Sports Medicine (2019) 49:1309–1315
https://doi.org/10.1007/s40279-019-01131-8

COMMENTARY

Causal Mediation Analysis Could Resolve Whether Training-Induced Increases in Muscle Strength are Mediated by Muscle Hypertrophy

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Published online: 3 June 2019

Abstract

Resistance training increases muscle size (i.e., causes hypertrophy) and muscle strength, particularly in untrained individuals. Hypertrophy is widely believed to be one of the mechanisms (i.e., a mediator) by which resistance training increases strength. However, some researchers have questioned whether training-induced hypertrophy causes increases in strength. One approach to resolving this issue has been to use correlations between training-induced changes in muscle size and strength to infer the effect of hypertrophy on strength. This is problematic because correlations between changes in muscle size and strength may be confounded (i.e., correlation is not causation). Another approach has involved randomizing participants to different volumes of exercise to create different levels of hypertrophy and then comparing the strength increases associated with different levels of hypertrophy. This approach is also problematic because the unit of randomization is exercise volume rather than hypertrophy, and the potential for confounding remains. Thus, a new approach is needed to determine the extent to which hypertrophy increases muscle strength. Here, we introduce resistance training researchers to causal mediation analysis and recommend that it be used to resolve the current debate. Causal mediation analysis potentially provides an unconfounded estimate of the effect of a mediating variable (hypertrophy) on an outcome (strength). This analysis is supplemented by causal maps that help conceptualize research questions and identify potential confounders. In addition to resolving the debate on hypertrophy, causal mediation analysis can be used to answer a host of other questions about mechanisms in the health sciences.

Key Points

The degree to which training-induced increases in muscle strength are mediated by muscle hypertrophy is under debate.

Experimental approaches that have been suggested are unable to resolve this debate. A new approach is needed.

We propose the application of causal mediation analysis to resolve the debate. Causal mediation analysis can provide an unconfounded or minimally biased estimate of the effect of hypertrophy on strength. This approach could also be used to answer other important questions in the health sciences.

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1 Introduction

Resistance training is a form of physical exercise that involves repeated muscle contractions against external resistance. When performed for several weeks in untrained individuals, resistance training usually increases muscle size (i.e., causes hypertrophy) and muscle strength. However, the nature of the relationship between hypertrophy and increased muscle strength with resistance training is a point of debate [1–7].

We believe this debate is misguided because it has been informed by experimental designs and analyses that do not allow conclusions to be made about the causal effect of training-induced hypertrophy on muscle strength. The purpose of this commentary is to introduce resistance training researchers to causal mediation analysis and explain how it can inform the debate on whether and when hypertrophy mediates the increases in muscle strength caused by resistance training.

2 The Debate

The central question in this debate is whether or not training-induced changes in muscle size in untrained individuals *cause* training-induced changes in muscle strength. In other words, researchers want to know whether training-induced changes in strength would have been different if the change in muscle size had, hypothetically, been other than what was observed [8].

In two experiments, Balshaw et al. [1] and Erskine et al. [6] reported moderate correlations between changes in muscle strength and muscle size with resistance training in untrained individuals ($r = 0.46$–0.53). This led them to conclude that hypertrophy "contributes to" increased muscle strength after resistance training [1, 6]. The implication was that changes in muscle size *cause* some of the change in muscle strength after training, although Balshaw et al. [2] have since clarified that they were not implying causation. In our opinion, the association between muscle size and strength would be of little interest if it were not causal.

The conclusions reached by Balshaw et al. [1] and Erskine et al. [6] have been criticized [4, 5, 7]. The main criticism has been that simple correlation analyses cannot be used to determine causation – a point with which we agree. Dankel et al. [5] stated that the best way to determine whether training-induced changes in muscle size cause training-induced improvements in muscle strength is to design a study that produces "differential effects on muscle size based on group membership (i.e., one group increases muscle size and one does not) and observe how this impacts muscle strength".

Recently, Mattocks et al. [7] used this design to investigate the relationship between training-induced changes in muscle size and training-induced changes in muscle strength. Untrained individuals were randomized to two groups. Both groups completed training two times per week for 8 weeks. One performed high-volume resistance training for 8 weeks – a protocol designed to induce hypertrophy. This training involved 4 sets of 8–12 repetitions with loads that permitted volitional failure within this repetition range. The other group "practiced" the maximal strength test. This training involved up to five attempts to lift the heaviest weight for 1 repetition. After 8 weeks, both groups improved muscle strength by similar amounts. However, only the group that performed high-volume exercise experienced hypertrophy. Because both groups improved strength by a similar amount but only the high-volume exercise group experienced hypertrophy, the authors concluded that hypertrophy is likely not a cause of increased strength after resistance training [5, 7] and increases in muscle size and strength after resistance training may be completely separate phenomena [3–5, 7, 9].

3 Debate Continued

We believe three general conclusions can be drawn from the study by Mattocks et al. [7]. First, different volumes of resistance exercise can cause different levels of hypertrophy. Second, different volumes of exercise can cause the same degree of improvement in muscle strength. Third, muscle strength can increase without hypertrophy. However, we do not agree the study's design permits the authors to conclude that muscle hypertrophy does not contribute to improvements in muscle strength.

The two groups in the study performed different training interventions [7]. Thus, the two interventions may have caused improvements in strength through different mechanisms. Clearly, for the group that did not experience hypertrophy, hypertrophy could not have contributed to their strength increase. However, the hypertrophy exhibited by participants in the high-volume exercise group could have contributed to *their* strength increase. In other words, just because strength can increase without hypertrophy does not mean that hypertrophy, when it occurs, does not contribute to improvements in muscle strength.

The fundamental issue in the design of the study that precludes a conclusion about the causative role of hypertrophy on muscle strength is that participants were not randomly assigned a level of hypertrophy. They were assigned a volume of exercise. Hypertrophy was *indirectly* manipulated by exercise volume [7], which is problematic because it leaves the hypertrophy–strength relationship (i.e., mediator–outcome relationship) at risk of confounding [10, 11]. The inability to directly randomize hypertrophy is the central yet unrecognized issue in the current debate.

4 Confounding and Causal Mediation Analysis

Confounding of the mediator–outcome relationship occurs when confounders—which can be thought of as variables that have causal effects on both the mediator (hypertrophy) and the outcome (muscle strength; but see VanderWeele and Shpitser [12] for a more rigorous definition of a confounder)—create a "discrepancy between what we want to assess (the causal effect) and what we actually do assess using statistical methods" [13]. In randomized controlled trials, randomization controls for confounding between the intervention and outcome (i.e., resistance training and muscle strength) and between the intervention and mediator (i.e., resistance training and hypertrophy). However,

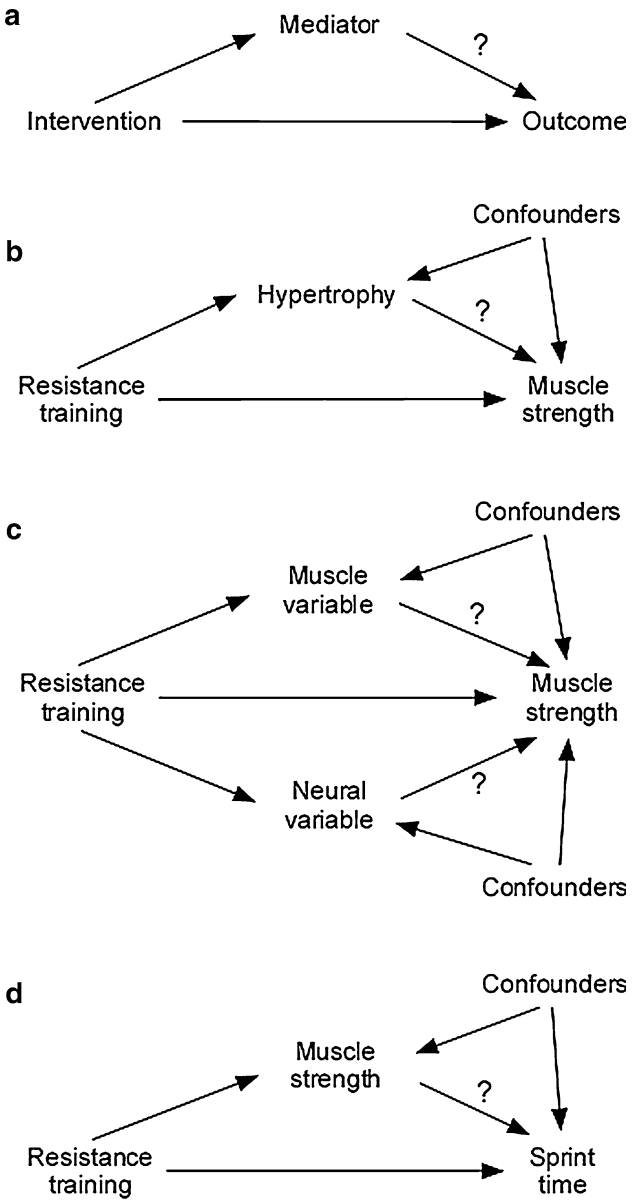

Fig. 1 Directed acyclic graphs (DAGs). **a** This rudimentary DAG depicts the possible causal relationships between an intervention, an outcome, and a mediator. The direction of the arrows illustrates the proposed direction of the causal effects between pairs of variables. **b** This DAG depicts a causal pathway from resistance training to muscle strength, potentially mediated through muscle hypertrophy. Randomization of resistance training permits unbiased estimation of two effects: (1) the effect of resistance training on muscle strength and (2) the effect of resistance training on hypertrophy. However, mediation analysis is needed to determine the indirect effect of the intervention on muscle strength that is mediated through hypertrophy. In a well-conducted randomized trial, there is no confounding of the relationships between resistance training and muscle strength and resistance training and hypertrophy. However, the relationship between hypertrophy and muscle strength remains at risk of confounding, even when resistance training is randomized. Confounders that might influence this relationship include sex; age; previous resistance training experience; presence of a neurological or musculoskeletal impairment; baseline body mass, muscle size, and muscle strength; exercise adherence; and concurrent exercise participation and nutrition and supplement intake. **c** This DAG depicts the two broad physiological and anatomical pathways likely to mediate the effects of resistance training on strength: training could change the muscle (peripheral mechanisms) or the nervous system (central mechanisms). **d** This DAG depicts a causal pathway of improved sprint time from resistance training, putatively mediated through increased muscle strength

randomization does not control for confounding of estimates of the effect of the mediator on the outcome [11] – in this case, the effect of hypertrophy on strength. Thus, exploration of the causative role of hypertrophy on increases in muscle strength with resistance training necessitates control of confounding of the hypertrophy–strength relationship.

Causal mediation analysis seeks to obtain unbiased (unconfounded) estimates of the part of the effect of an intervention that is mediated through a specific variable or pathway. Causal mediation analysis advances earlier approaches to mediation analysis [14], which are rooted in linear structural equation modelling (SEM) and susceptible to confounding [11, 13, 15, 16]. *Causal* mediation analysis is based on a rigorous definition of causal effects, makes assumptions explicit, and may be nonparametric or nonlinear (e.g., curvilinear dose–response relations) [13]. Moreover, causal mediation analysis allows for control of confounding of the mediator–outcome relationship when the appropriate variables are measured, and it can be applied to data from both randomized controlled trials (our focus here) and observational studies. In their recent book, *The Book of Why*, Pearl and Mackenzie [13] describe the history of causal mediation analysis, its philosophical underpinnings, and how the analysis represents a "symbiosis" between counterfactual thinking and causal maps (e.g., directed acyclic graphs [DAGs]).

Traditional approaches to mediation analysis, which have been used in a small number of resistance training studies [17, 18], can sometimes generate the same results as causal mediation analysis. The conditions that must be met to use these earlier approaches to mediation have been discussed by Valeri and VanderWeele [11]. SEMs have also been used in exercise and sports science [19–21]. Discussions on the historical development of SEMs and myths and truths about their use can be found elsewhere [22, 23].

5 Directed Acyclic Graphs (DAGs)

DAGs are a type of path diagram or causal map that informs causal mediation analysis and depicts putative causal pathways between interventions and outcomes. DAGs were first introduced to the field of sports medicine in 2007 [24], but they have not yet been widely adopted. Figure 1a is a rudimentary DAG depicting a hypothetical intervention, mediator, and outcome, and the directions of their relationships.

DAGs help conceptualize research questions. They force scientists to consider and identify potential confounders and mediators for their models. Rigorous rules can be applied to DAGs to identify the variables that must be controlled to reduce confounding [8, 13, 25–31]. We do not discuss these rules in any detail, but they are critical for developing causal models. Moreover, as pointed out by others [32], DAGs will provide the strongest evidence when they arise from pre-registered studies where the potential causal mechanisms, potential confounders, and analysis are specified a priori.

Publicly available software is available to assist in the development and interpretation of DAGs (http://www.dagitty.net) [33]. However, knowledge of the rules and assumptions that underlie causal models is still needed to construct plausible DAGs. Collaboration between exercise scientists and those with expertise in causal mediation analysis is recommended to ensure DAGs and causal models are constructed appropriately, just as collaborations would be recommended for the use of other analysis techniques.

A secondary benefit of developing and publishing DAGs is that they can continue to be modified or built upon by other researchers as new knowledge is discovered.

6 Applying Causal Mediation Analysis and DAGs to the Debate

One approach to conducting causal mediation analysis of the mediating role of hypertrophy on strength would be to randomize participants to receive or not receive a training intervention, measure muscle size and strength of all participants before and after the intervention, and measure potential confounders of the hypertrophy–strength relationship. Then, so long as the assumptions underlying causal mediation analysis are met, one can use an applicable program or macro in Statistical Analysis Software (SAS) [11], Statistical Package for the Social Sciences (SPSS) [11], Stata [34], or R [35] to estimate the direct effect of resistance training on muscle strength and the indirect effect mediated through hypertrophy.

Figure 1b is a DAG that illustrates a causal pathway between a resistance training intervention and muscle strength. Hypertrophy is shown as a potential mediator. We have also depicted confounders in the DAG. Sex is an example of a potential confounder. To the extent that sex has a direct causal effect on both muscle size and strength [36], it is a confounder of the causal relationship between muscle size and strength. However, if the effect of sex on strength is entirely mediated by the effect of sex on muscle size, so that there was no pathway through which sex acts on strength independently of muscle size, then there would be no arrow from sex to strength in Fig. 1b, and sex would not be a confounder. Indeed, some evidence suggests the effect of sex on strength is largely mediated by the effect of sex on muscle size [37]. It is important to note that because a resistance training program cannot change someone's sex to increase their strength, sex is not a mediator of the effect of resistance training on strength. Other variables that might confound the hypertrophy–strength relationship in the context of a resistance training study include age; previous experience with resistance training; presence of a neurological or musculoskeletal impairment; baseline body mass, muscle size, and muscle strength; exercise adherence; concurrent exercise participation; and nutrition and supplement intake. Here, it is also important to note that control for confounding requires that a potential confounder be measured with little or no error. When a confounder is measured with error, regression adjustments for confounding still yield estimates of effects that are subject to residual confounding.

7 Two Broad Causal Pathways: The Muscle and Nervous Systems

The debate examined in the current paper focuses on one potential mediator: muscle hypertrophy. However, resistance training likely improves muscle strength through multiple pathways, and this needs to be considered when developing a causal model. The DAG in Fig. 1c illustrates the two broad physiological and anatomical pathways that likely mediate the relationship between a resistance training intervention and a change in muscle strength. These two pathways are the nervous system and the muscle.

We highlight these two broad pathways for two reasons. First, we want to illustrate that the long-standing debate about the causal roles of neural versus muscle adaptations with resistance training can be depicted with a DAG. Second, we want to point out that many mediators are likely to fall within these two broad categories, and care must be taken when measuring them. Careful measurement is necessary because causal mediation analysis cannot prevent bias from measurement error. For example, causal mediation analysis cannot account for measures of muscle architecture that are invalid due to post-training edema [38, 39] or inconsistent orientation or pressure of ultrasound probes [40]. Causal mediation analysis also cannot account for potential conceptual errors on the part of the investigator. Such errors may include specifying an incorrect theoretical model and thus collecting the wrong data. For example, the researcher may make an error related to the site selected for the muscle measurement or whether an anatomical or physiological cross-sectional area is measured [41, 42].

The nervous system is the other major pathway by which muscle strength may improve after resistance training. Neural adaptations to resistance training must culminate in either (1) enhanced activation (i.e., increased recruitment

or firing frequency) of agonist or synergist motoneurons and/or (2) reduced activation of antagonist motoneurons. Surface electromyography (EMG) and twitch interpolation are commonly used to quantify this neural drive to muscles. A few points on these two methodologies are warranted. First, surface EMG is limited in its capacity to capture neural adaptations with resistance training. It measures the sum of electrical contributions of active motor units during a contraction, but amplitude cancellation at high forces complicates its use as a gold-standard measure of neural drive [43, 44]. If reported, the amplitude of the EMG signal should be normalized to the amplitude of the maximal compound muscle action potential (M_{max}) from the same muscle. This is because training-induced changes in muscle size are likely to alter the number of muscle fibers under the recording surface of the electrodes. In the study by Mattocks et al. [7], surface EMG was *not* normalized to M_{max}. This is problematic because hypertrophy occurred in the participants who performed high-volume exercise but not the participants who performed low-volume exercise. Causal mediation analysis would offer no solution for this methodological issue.

An alternative measure of neural drive to the muscle is voluntary activation from twitch interpolation [45–48]. A number of methodological issues can preclude a valid measure of voluntary activation. These include issues with myograph compliance and sensitivity, stimulation location and intensity, and the resting twitch [46]. Awareness of these potential issues is necessary to acquire a valid measure of voluntary activation to enter into a causal analysis. A number of reviews provide guidance on how to best measure voluntary activation [45–48].

8 Additional Points on Causal Mediation Analysis

Our primary purpose has been to introduce resistance training researchers to causal mediation analysis and explain how it may help resolve a current debate in the literature. However, challenges exist in using the technique. First, estimating direct and indirect effects is only valid when certain assumptions hold true. We have not discussed these scenarios with respect to causal mediation analysis in any detail, but examples include when the intervention affects a confounder of the mediator–outcome relationship [49] and when mediators interact [31, 50]. Second, causal models are developed using existing knowledge. Thus, the causal network implied by a DAG may not be known at the time of a study. This, however, does not mean researchers should avoid trying to identify confounders or avoid developing causal models. As Shrier and Platt [30] explain, "Not using the causal approach because of uncertainty on which is the correct DAG simply means that one is allowing chance rather than rational deliberation to make the choice among the different causal diagrams."

Also, with randomized controlled trials of resistance training, some confounders can be controlled by the study's inclusion and exclusion criteria. Potential confounders such as sex and resistance training status can be controlled by recruiting only one sex or only those with a given level of resistance training experience. In the initial stages of identifying a causal mechanism, a more homogenous sample (e.g., monozygotic twins) may be desirable because it will usually (but not always) reduce the influence of potential confounders.

Finally, we acknowledge that attempts to use causal mediation analysis to answer questions in the health science literature have been limited. Whittle et al. [51] recently used the technique to investigate the mechanisms by which a psychosocial intervention reduced disability from back pain. Their paper involved an explicit step-by-step analysis of data from a randomized trial. They developed a DAG; declared the primary outcome (disability score) and mediators (pain catastrophizing, fear-avoidance beliefs, distress, and physician's advice); identified potential confounders (age, sex, and baseline measures); used linear models of the effect of treatment allocation on potential mediators to determine which mediators to include in the causal mediation analysis; and performed causal mediation analysis to estimate the causal effects of the mediators. The unadjusted analysis suggested that fear-avoidance beliefs mediated the relationship between the intervention and disability score. However, when there was adjustment for confounding from baseline scores of disability and fear-avoidance beliefs, the mediating effect of fear-avoidance beliefs disappeared, suggesting the effects of the intervention were not mediated by changing fear-avoidance beliefs.

9 Conclusion

The role that muscle hypertrophy plays in increasing muscle strength after resistance training in previously untrained individuals is still unclear. Studies by Balshaw et al. [1] and Erskine et al. [6] demonstrated a moderate correlation between hypertrophy and training-induced increases in strength. Thus, muscle size warrants consideration as a mediator of the causal pathway between resistance training and muscle strength. However, the relationship between training-induced hypertrophy and strength is likely confounded by other variables, so the crude association might not be purely causal.

Studies by Mattocks et al. [7] and others [52–54] have indicated that muscle strength can increase without a change in muscle thickness. However, the observation of similar increases in strength in participants randomized

to interventions that involve different volumes of exercise [7] does not rule out the possibility of a causal influence of hypertrophy on strength, because volume of exercise rather than hypertrophy was the unit of randomization. Consequently, in such experimental designs, the hypertrophy–strength relationship is still at risk of confounding.

Causal mediation analysis has the potential to provide an unbiased estimate of the size of an effect of an intervention on an outcome mediated through a specific variable. This analysis may help to clarify whether training-induced changes in muscle size contribute to increased muscle strength and whether different exercise prescriptions alter the degree to which hypertrophy mediates the increase in strength from resistance training. Moreover, causal mediation analysis has the potential to be used to clarify a host of other questions in exercise science, such as whether training-induced changes in muscle strength cause improvements in functional performance (e.g., Fig. 1d).

Compliance with Ethical Standards

Funding James Nuzzo and Robert Herbert are supported by the National Health Medical Research Council of Australia. Harrison Finn is supported by an Australian Postgraduate Award.

Conflict of Interest James Nuzzo, Harrison Finn, and Robert Herbert have no conflicts of interest that are directly relevant to the content of this article.

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