**Editorial**

**Relative skeletal muscle mass and incident hypertension:**

**Associations, caveats, and future perspectives.**

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Sarcopenia (attenuated muscle mass) often occurs with older age, and represents an enhanced risk of cardiovascular disease, and all-cause mortality [1–3]. Hypertension is one of the strongest risk factors for cardiovascular disease [4] and recent (typically cross-sectional) research has suggested an inverse relationship between skeletal muscle mass and blood pressure [5]. However, positive associations between lean body mass and blood pressure have also been reported [6,7]. These studies included relatively small sample sizes and cross-sectional designs, thus, the relationship between skeletal muscle mass and hypertension is not yet fully understood.

In this issue of the *Journal of Hypertension*, Han *et al*. conducted a large prospective cohort study that demonstrated a decrease in skeletal muscle mass index (SMI), as measured by bioelectrical impedance, was associated with an increased risk of incident hypertension [8]. Specifically, low SMI was associated with increases in systolic and diastolic blood pressure and the number of new patients receiving antihypertensive medication at 4-year follow up. These findings corroborate and extend findings from the only previous longitudinal study, the Tobago Health Study, which found that skeletal muscle attenuation was a risk factor for incident hypertension [9]. The Tobago Health Study, however, did not directly evaluate skeletal muscle mass, and therefore, the study by Han *et al*. is the first large prospective longitudinal study to suggest a relationship between skeletal muscle mass and hypertension.

The large sample size of the study by Han *et al*. is noteworthy, including 72,560 men and 59,764 women who were followed up for 4 years and evaluated for incident hypertension. At 4 years, 5.4% participants developed hypertension. When the sample was categorised into ascending quartiles of SMI, the cumulative incidences of hypertension were 12.1%, 8.6%, 6.9%, and 4.4% in men and 4.0%, 2.3%, 1.7%, and 1.2% in women for Q1, Q2, Q3, and Q4 quartiles, respectively.

Nonetheless, the precise mechanism(s) linking sarcopenia with increased risk of hypertension is not well understood, although several hypotheses have been proposed by Han and colleagues [8] and previous work [5], which warrant further investigation:

1. Loss of muscle mass promotes insulin resistance, which is an established risk factor for hypertension.

2. Loss of muscle mass may enhance inflammatory and oxidative pathways.

3. Loss of muscle mass may increase blood pressure potentially mediated via myokines, especially when linked to altered physical activity or exercise levels.

4. Loss of muscle mass has been associated with increased arterial stiffness, which may mediate both sarcopenia and hypertension.

One important strength of a large sample size is the ability to control for a number of potential confounders. In the study by Han *et al*. this included age, BMI, education level, systolic blood pressure, diabetes, dyslipidaemia, eGFR, HOMA-IR, hsCRP, current smoking, alcohol intake, physical activity, and energy intake [8]. After adjusting for these hypertension risk factors and confounders, SMI had an inverse association with incident hypertension in men only. Therefore, it seems that males who experience skeletal muscle mass loss are more at-risk of developing hypertension than females. The sex-dependent relationship between sarcopenia and hypertensions is unclear but potentially explained via the independent age-related sex hormone changes in men and women. These potential mechanisms have been previously discussed by Yoon *et al*. who postulate that the time course of sex hormone levels may explain the sex-specific associations between skeletal muscle mass and albuminuria [10]. Indeed, the sample within the study by Han *et al*. were relatively young and healthy, therefore sex-specific associations between SMI and hypertension may not be the same in older populations and warrants future investigation.

Further limitations acknowledged by Han *et al*. that are of note include a lack of causal inference due to the observational study design and the potential of residual confounding. Nearly all measured risk factors in both men and women demonstrated a significant trend with quartiles of SMI. Although these were controlled for in regression models, it is possible that other factors not measured within the study may be involved in this complex and interrelated relationship between body composition and cardiovascular health. For example, Li *et al*. found that low muscle strength was more strongly and significantly associated with all-cause mortality than low muscle mass [11].

Nevertheless, the results of Han *et al*. are promising for the concept of exercise as medicine and suggest interventions that conserve (or improve) muscle mass can help reduce the incidence of hypertension and cardiovascular complications. In a seminal paper by Naci & Ioannidis, exercise was found to be as effective as pharmacology in the reduction of all-cause mortality [12]. In a more recent network meta-analysis of 391 randomised controlled trials, Naci *et al*. demonstrated that among hypertensive populations, there were no detectable differences in the systolic blood pressure-lowering effects of common anti-hypertensive medication when compared with exercise [13]. Traditionally, the benefits of exercise training on blood pressure have been linked to remodelling of the (cardio)vascular system. This paper suggests that these blood pressure lowering effects may also relate to effects directly related to muscle mass. Such effects may contribute to explaining the remarkable anti-hypertensive effects of local handgrip exercise [14].

Collectively, the work from Han *et al*. in this issue of the *Journal of Hypertension* warrants a focus on the preservation (or improvement) of muscle mass as an integrated part of anti-hypertensive treatment. Whilst anti-hypertensive pharmacology has dominated the hypertensive therapy research arena, its affects are limited to blood pressure, often elicit negative side-effects, and do not affect muscle mass. In contrast, physical activity and exercise may enhance muscle mass, subsequently contributing to blood pressure lowering properties, but also offer a systemic benefit (physical and mental) at a relatively low cost. Therefore, renewed attention is warranted for non-pharmacological strategies to promote muscle mass, possibly through physical activity and exercise, to prevent and manage hypertension.

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