Dose-dependent association between muscle-strengthening activities and all-cause mortality: Prospective...
Dose-dependent association between muscle-strengthening activities and all-cause mortality: Prospective cohort study among a national sample of adults in the USA

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KEYWORDS
Epidemiology; Health promotion; NHANES; Strength; Resistance training

Summary
Background. – We have a limited understanding of the association between behavioural participation in muscle-strengthening activities (MSA) and all-cause mortality.
Aim. – To determine the effect of MSA on all-cause mortality, and examine a potential dose-response relationship between the frequency with which MSA are performed and the incidence of all-cause mortality.

Abbreviations: ACSM, American College of Sports Medicine; AHEI, average healthy eating index; CI, confidence interval; HR, hazard ratio; ICD, International Classification of Diseases; MSA, muscle-strengthening activities; NHANES, National Health and Nutritional Examination Survey; USDHHS, United States Department of Health and Human Services.

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Methods. — Individuals (8772 adults aged ≥ 20 years) from the 2003–2006 National Health and Nutritional Examination Survey were evaluated for baseline characteristics, then followed for an average of 6.7 years. MSA were assessed at baseline as the number of self-reported sessions completed within the past 30 days. Analyses were performed in 2015.

Results. — Only 18.6% of individuals met MSA guidelines (2–3 MSA sessions/week) at baseline, while those performing any form of MSA had a 23% reduced risk of all-cause mortality (hazard ratio [HR]: 0.77; 95% confidence interval: 0.60–0.98; P = 0.04). Additionally, we created a five-category variable to determine whether a dose-response relationship existed between MSA and premature mortality; only individuals performing 8–14 sessions over a 30-day period (current MSA guidelines) had a reduced risk of all-cause mortality (HR: 0.70; P = 0.02). Results were similar for CVD-specific mortality.

Conclusion. — The national recommendations that 2–3 MSA sessions be performed per week appear to be most effective at reducing the risk of premature all-cause mortality; however, despite these recommendations, the majority of the adult population in the USA still fails to perform any MSA. Future studies should determine strategies for increasing adherence to these established guidelines.

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Background

The American College of Sports Medicine (ACSM) and the United States Department of Health and Human Services (USDHHS) recommend that muscle-strengthening activities (MSA) be performed 2–3 times per week as part of a comprehensive exercise programme [1,2]. The most commonly documented adaptations resulting from MSA involve increased muscle size and strength, both of which have been shown to be inversely associated with all-cause mortality [3–8]. In addition to local muscle adaptations, MSA have been shown to provide a wide range of health benefits, including improvements in glucose metabolism [9,10], cholesterol concentrations [11,12], body

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composition [13], blood pressure [14] and other cardiovascular variables [15–17] that have been shown to help prevent or attenuate risks associated with a wide range of chronic diseases (e.g. cancer, diabetes) [9–23].

While an inverse association appears to exist between aerobic-based physical activity and all-cause mortality [24–26], much less is known about the potential attenuating effects of behavioural participation in MSA, and its association with all-cause mortality. The majority of studies illustrating that muscle strength is associated with a decreased risk of all-cause mortality [3,5–8], along with the beneficial effects of MSA on various chronic diseases [9–23], would seem to suggest that participation in MSA may help to reduce the risk of premature mortality. Although strength is influenced by MSA, a large number of studies (aside from those previously mentioned) [3,5–8] have illustrated an association between strength and mortality centred on hand-grip strength [27–35], which has been shown to be unaffected by participation in a full-body MSA intervention [36], and thus these studies may not be representative of behavioural participation in MSA. Additionally, all studies associating muscle strength with all-cause mortality are highly dependent on the mode of strength testing, which probably modulates the association between strength and all-cause mortality. Therefore, studies specifically examining the association between behavioural participation in MSA and mortality are needed, as MSA may be associated with mortality from factors other than strength gains (e.g. contraction-facilitated glycaemic control). The importance of behavioural participation in MSA and its effect on all-cause mortality may differ from that of strength because of the variability in baseline strength levels, as well as the variations in individual responses to MSA [37]. To illustrate, some individuals completing 12 weeks of MSA increased muscle strength by 250%, while others saw minimal to no increase in strength [37]; however, these “non-responders” may have still benefited from the various other positive effects of MSA mentioned previously (e.g. reduced blood pressure). Therefore, the importance of examining behavioural participation in MSA is critical for a more precise measure of the true beneficial effects of MSA; after all, the nationally accredited government-issued guidelines are not based on muscle strength, but are rather centred on the behavioural participation in MSA [2].

Despite the importance of determining an association between MSA and all-cause mortality, to our knowledge, only three published studies have examined this association, demonstrating that individuals who engaged in ≥ 2 MSA sessions per week were at a small, non-significant, reduced risk of premature all-cause mortality after adjustment for potential confounding variables [38–40]. These studies, however, applied dichotomous variables to determine the effectiveness of MSA, and therefore could not delineate whether additional participation in MSA, above meeting established guidelines, had a more protective effect against premature mortality. Therefore, the purpose of our study was to determine the effect of MSA on all-cause mortality, and to examine a potential dose-response relationship between the frequency with which MSA is performed and the incidence of all-cause mortality.

Methods
Study design
The 2003–2006 National Health and Nutritional Examination Survey (NHANES) data were used for the calculation of baseline characteristics of 8772 adults (age ≥ 20 years). The NHANES is an ongoing survey conducted by the Center for Disease Control and Prevention, designed to evaluate the health of citizens of the USA through a complex, multi-stage, stratified, clustered probability design. All individuals included in the analyses provided informed consent, and all study procedures were approved by the ethics review board of the National Center for Health Statistics. Participants were followed for a period of up to 9 years, with the average follow-up being 6.7 years (standard error: 0.20 years).

Muscle-strengthening activities
Individuals self-reported their involvement in MSA at the initial baseline assessment by responding to two questions: “Over the past 30 days, did you do any physical activities specifically designed to strengthen your muscles, such as lifting weight, push-ups or sit-ups?”; and if so “Over the past 30 days, how many times did you do these activities designed to strengthen your muscles, such as lifting weights, push-ups or sit-ups?” Those answering “no” to the first question were coded as engaging in “0” MSA in the past 30 days. Evidence of the validity of self-reported participation in MSA has been demonstrated [41].

All-cause mortality
All-cause mortality was determined as the number of individuals who died during the follow-up period, by matching the individual’s identification information with the National Death Index of the National Center for Health Statistics. Individuals from the NHANES were linked to the National Death Index using common identifiers (e.g. name, age, sex, date of birth, etc.), and positive matches were then examined manually for further verification, while individuals who had no signs of mortality were considered alive at the census measure. CVD-specific mortality was assessed from diseases of the heart, spanning International Classification of Diseases (ICD)-9 and ICD-10 coding (I00–I09, I11, I13, I20–I51).

Statistical analysis
Statistical analyses were performed using Stata, version 12.0 (StataCorp, College Station, TX, USA), and all analyses accounted for the complex survey design employed in the NHANES (analysed in 2015). An adjusted Wald test was used to examine statistical differences for continuous variables (e.g. age), and a design-based likelihood ratio test was used for categorical variables (e.g. sex) (Table 1). To examine the associations between engagement in MSA and all-cause mortality, a weighted Cox proportional hazard model was employed to calculate hazard ratios (HRs) and 95% confidence intervals (CIs), while adjusting for the following covariates (Table 2): age (years; continuous); sex; ethnicity (white/other); education (some college or more/high school or less); self-reported physical activity

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Table 1  Unweighted baseline characteristics, 2003–2006 NHANES (n = 8772).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline point estimates (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alive at follow-up (n = 7915)</td>
<td>Dead at follow-up (n = 857)</td>
</tr>
<tr>
<td></td>
<td>Alive at follow-up (n = 7915)</td>
<td>Dead at follow-up (n = 857)</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>46.6 (46.2–47.0)</td>
<td>72.7 (71.8–73.6)</td>
</tr>
<tr>
<td>Women (%)</td>
<td>52.7 (51.6–53.8)</td>
<td>42.2 (38.9–45.5)</td>
</tr>
<tr>
<td>Non-Hispanic white (%)</td>
<td>50.5 (49.4–51.6)</td>
<td>64.9 (61.7–68.1)</td>
</tr>
<tr>
<td>Some college education (%)</td>
<td>48.9 (47.8–50.0)</td>
<td>33.0 (29.8–36.1)</td>
</tr>
<tr>
<td>Participation in MSA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Engaged in MSA in past 30 days (%)</td>
<td>26.7 (25.8–27.7)</td>
<td>12.9 (10.7–15.2)</td>
</tr>
<tr>
<td>Mean number of MSA sessions in past 30 days</td>
<td>3.85 (3.64–4.06)</td>
<td>2.46 (1.78–3.15)</td>
</tr>
<tr>
<td>Average level of daily physical activity (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sits during the day without walking about very much</td>
<td>21.6 (20.7–22.6)</td>
<td>44.5 (41.2–47.9)</td>
</tr>
<tr>
<td>Stands or walks about a lot during the day, but does not have to carry or lift things often</td>
<td>52.9 (51.8–54.0)</td>
<td>43.9 (40.6–47.3)</td>
</tr>
<tr>
<td>Lifts light loads or climbs stairs or hills often</td>
<td>17.3 (16.4–18.1)</td>
<td>9.1 (7.1–11.0)</td>
</tr>
<tr>
<td>Does heavy work or carries heavy loads</td>
<td>8.0 (7.4–8.6)</td>
<td>2.3 (1.3–3.3)</td>
</tr>
<tr>
<td>Health variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean CRP (mg/dL)</td>
<td>0.45 (0.43–0.47)</td>
<td>0.71 (0.61–0.81)</td>
</tr>
<tr>
<td>Overweight/obese (%)</td>
<td>69.6 (68.6–70.6)</td>
<td>65.2 (62.0–68.4)</td>
</tr>
<tr>
<td>Mean number of comorbidities</td>
<td>0.72 (0.70–0.74)</td>
<td>1.88 (1.78–1.98)</td>
</tr>
</tbody>
</table>

CI: confidence interval; CRP: C-reactive protein; MSA: muscle-strengthening activities; NHANES: National Health and Nutritional Examination Survey. An adjusted Wald test was used to examine statistical differences for continuous variables (e.g. age), and a design-based likelihood ratio test was used for categorical variables (e.g. sex).

Table 2  Weighted Cox proportional hazard model examining the association between engagement in muscle-strengthening activities and all-cause mortality, 2003–2006 NHANES (n = 8772).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total mortality HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSA in past 30 days: Yes versus No</td>
<td>0.77 (0.60–0.98)</td>
<td>0.04</td>
</tr>
<tr>
<td>Covariates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, 1-year increase</td>
<td>1.08 (1.07–1.09)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Female versus male</td>
<td>0.62 (0.52–0.75)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Other versus Non-Hispanic white</td>
<td>1.08 (0.91–1.29)</td>
<td>0.34</td>
</tr>
<tr>
<td>Some college education versus less</td>
<td>0.82 (0.69–0.97)</td>
<td>0.02</td>
</tr>
<tr>
<td>Stands or walks about a lot during the day, but does not have to carry or lift things often versus Sits during the day and does not walk very much</td>
<td>0.50 (0.40–0.63)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Lifts light loads or climbs stairs or hills often versus Sits during the day and does not walk very much</td>
<td>0.38 (0.27–0.54)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Does heavy work or carries heavy loads versus Sits during the day and does not walk about very much</td>
<td>0.50 (0.25–0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Cotinine, 50 ng/mL increase</td>
<td>1.04 (1.02–1.07)</td>
<td>0.001</td>
</tr>
<tr>
<td>C-reactive protein, 1 mg/dL increase</td>
<td>1.08 (1.02–1.15)</td>
<td>0.004</td>
</tr>
<tr>
<td>Overweight/obese versus Not</td>
<td>0.70 (0.59–0.83)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Comorbidities, one comorbidity increase</td>
<td>1.30 (1.22–1.38)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

CI: confidence interval; HR: hazard ratio; MSA: muscle-strengthening activities; NHANES: National Health and Nutritional Examination Survey.

(see Table 2 for categorization); serum cotinine (ng/mL; continuous); serum C-reactive protein (mg/dL; continuous); overweight/obese (body mass index ≥ 25.0 kg/m²); and comorbid illness. With regard to the comorbid illness variable [42,43], participants were classified as having 0–8 of the following physician-diagnosed conditions: arthritis; chronic bronchitis; congestive heart failure; coronary artery disease; emphysema; heart attack; hypertension; and stroke. Additional analyses were computed with several of the morbidities split out as independent covariates, as
opposed to using a morbidity index, and the results were unchanged.

We then computed the same analyses with the addition of the average healthy eating index (AHEI), assessed by interview, included as a binary covariate, with individuals in the lower 60% recorded as not meeting dietary guidelines, and those in the upper 40% recorded as meeting dietary guidelines [44].

**Results**

Table 1 reports the unweighted baseline characteristics of the analysed sample, stratified by those who were alive or dead at follow-up. Compared with those who were alive at follow-up, those who had died were older, more likely to be male, non-Hispanic white, comorbid, less likely to be overweight/obese, had less formal education, had higher concentrations of serum C-reactive protein and were less likely to have participated in MSA within the past 30 days (Table 1).

Table 2 reports the weighted Cox proportional hazard model examining the association between engagement in MSA and all-cause mortality. After adjusting for covariates, those engaging in MSA at baseline had a 23% reduced risk of all-cause mortality (Table 2). Harrell’s C concordance statistic for this model was acceptable (0.87). The test of proportional hazards assumption, using the Schoenfeld residuals, was not violated (P = 0.15).

Fig. 1 illustrates the number of individuals meeting MSA guidelines (18.6%), as well as those not meeting guidelines (81.4%). Of the individuals meeting MSA guidelines, the number of sessions performed within the previous 30-day period were as follows: 8–14 (53.9%); 15–21 (21.1%); and ≥ 22 (25%). Among those not meeting MSA guidelines, 91.6% of individuals performed 0 MSA sessions, while 8.4% performed 1–7 sessions within the prior 30-day period.

Additional analyses were computed to examine whether a dose-response relationship between engagement in MSA and all-cause mortality risk was present. We created a five-category variable, indicating the number of MSA sessions that participants engaged in over the past 30 days: 0 (n = 6541); 1–7 (~1–2 sessions/week, n = 598); 8–14 (~2–3 sessions/week, n = 880); 15–21 (~3–5 sessions/week, n = 344); and ≥ 22 (> 5 sessions/week, n = 409) (Fig. 1). These categories were created to provide an indication of weekly MSA sessions, using the equation ([MSA sessions/30] × 7). Compared with those not engaging in MSA during the past 30 days, and after adjustments for covariates (the same as mentioned previously), the HRs (95% CIs) for the respective groups for all-cause mortality were as follows: 1–7 MSA sessions (HR: 0.72; 95% CI: 0.35–1.49; P = 0.37); 8–14 MSA sessions (HR: 0.70; 95% CI: 0.52–0.94; P = 0.02); 15–21 MSA sessions (HR: 0.86; 95% CI: 0.49–1.50; P = 0.59); and ≥ 22 MSA sessions (HR: 0.86; 95% CI: 0.56–1.34; P = 0.52).

Additional analyses were computed with CVD mortality as the outcome, but these results should be interpreted with caution, as relatively few CVD-specific deaths occurred (n = 192). Results were similar when CVD mortality was the outcome: 1–7 MSA sessions (HR: 1.91; 95% CI: 0.71–5.1; P = 0.18); 8–14 MSA sessions (HR: 0.50; 95% CI: 0.24–1.05; P = 0.06); 15–21 MSA sessions (HR: 0.20; 95% CI: 0.02–1.56; P = 0.12); and ≥ 22 MSA sessions (HR: 1.38; 95% CI: 0.55–3.49; P = 0.47).

Interestingly, with the inclusion of AHEI as a covariate, participation in MSA as a binary variable no longer reduced the risk of premature all-cause mortality significantly (HR: 0.80; 95% CI: 0.61–1.06; P = 0.12). However, even when adjusting for AHEI, the five-category variable we created still demonstrated that only individuals performing between 8–14 MSA sessions over the past 30 days were at a reduced risk of premature all-cause mortality (HR: 0.69; 95% CI: 0.48–0.97; P = 0.03).

**Discussion**

The majority of studies illustrating that muscular strength is associated with a decreased risk of all-cause mortality [3,5–8], along with the beneficial effects of MSA on various chronic diseases [9–23], would lead to the assumption that participation in MSA may help to reduce the risk of all-cause mortality. Interestingly, to our knowledge, only three previous studies have explored the relationship between MSA and all-cause mortality, demonstrating that individuals reporting at least 2 MSA sessions per week were at a small, albeit not statistically significant, reduced risk of all-cause mortality [38–40]. In an extension of these previous findings, we found that participation in MSA was associated with a reduced risk of all-cause mortality (Table 1) and, furthermore, created a five-category variable to tease out the importance of the frequency with which MSA was performed. We found that only individuals engaging in 8–14 MSA sessions within

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the past 30 days (2–3 times per week) were at a reduced risk of all-cause mortality. Despite the inverse relationship between MSA and premature all-cause mortality, only 18.6% of the study population met the ACSM and USDHHS guidelines for MSA (Fig. 1), which was similar to the 17.7% reported previously [36].

The prevalence of individuals (18.6%) not meeting guidelines for MSA (Fig. 1) is alarming, considering the wide range of beneficial effects associated with MSA [9–17]. Of the individuals not meeting established guidelines, only 8.4% performed an insufficient number of MSA (1–7) over the 30-day period, while the other 91.6% did not engage in any MSA. This illustrates that individuals who do not meet MSA guidelines are not doing so because of an inadequate frequency of exercise, but rather a complete absence of participation in MSA (Fig. 1). As a result, strategies not only to help individuals maintain their MSA behaviour, but also to help facilitate the initiation of MSA, are needed. In contrast, the prevalence of individuals meeting guidelines for aerobic-based physical activity (≥ 150 min/week) appears to be about twice as high as those meeting MSA guidelines (34.9% vs. 17.7%), with 33% of individuals not engaging in sufficient physical activity still performing some form of leisure physical activity [40]. Several reasons can be offered as to why this may occur, including, but not limited to, greater accessibility, inclusivity and greater presumed health benefits. Therefore, a more widely recognizable explanation of the beneficial effects of participating in MSA should be made available to the general public, in an attempt to increase adherence to these established guidelines.

The 23% reduced risk of all-cause mortality for individuals participating in MSA can probably be attributed to the various beneficial effects occurring to prevent numerous chronic diseases, as well as potential risks associated with the age-related loss of muscle size and strength, termed sarcopenia [45]. However, there does not appear to be a dose-response relationship between the frequency of MSA and all-cause mortality. In fact, only individuals engaging in an average of 2–3 MSA sessions per week had a reduced risk of all-cause mortality, which is in alignment with the recommendations from the ACSM and USDHHS that MSA be performed 2–3 times per week [1,2]. Interestingly, this opposes that of aerobic-physical activity, with a meta-analysis demonstrating an inverse dose-response relationship between the volumes of physical activity performed and risks of premature mortality [26].

Our analyses suggest that behavioural participation in MSA may be threshold driven, with a plateau occurring at a frequency of 2–3 sessions per week, as this was the only frequency producing a significant reduction in the risk of all-cause mortality. These results may follow a similar pattern to that of muscle strength, in that individuals in the lower tiers for muscle strength appear to be at an increased risk of mortality [3,5–8], yet individuals with high muscle strength do not appear to have a further reduced risk of all-cause mortality compared with individuals with moderate strength levels [5,7]. Therefore, 2–3 sessions per week may provide a sufficiently high volume of exercise to reduce the risk of all-cause mortality, without increasing the acute cardiovascular risks associated with exercise [46–50], which, although rare, may occur in at-risk individuals (e.g. heart attack survivors) [50]. It is also plausible that individuals who adhere strictly to these established guidelines are simply more likely to be compliant with other physician-based recommendations or health-enhancing behavioural guidelines; or, that individuals engaging in 2–3 MSA sessions per week are more likely to maintain that volume of exercise as part of a scheduled routine, whereas individuals engaging in > 5 sessions per week may be less likely to maintain that volume over a prolonged period of time. These possibilities should be investigated in future research. It is of importance to note that, while not statistically significant, all frequencies of participation in MSA attenuated the risk of premature mortality compared with individuals not partaking in any MSA.

Our study was limited by the self-reported nature of the MSA variable used, and therefore may have been subject to individual recall or social desirability bias; however, as previously mentioned, some evidence of the validity of self-reporting of MSA has been demonstrated [38]. Despite this limitation, a major strength of our study included the length of the follow-up period, which averaged 6.7 (0.2) years and extended for as long as 9 years, allowing us to examine the effects of MSA on all-cause mortality over a reasonable length of time. Additionally, the large, representative sample size used in our study allowed for greater generalizability of our results. Finally, we were able to expand on previous studies [40,42,44], by assessing the effect of the frequency of MSA participation on reducing the risks of all-cause mortality.

Conclusions

In a large, representative sample of adults in the USA tracked for an average of 6.7 years, we observed some evidence that individuals engaging in MSA were at a reduced risk of all-cause mortality (and CVD-specific mortality), with the most robust evidence showing that 2–3 MSA sessions per week produced the only statistically significant reduction in all-cause mortality risk. Interestingly, individuals exceeding the established guidelines by performing > 3 MSA sessions per week were no longer at a reduced risk of all-cause mortality. Owing to the low prevalence of individuals meeting established guidelines for participation in MSA, future studies should determine strategies for increasing adherence to these established guidelines.

Disclosure of interest

The authors declare that they have no competing interest.

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Association between muscle-strengthening activities and mortality


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