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# Predicting cardiovascular disease from handgrip strength: the potential clinical implications

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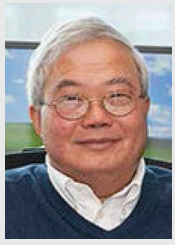

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The measurement of handgrip strength has proven prognostic value for all-cause and cardiovascular death, and for cardiovascular disease. It is also an important indicator of frailty and vulnerability. The measurement of handgrip strength may be most useful in the context of multi-morbidity, where it may be a simple tool to identify the individual at particularly high risk of adverse outcomes, who may benefit from closer clinical attention. Research into dietary, exercise, and pharmacologic strategies to increase muscle strength is ongoing. Important issues will be the feasibility and sustainability of increases in muscle strength, and whether these increases translate into clinical benefit.

## The measurement and interpretation of handgrip strength

Quantitative measurement of handgrip strength (HGS) is performed using a handheld dynamometer, and it is simple, quick to perform, and reproducible.[1,2] Several studies have reported reference ranges for HGS; however, the choice of dynamometer and approach to HGS measurement (e.g. one hand or both; average or maximum values) vary. To date, most reference ranges have been derived from Caucasian populations [3,4]; there is a paucity of data from populations of other ethnicities,[5] which clearly differ in age-, height-, and sex-standardized HGS from Caucasian populations.[6]

## The prognostic importance of HGS

There is now a large body of evidence indicating that low HGS is independently associated with an increased risk of all-cause [7] and cardiovascular (CV) mortality,[8] and with a more modest increase in the risk of incident cardiovascular disease (CVD).[9] HGS has also been associated with clinical outcomes in various specific patient groups. Among adults aged ≥70 years with hip fracture, high HGS predicts walking recovery.[10] In Japanese men with heart failure, HGS predicted survival independently of $VO_{2MAX}$.[11]

The PURE study has recently confirmed the prognostic importance of low HGS in general adult populations from 17 countries of all income strata.[6] Compared with blood pressure, HGS demonstrated similar predictive value for CV death, and weaker, although still significant, predictive value for incident CVD.[6] The stronger relationship between HGS and CV death, as compared with (non-fatal) CVD, is partly attributable to the observation that low HGS has a profound association with a high case-fatality rate for a variety of incident diseases, including CVD,[6] suggesting that HGS is an important marker of one's ability to withstand or recover from an illness. This finding supports the measurement of muscle strength as a key indicator of frailty.

## The functional and physiologic meaning of low HGS

In a recent consensus statement, frailty was defined as a state of "diminished strength, endurance, and physiologic

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function that increases an individual's vulnerability for developing increased dependency and/or death".[12] The measurement of HGS is part of a clinical battery that has been suggested as a screening tool for frailty. Fried *et al.* characterized frailty by the presence of unintentional weight loss, low HGS, self-reported lack of energy, physical slowness, and low physical activity levels.[13] By these criteria, there was a strong positive association between frailty and reduced survival among 5317 community-based individuals.[13] Frail participants exhibited an adjusted hazard ratio (95% confidence interval) for three-year mortality of 2.24 (1.51–3.33) compared with those who were not frail. In another study of 1829 older individuals, in which frailty was measured by a battery of characteristics, including HGS, those in the frailest quarter demonstrated a hazard ratio for death of 2.5 (1.8–3.6) compared with those in the least frail quarter.[14]

It is intuitive that low HGS is a marker of poor general health, and conversely, that high HGS is an indicator of good overall health. The extent to which good muscle quality or strength can directly protect against death and CVD (over and above serving as a marker of general health) is unknown. There are, however, a number of potential mechanisms through which improved muscle quality might reduce CVD risk. Studies of exercise training suggest that exercise can upregulate antioxidant mechanisms, which can protect against ischemic myocardial injury, and can improve neurohormonal balance in heart failure.[15] Exercise training also improves endothelial function[15]; endothelial dysfunction has been implicated as an important mechanism underlying CVD. Many studies of exercise training have employed aerobic exercise, rather than resistance training, and further research is necessary to better understand the relationship between the type of exercise regimen, muscle strength, and favourable physiologic adaptation.

## The potential clinical role and implications of low HGS

Even though low HGS predicts adverse outcomes in healthy populations, the absolute risk of adverse outcomes and CVD among these individuals is low, so the yield of HGS testing among the healthy will be modest. Health gains using a screening tool have the largest potential in populations at high absolute risk of adverse outcomes. Individuals with multimorbidity are therefore most likely to represent a group who will benefit from evaluation of HGS. The proportion of individuals with multi-morbidity is expected to increase as populations age, and as treatments for many diseases improve patient survival. Indeed, multi-morbidity is itself recognized as an important contributor to frailty.[16] For these reasons, we suggest that the measurement of HGS is most likely to deliver clinically important information among individuals with multi-morbidity.

The finding of low HGS in a given individual should prompt (1) the identification of reversible causes of sarcopenia, including low physical activity levels, poor nutrition, and harmful alcohol use; (2) evaluation for cachexia, which is a sign of (potentially undiagnosed) chronic disease or malignancy; and (3) awareness of the individual's vulnerability to intercurrent illness. This heightened awareness might lead to closer surveillance, preventive strategies, such as influenza and pneumococcal vaccination, and perhaps a lower threshold for the initiation of therapies for communicable diseases. Despite its predictive value for incident CVD, it is unknown whether low HGS identifies a group of people who would benefit from pharmacotherapy for the primary prevention of CVD.

## Interventions targeting low muscle strength

Further research is needed to determine whether, firstly, muscle strength can be sustainably increased, and secondly, whether strategies targeting muscle strength will translate into improved CV outcomes.

Approaches to increase muscle strength that have been evaluated in either the general population, or in groups with specific illnesses, include resistance and exercise training, dietary supplements (e.g. protein, vitamin D), and pharmacologic interventions. A Cochrane meta-analysis of 42 trials that randomized older individuals found that oral protein and energy supplementation resulted in a 2.2% (95% confidence interval 1.8%–2.5%) increase in weight, but no significant reduction in mortality (relative risk 0.92, 95% confidence interval 0.81–1.04, in n = 8031).[17] The trend towards mortality reduction in this meta-analysis does lend to the hypothesis that particular high risk groups may benefit from dietary protein supplementation. Whether exercise training to increase muscle strength improves CV outcomes is the subject of an ongoing systematic review.

Among pharmacologic interventions for low muscle strength, there have been numerous randomized trials comparing the effects of testosterone supplementation with placbeo. A meta-analysis of these trials found no significant harmful effect of testosterone with respect to adverse CV events (pooled odds ratio 1.01, 95% confidence interval 0.57–1.77), and also no evidence of CV benefit.[18] Early studies have also been conducted using the β-blocker, espindolol, the angiotensin-converting enzyme inhibitor, perindopril, and appetite stimulators, such as ghrelin.[19] While there is presently insufficient evidence to support the use of these agents to increase muscle strength, ongoing clinical trials will address the potential value of these pharmacological strategies to increase muscle strength, and to improve clinical outcomes including CVD.

## Future directions

Further research is needed to identify the determinants of low HGS. The PURE study demonstrated using the same make of dynamometer, that age-, height-, and sex-standardized HGS varies substantially among populations in different countries. The extent to which this variation at a population or an individual level is driven by genetic factors versus

environmental factors is uncertain. More work is necessary to identify which are the most important modifiable determinants of muscle strength, and the time of life at which these exposures have their largest impact. Resolution of these issues would guide public health initiatives as well as clinical approaches to patients, with the goal of the primary prevention of frailty, CVD, and premature mortality.

## Financial & competing interests disclosure

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