

Beyond BMI: The Janus-like effect of muscle versus fat on midlife women's health

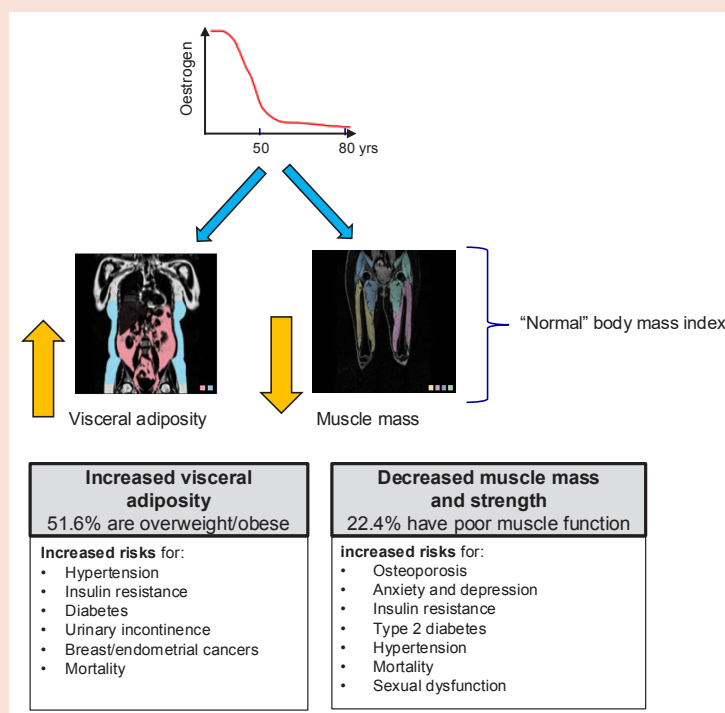
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Janus—the Roman goddess of natural cycles, change and transitions—is an appropriate symbol for the life-changing shift from the reproductive period to the post-menopausal stage of life. Since the average age of menopause is 50 years,¹ it is a universal life stage for long-living Singaporean women. The menopausal transition is associated with a profound decline in circulating oestrogen levels, resulting in the slowing of basal metabolism and marked changes in body composition.² On average, women gain approximately 2 to 3 kg during the menopause transition. Remarkably, many Singaporean women maintain relatively stable “healthy” BMI, even though deleterious changes in their body composition are occurring.² These changes in body composition involve 2 variables, both of which increase BMI. However, 1 variable

has positive, while the other has negative health effects. Muscle mass/strength—a positive factor that increases BMI—is necessary for cardiometabolic and skeletal health, activities of daily living and mobility.³ Lack of muscle mass, or sarcopenia, results in frailty and increased risk of death.³ On the other hand, abdominal (visceral) adiposity also increases BMI but is a strong negative factor for cardiometabolic health.²

This commentary considers the consequences of oestrogen decline to increase visceral adiposity and decrease muscle mass on cardiometabolic health and other important conditions important to midlife women. We argue that beyond BMI, it is appropriate to measure the Janus-like changes in visceral adiposity and muscle mass/strength as women face the menopause transition.

Fig. 1. Visceral adiposity and muscle mass at onset of menopause.



Abrupt drop in oestrogen around menopause (~50 years) causes increase in visceral adiposity (pink) and reduced muscle mass (coloured) as indicated by the MRI scans. Reduction in muscle mass/strength coupled with increase in visceral adiposity can result in apparently “normal” body mass index despite abnormal body composition and associated increased health risks.

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Menopause onset is associated with decreasing energy expenditure and fat oxidation leading to increasing abdominal (i.e. visceral) fat (Fig. 1). Asian women tend to transit from a pre-menopausal gynaecoid “pear” shape with fat around the hips, buttocks and thighs, to the post-menopausal “apple” shape with increasing fat deposition around the abdomen. Asian women appear to store more fat abdominally than Caucasian women of comparable BMI.⁴

Ovariectomy stops oestrogen production and is used as a model of menopause in laboratory animals to study how the loss of ovarian function causes fat mass accumulation. Ovariectomy is associated with increased body weight and abdominal adiposity, and oestrogen replacement reverses this effect.⁵ Oestrogen receptor knockout mice were shown to have increased fat mass, as well as adipocyte number and size.⁶ Brain-specific oestrogen receptor knockout mice have increased abdominal obesity, mediated through hyperphagia and hypometabolism, and induced by decreased heat production and decreased physical activity.⁷

The Study of Women’s Health Across the Nation (SWAN)—the most comprehensive study on menopause funded by the US National Institutes of Health—provided very compelling evidence that an accelerated gain in fat mass and loss of muscle mass were related to the menopause transition rather than ageing.⁸ Although an increase in fat mass and a decline in fat-free mass were observed during pre-menopause, these changes accelerated during peri-menopause before stabilising in the postmenopausal years.⁹ This perimenopausal increase in fat mass was attributed to increased abdominal fat.² Several large randomised clinical trials on oestrogen replacement therapy indicate that women who received oestrogens gained less body weight and had smaller increases in waist girth than women randomised to placebo.^{10, 11}

Collectively, these studies suggest that the loss of ovarian oestrogen promotes abdominal fat accumulation and a decline in energy expenditure, leading to markedly poorer cardiometabolic health, an effect that is more marked in Asian women. Oestrogen replacement tends to slow down this trend towards abdominal adiposity.

Emerging evidence indicate that oestrogen has important functions related to muscle mass and strength (Fig. 1). In animal studies, ovariectomy results in a 10% decrease in strength that corresponded with an 18% decrease in fibre cross-sectional area¹² and, in the absence of oestrogen, muscle is more prone to injury and regrowth is limited.¹³

In human studies, postmenopausal women experience a rapid decrease in muscle mass and

strength and are more vulnerable to age-related frailty.¹⁴ Muscle area and grip strength were greater in oestrogen replacement therapy users than in non-users, and oestrogen replacement therapy can improve muscle protein synthesis following resistance training.¹³ Although less extensive than for visceral adiposity, there is increasing evidence that oestrogen decline at menopause decreases muscle mass and physical performance, and oestrogen replacement therapy can slow down this process.¹⁵

One of the main challenges in assessing disease risk for postmenopausal women is the over-reliance on BMI as an indicator of health. BMI encompasses both fat and muscle, which does not sufficiently account for shifts in body composition during menopausal transition. For example, women from the SWAN cohort had a simultaneous occurrence of an accelerated increase in fat mass and reduction in lean mass, leading to a 3.6% cumulative rise in proportion fat mass and 1.9% cumulative decline in proportion of lean mass over the course of the menopause transition.⁹ This phenomenon presents a Janus-like effect wherein many women undergoing menopausal transition may experience a concurrent loss of muscle mass and gain in excessive levels of visceral fat, while retaining a “normal” BMI. This gives rise to a unique scenario—the Y-Y paradox in which 2 individuals possessing similar BMI can have different adiposity levels.¹⁶

Studies from the Singapore Integrated Women’s Health Program (IWHP) cohort¹⁷ indicate that visceral adiposity and poor physical performance were independent determinants of insulin resistance.^{18, 19} Muscle strength was also a risk factor of diabetes, independent of visceral adiposity.²⁰ The risk of developing type 2 diabetes was significantly reduced in postmenopausal women who used oestrogen therapy in several randomised clinical trials, including the Women’s Health Initiative and Heart and Estrogen/progestin Replacement Study from the US.² Although those studies were not unanimous, the evidence indicate a plausible link between visceral adiposity during the menopause transition to increased risk of insulin resistance and risk of type 2 diabetes.

Vascular function appears to be preserved up until the menopause transition, after which it progressively deteriorates, possibly due to a shift in redox balance and the loss of the antioxidant and anti-inflammatory effects of oestradiol.²¹ Postmenopausal women experience an increase risk in cardiovascular disease (CVD), that is primarily thought to be due to ovarian failure and the loss of oestrogen that occurs across the menopause transition.² The Framingham Heart Study found that visceral adiposity, compared to BMI, was

more strongly associated with incident diabetes, hypertension, low HDL and CVD events in women, including CVD death.²² Studies from the Singapore IWHP cohort indicate that visceral adiposity increased systolic blood pressure by 9.8 mmHg (95% confidence interval [CI] 6.2–13.4).²³ In addition, reduced physical performance was independently associated with increased risk for hypertension (adjusted odds ratio 2.83, 95% CI 1.46–5.47), even after adjustment for visceral obesity.²⁴

During menopause, obesity was reported as a protective factor against osteoporosis, due to the mechanical effect of body weight on bone.²⁵ However, the true protective effect on bone density comes from an increase in muscle, not fat.^{25,26} While visceral adipose tissue (VAT), not BMI, was associated with a greater fracture risk in men,²⁷ the effects of VAT and BMI on fracture risk and bone microarchitecture were similar in women.^{27,28} We found that handgrip strength reduced the likelihood of spinal osteoporosis by 50% in Singaporean women,²⁹ supporting findings that resistance training increases bone mineral density in other studies.³⁰

Sarcopenic obesity, defined using visceral fat attenuation, was linked to poorer survival rates, regardless of BMI.³¹ In the UK Biobank, women in the top VAT quintile had the highest hazard ratio for all-cause mortality.³² These findings highlight mechanisms of fat inflammation, sex-related body fat distribution and hormonal differences. In addition to a low muscle mass, poor handgrip strength was also associated with mortality prediction.³³ although some studies argue that muscle strength is a better predictor.³⁴

Over the past decade, the IWHP cohort has inspired publications giving unique insights on the Janus-like opposing effects of adiposity and muscle strength. Visceral adiposity was independently associated with increased risks for hypertension,²⁴ insulin resistance,¹⁸ incident diabetes¹⁹ and mortality²² (Fig. 1). Besides visceral adiposity, our studies highlight the important contribution of poor muscle function to midlife women's health. Weak hand grip strength, present in 22.1% of Singaporean women, was independently associated with increased risks for osteoporosis,²⁹ hypertension, insulin resistance,¹⁸ type 2 diabetes,¹⁹ and mortality.³³ The 2023 Singapore National Population Health Survey found that among midlife women (aged 50–59 years), only 26.4% reported sufficient muscle strengthening activities. The population attributable risk of sarcopenia for mortality is 5.2% in the US National Health and Nutrition Examination Survey.³⁵ The total costs of hospitalisation among those with sarcopenia was USD19.12 billion, with total costs higher in women than men.³⁶ The evidence presented above strongly supports

the current Singapore Ministry of Health recommendation to improve physical performance as outlined in the Singapore Clinical Practice Guidelines for Sarcopenia.³⁷

Women with a higher waist circumference (≥ 95 cm) have 22% increased future healthcare costs compared to those with a normal waistline.³⁸ Visceral adiposity contributed to 50.4% of type 2 diabetes cases in the Shanghai Men's and Women's Health Studies.³⁹ Menopausal hormone therapy for 15 years among younger women (about 50 years old) was associated with a higher gain in quality-adjusted life years (1.49 versus 0.11) compared to older women (around 65 years old),⁴⁰ suggesting it might be more cost-effective to start hormone therapy at a younger age.

In summary, beyond BMI and reduction of visceral obesity, exercises to improve physical performance and muscle strength and menopausal hormone therapy have emerged as key lifestyle factors that would increase healthy lifespan in midlife Singaporean women.²⁰ Targeted implementation programmes are needed to improve muscle strength especially in Chinese women with Chinese language preference, Indians and Malays.⁴¹

Ethics statement

This study was approved by the National Healthcare Group's Domain Specific Review Board (Reference numbers: 2014/00356 and 2020/00201).

Declaration

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