

## Association of low muscle mass with cardiovascular disease mortality in patients with diabetes

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**Background and aims:** Sarcopenia is associated with cardiovascular disease (CVD) and mortality in patients with diabetes. However, it is unclear to what extent sarcopenia contributes to these risks independently or in conjunction with glycemic control or microvascular complications.

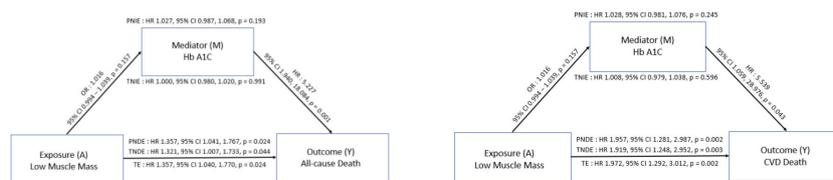
**Materials and methods:** This cross-sectional analysis used data from the National Health and Nutrition Examination Survey (NHANES) 1999-2006 and 2011-2018. Participants aged over 20 years and with reported whole-body DEXA data were included. Low muscle mass was defined as an ASMI <7 kg/m<sup>2</sup> in men or <5.5 kg/m<sup>2</sup> in women. The hazard ratios (HRs) were determined using multiple Cox regression analysis adjusted for the following confounding variables: Age, sex, race, smoking status, alcohol consumption, obesity, history of cancer, HTN, dyslipidemia, past CVD, duration of DM, microvascular complications and HbA1c. Follow-up duration was computed as the time from the first anthropometric and clinical measurement to death or the last follow-up (December 31, 2019). To investigate the direct effect of low muscle mass on mortality independent of the effects of glycemic control or microvascular complications, we conducted a regression-based causal mediation analysis.

**Results:** The present study enrolled a total of 2119 patients with diabetes from the NHANES database. Low muscle mass was found to be associated with a higher risk of all-cause mortality (HR, 1.41; 95% CI, 1.08-1.84) and CVD mortality (HR, 2.03; 95% CI, 1.32-3.13). Furthermore, the RCS plot analysis demonstrated that low ASMI was consistently linked to an increased risk of all-cause mortality. The mediation analysis revealed that low muscle mass had a direct impact on the risk of all-cause mortality and CVD mortality, rather than indirectly mediated by HbA1c or microvascular complications. Notably, low muscle mass did not exhibit any significant association with high HbA1c or microvascular complications.

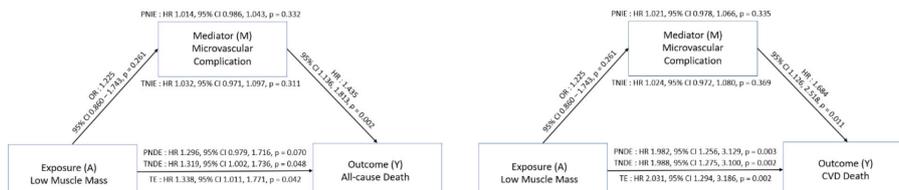
**Conclusion:** Our results suggest that low muscle mass may play a direct role in the pathogenesis of all-cause mortality and CVD mortality in patients with DM, independent of high HbA1c or microvascular complications.

**Figure.** Mediation analysis of effect of low muscle mass through HbA1c and microvascular complications in patients with DM on all-cause and CVD mortality

(A) Through HbA1C



(B) Through microvascular complications (nephropathy or retinopathy)



Adjusted for age, sex, race, smoking status, alcohol consumption, central obesity, history of cancer, HTN, dyslipidemia, previous CVD events, duration of DM, microvascular complications, and hemoglobin A1c (HbA1c)

**Abbreviations:** PNIE, pure natural indirect effect; TNIE, total natural indirect effect; PNDE, pure natural direct effect; TNDE, total natural direct effect; TE, total effect.