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**Commentary:** Is a reduction in brown adipose thermogenesis responsible for the change in core body temperature at the menopause?

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**Abstract**

Maintenance of thermal homeostasis within a tight range is regulated not only by a variety of internal and external cues but also by sex and biological age. The major organ responsible for adaptive thermogenesis is brown adipose tissue (BAT) and the recent re-discovery of its presence in adult humans has led to huge interest in the role that it may play in modulating cardiometabolic health. Interestingly, as with maintenance of thermal homeostasis, the total amount and metabolic activity of BAT is modulated by sex and biological age. In this short commentary we discuss the recent finding that core-body temperature is reduced in women post-menopause, a period when excess adiposity and increased risk of cardiometabolic disease is evident and postulate that alterations in sex hormones downregulated the thermogenic activity of BAT cold contribute to this deleterious phenotype.

**Commentary**

Following the menopause, women are at greater risk of becoming obese and suffering from associated cardiometabolic diseases[1,2]. The transition towards greater visceral adiposity and metabolic dysregulation after the menopause is likely to be a consequence of changes in energy metabolism, primarily mediated by a reduction in circulating sex hormones such as estrogen or progesterone[1,2]. In the recent edition of *Cardiovascular Endocrinology*, Neff et al.[3] describe that core body temperature is lower in women who have reached the menopause, to similar temperatures seen in men. Their observation that the lower core body temperatures in those women who had reached the menopause raises the possibility that this little studied factor could itself play a role in the increase in disease risk after this time[1,2], although whether the associated higher body mass index and adiposity is an effect of age or the menopause per se cannot be determined from their study. Whilst the researchers acknowledge the study was an exploratory post-hoc analysis of data synthesised from temporally distinct studies, it is worth further consideration given current interest in brown adipose tissue (BAT) as a therapeutic target to combat cardiometabolic diseases[4]. BAT is a thermogenic organ located mainly in the supraclavicular regions and in much smaller amounts[5] in other locations such surrounding the kidneys and heart. Most abundant at birth[6], BAT is responsible for non-shivering thermogenesis and the maintenance of thermal homeostasis. This is achieved through the uncoupling of oxidative metabolism from ATP production via mitochondrial uncoupling protein 1 which dissipates chemical energy as heat[7]. We now know that a majority of adults retain metabolically active BAT into adulthood[8], in declining amounts with age, and that sex hormones such as estrogen are likely to play a key role in the development of brown adipocytes and their function[9,10]. Pre-clinical research has long demonstrated that exogenous sex hormones play a key role in the metabolic activity of BAT, whilst more

recently it has been shown that cerebroventricular estradiol administration stimulates BAT function, increasing core body and BAT temperatures[11-13].

Another feature of Neff et al's study is the large variation in body temperatures within women irrespective of age and this appears to be most marked in the group described as post-menopausal. Whilst the authors do not define how many of the so-called post-menopausal women in the study were still experiencing hot flashes, a stage already know to be associated with lower body temperature[14,15] and a truly age-matched group of men is omitted, their observations fit with studies showing that women are more sensitive to cold than men[16,17]. This is likely to be a primary factor contributing to their higher incidence of BAT[18]. Moreover, a recent small study in pre-menopausal women demonstrated a potentially important relationship between salivary cortisol and basal temperature of BAT within the neck[19]. A combination of differences in the hypothalamic-pituitary-adrenal axis, BAT abundance, stress and thermal sensitivity could explain the large variation in body temperatures of healthy women. These relationships may shift after the menopause as BAT activity declines.

However, whether a decline in BAT after the menopause occurs in humans and, therefore, contributes to greater body mass index and fat mass remains to be determined. Given the role of BAT in metabolic homeostasis[20,21] and the recent associations between BAT activity and cardiovascular events[22], investigation of changes in BAT around the menopause and any effects of hormone replacement therapy are warranted. Maintenance of active BAT after the menopause has potential to attenuate the development of adiposity. Future investigations would require well-matched groups as differences in age, body mass and seasonality can all

have a significant impact on BAT functionality as highlighted by the authors. Future studies should employ additional methods to core body temperature measurements in order to determine thermal homeostasis and should include supraclavicular skin temperature[23-26] and thermal imaging[23,26] to assess BAT function.

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**Figure 1.** Overview of phenotypic differences between pre/post-menopausal women and possible mechanisms involved. Histological image adapted from Ravussin and Galgani[27].