimenopausal years. Additionally, data from the large, multi-site MsFLASH trial also found that aerobic exercise training had small improvement on depressive symptoms, insomnia, and sleep quality [81]. With regards to the mode of exercise, both aerobic and resistance exercise have been shown to elevate mood among older adults [110, 111], possibly due to its impact on the serotonergic and adrenergic systems [112].

Summary

Menopause signals the permanent cessation of ovarian production of estrogens, thereby predisposing women to increased cardiometabolic risk factors (e. g. obesity, insulin resistance, and vascular dysfunction). The menopause transition is also associated with the onset of bone loss, sleep disturbances, and mood changes, which occur alongside declines in PA. To combat these, many women undertake diets (calorie restriction), which can further accelerate bone and muscle loss if PA and/or exercise is not also prioritized in tandem. Alarmingly, the loss of bone density and muscle mass, as well as increased fat mass, is associated with loss of balance. Combining both aerobic and resistance training is better than aerobic or resistance training alone at improving body composition (i. e. increase fat mass loss, retention of fat-free (muscle) mass, maintenance of bone density). Finally, a significant, positive impact of PA on physical and psychological symptoms has been consistently observed across studies in midlife women, including better sleep and mood. Given the well-studied benefits of PA, a personalized approach should be used to encourage and maintain PA in perimenopausal and postmenopausal women. Women should be counseled on the potential benefits of PA on symptom relief (e. g. mood and sleep improvements), but it is also important to convey the broad spectrum and lifelong benefits of regular PA and exercise.

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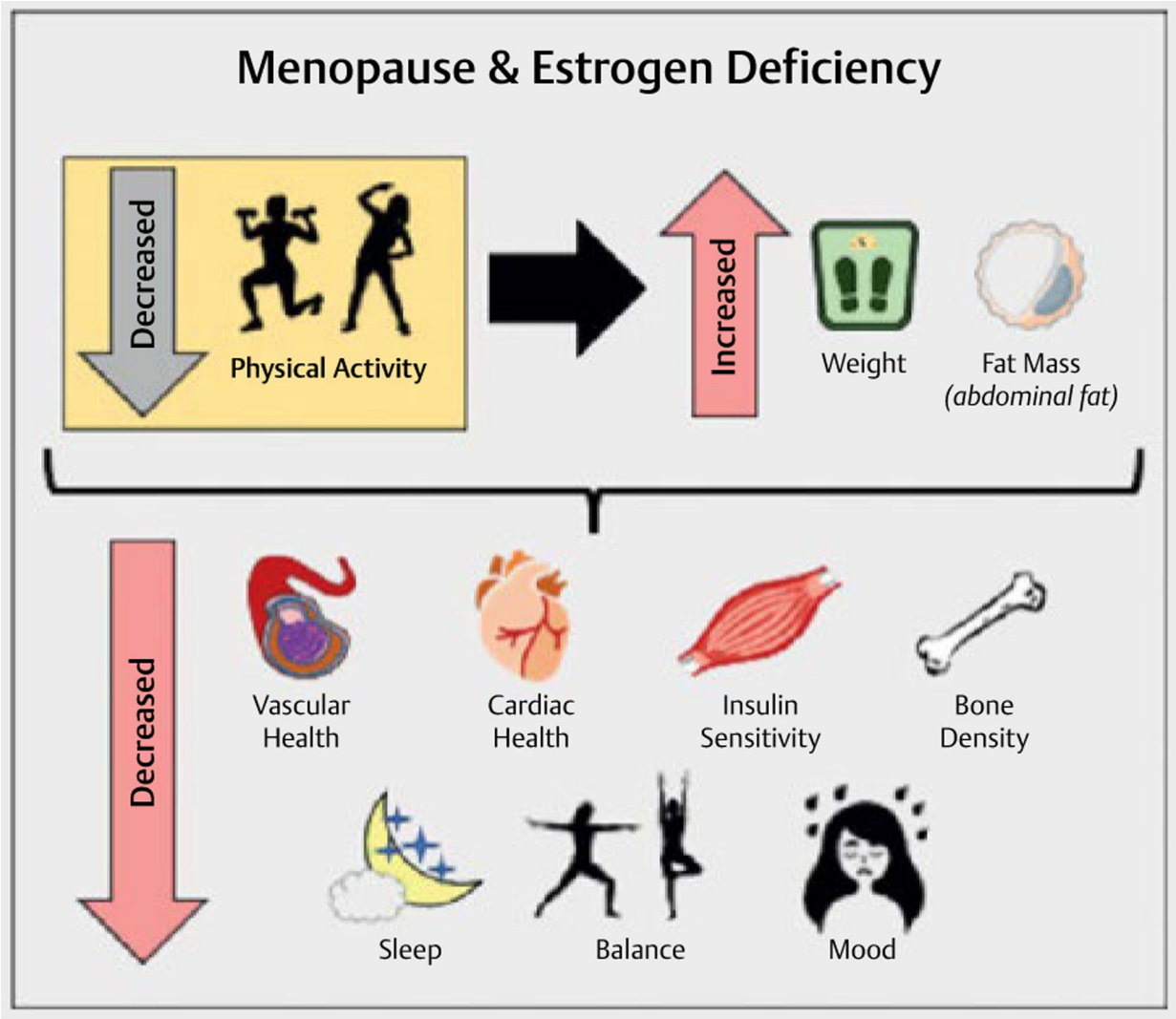

Fig. 1.
Menopause and Estrogen Deficiency Outcomes.