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Opinion

How much resistance exercise is beneficial for healthy aging and longevity?

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Regular physical activity (PA) promotes healthy aging, and activities aiming to increase muscular strength (i.e., resistance exercise (RE)) are important PA modalities for achieving health benefits. Previous meta-analyses demonstrated that both RE[1] and muscular strength[2] were associated with mortality benefits, even when RE was performed above the PA targets recommended by current guidelines.[1,3]

While optimal volumes of endurance-type exercise (aerobic moderate-to-vigorous PA (MVPA)) to reduce mortality from all causes have been suggested to amount to or even exceed 700 min per week,[4] 3 recent meta-analyses suggest that large amounts of RE may be associated with adverse outcomes.[5−7] Although these analyses demonstrated an overall inverse association between RE and mortality risk from all causes and/or from cardiovascular diseases, diabetes, and cancers, this was only true up to a certain threshold of RE volume per week (i.e., there is a U-shaped dose−response relationship between RE and mortality).[5−7] Should the many individuals engaging in RE volumes exceeding the reported cutoffs for optimal benefits be worried? Critical appraisal of these findings is urgently needed.

1. Recent meta-analyses reporting upper limits of RE volumes

The meta-analysis by Saeidifard et al.[7] comprised 1 randomized controlled trial and 10 cohort studies, and it included healthy and unhealthy (e.g., breast cancer patients during chemotherapy, cancer survivors) participants of both sexes from a broad age range. Overall, RE in this study was associated with a 21% reduction in all-cause mortality; when RE was combined with MVPA, the reduction was 40%. However, mortality benefits were only observed when participants performed no more than 2 RE sessions per week.[7] Momma et al.[6] analyzed 16 cohort studies including adults aged 18 years or older without severe health conditions. They observed a maximum reduction (about 10%−20%) of mortality risk at weekly RE volumes between 30 min and 60 min (which varied depending on specific diseases).[6] The meta-analysis by Shailendra et al.[5] (10 cohort studies including healthy adults aged ≥18 years) showed the lowest mortality risk from all causes (−27%) at a weekly RE volume of no more than 60 min (<10 min/day). Higher RE volumes were again associated with diminishing benefits, reaching zero benefit at around 150 min per week of RE; in fact, weekly RE volumes above 150 min were shown to increase mortality risk.[5] Similarities between these results and those reported by Momma et al.[6] also owe to an overlap of 8 studies that were included in both meta-analyses.

Altogether, these findings are puzzling. No conclusive evidence has been put forth to explain possible pathological mechanisms behind the adverse health effects of such brief or moderate volumes of RE performed by apparently healthy individuals.

2. Potential confounding of reported association between RE and mortality

The authors of these meta-analyses extensively referred to potential confounding.[5−7] For example, the volume of RE is typically recorded (often at only 1 time point) by questions like "What was your approximate time per week during the

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past month spent at weight lifting/strength training?"[8] Self-reported responses do not usually provide information on intensity or the duration of time loaded muscles were under tension. Moreover, information on type and characteristics of RE (i.e., weightlifting or calisthenics, dynamic or static executions, muscle groups used, number of repetitions/sets, *etc*.) is mostly lacking, but these represent key parameters for determining its potential benefits and adverse effects.[9]

Moreover, certain populations performing RE might be characterized by different patterns of everyday life behaviors (e.g., sleeping or dietary habits) compared to those primarily performing MVPA, which could modulate the health outcomes of PA. A large prospective cohort study ($n = 282{,}473$ adults, aged 18−84 years) recently demonstrated that long sleep duration was associated with increased mortality (independent of PA) and the combination of long sleep with either RE or physical inactivity appeared to be synergistic.[10]

3. Benefits of RE and potential pathological mechanisms contributing to the U-shaped relationship between volume of RE and mortality

The beneficial effects of RE are well accepted, including improvements in lean muscle mass and strength, the attenuation of visceral fat, favorable effects on blood pressure, glucose, and lipid metabolism.[1,2,5] Still, despite the consistent results of recent meta-analyses,[5−7] the reasons for the reported U-shaped dose−response relationship between RE and mortality remain largely unexplored.

Suggested pathological mechanisms include incidents due to harmful heart rate and blood pressure responses and/or long-term increase in arterial stiffness.[7] While the former is plausible, since the risk for such events increases with longer exposure time, the latter remains questionable, as recent meta-analyses did not find evidence for RE-related increases in arterial stiffness either in healthy individuals[11] or in persons at risk for cardiovascular disease.[12] However, due to the high heterogeneity found in the meta-analysis done by Ceciliato et al.[11] ($I^2 = 91\%$), their findings should be interpreted with caution. The study demonstrated an increase in arterial stiffness of 13% in studies of high-intensity RE interventions, that is, about 80% of 1-repetition maximum.[11] They argue that the large magnitude of intermittent increases in blood pressure during high-intensity RE, which alters arterial structure due to a decrease of elastin and increase of collagen in arteries, would at least partly explain increased arterial stiffness following RE training.[11] A closer look at the studies reporting an increase in arterial stiffness revealed that this adverse effect was specifically observed in young individuals. However, the levels of arterial stiffening commonly observed following RE in young adults with low baseline levels are likely not high enough to be of clinical relevance.[13] More important might be the risk for adverse cardiovascular events due to the (prolonged and repeated) acute heart rate and blood pressure elevations that occur during RE.

Overall, excessive RE may put a small number of individuals at a higher risk for adverse health outcomes, which is similar to the effect of extreme endurance exercise.[14] This risk may vary with age and sex (e.g., while young subjects may be more susceptible than older ones to arterial stiffness following RE,[13] men are much more likely than women to be injured performing RE[15]) and can increase with inappropriate execution of RE, overconfidence, and/or subtle pre-existing comorbidities.

Although low-to-moderate intensity RE is usually well-tolerated and widely recommended for individuals with and without cardiovascular disease,[16] heart rate and systolic blood pressure values in cardiac patients are higher during low-intensity as compared to high-intensity RE.[17] As low-intensity RE is typically performed at higher volumes than high-intensity RE, vulnerable individuals performing high volumes of low-intensity RE might be at higher mortality risk than previously assumed, which may offer some explanation for the findings of the meta-analyses discussed above.[5−7] Careful assessment and comparison of RE intensity and volume will be fundamental to unraveling this hypothesis.

4. Should I reduce my resistance training?

RE is complementary to aerobic MVPA. It confers major health benefits, particularly for aging people, by improving/maintaining the musculoskeletal functionality that is integral for everyday life. Appropriately individualized RE programs that take place under expert guidance and have adequate progression of volume and intensity along with proper execution of exercises are essential and remain crucial for prevention of the kind of injuries that may contribute to adverse outcomes of over-ambitious RE.[18] All things considered, there is no reason, in our opinion, to reduce or stop well-tolerated RE programs. This recommendation is particularly relevant for the older (weaker) generations (age $\geq$ 75 years) in frailty prevention and treatment programs.[19] Indeed, even small improvements in muscular strength (e.g., handgrip strength[20]) may translate into great benefits in mortality risk reduction in community-dwelling[21] and clinical populations.[22] However, practitioners who suffer from repeated or long-lasting complaints related to RE, particularly those who have any kind of pre-existing diseases and/or are taking medications, should consult with a general practitioner or sports physician.

5. Conclusion and future directions

Complementing MVPA with RE remains a valid recommendation, and future studies are necessary to explore when and for whom high RE volumes may pose health risks. Important tasks for future epidemiological studies include the comprehensive assessment of volume, intensity, and type of RE as well as proper standardization and appropriate consideration of confounders—that is, the impact of age, sex, pre-existing diseases, life-style behaviors like sleeping habits, diet, and overall PA on RE-related health outcomes. Though randomized controlled trials are challenging, they would be the study design of choice to minimize bias and confounding. Wearable technologies and advanced approaches to data analysis provide exciting and novel tools for evaluating the relationship between various types of RE and individual (patho)physiological responses even in large cohort studies. These will also allow for a more detailed assessment of physiological (e.g., cardiovascular) parameter changes following acute and long-term RE, depending on individual vulnerabilities and training characteristics, which could enable the definition of individual upper limits for RE. In addition to all-cause and disease-specific mortality, surrogate endpoints like fitness indices, quality of life, and cardiovascular risk factors should be taken into account. In absence of well-defined, individual upper limits, prevention of insufficient PA—for example, due to fear of the potential risks of too much RE—is key.

Authors' contributions

JB and MB wrote the first draft of the manuscript; BS, GDA, and GPM critically revised the manuscript. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Competing interests

The authors declare that they have no competing interests.

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