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A Nuanced Look at Statins

A note from the authors: In this month's article we put together a review of the cholesterol-lowering medications called statins. We will look at what statins do, how well they reduce the risk of cardiovascular disease, the role of lifestyle changes in lowering blood cholesterol levels, and much, much more. We'll be back next month to our normal reviews of single articles.

Key Points:

1. Statins reduce the concentration of circulating lipoproteins in the blood (e.g. low-density lipoprotein) that, when chronically elevated, increase the risk of atherosclerotic cardiovascular disease (ASCVD). Lowering blood levels of these lipoproteins reduces risk of atherosclerotic cardiovascular disease.
2. Individuals at elevated risk of ASCVD (e.g. heart attack, stroke, etc.) may require a greater reduction in lipoprotein levels than what can be accomplished by lifestyle changes like diet and exercise alone.
3. A substantial proportion of apparent statin intolerance (i.e., side effects) appear to be explained by a nocebo-type effect. Unfortunately, this results in many people who would otherwise have a significant reduction in risk of cardiovascular disease being undertreated or untreated altogether.

Introduction

Statins are the most widely prescribed class of medications in the United States. In 1987, lovastatin was the first statin approved for commercial use. Since then, tens of millions of Americans have been treated with this class of medications (Harrington 2017) in order to reduce blood lipid levels. Statins work by inhibiting a critical enzyme involved in cholesterol synthesis called HMG-CoA reductase, thereby reducing intracellular cholesterol production. The decrease in intracellular free cholesterol triggers the up-regulation of low-density lipoprotein receptors (LDL-R) on the cell surface, which ultimately remove circulating LDL particles (LDL-P) from the blood (Conde 1996 and Arad 1990). However, they have been met with heavy skepticism and increasing controversy regarding their effectiveness and potential risks for adverse effects, and this piece will aim to clarify these issues.

Lipoproteins & Blood Cholesterol

Lipoproteins are particles comprised of both lipid and protein components that serve to transport various lipid and fat-soluble molecules through the aqueous bloodstream. To further complicate things, there are numerous classes and subclasses of lipoproteins. Lipoproteins are broadly classified by their "density", i.e., their ratio of protein to lipid content. They include the categories of high-density lipoprotein (HDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL), and chylomicrons (or "ultra" low density lipoproteins), and each of these categories contain subclasses of various lipoprotein species.

Various surface proteins -- known as *apolipoproteins* -- are involved in mediating specific lipoprotein functions. The totality of the evidence strongly implicates lipoproteins containing apolipoprotein B (*apoB*) as the causative factor in atherosclerotic cardiovascular disease (ASCVD) (Ference 2017). Atherosclerosis can involve the arteries supplying the heart, brain, organs, and other peripheral tissues, and increases the risk of acute coronary syndromes (e.g., heart attacks), cerebrovascular events (e.g., stroke), symptomatic peripheral arterial disease (PAD), and many others (NCEP 1988, Romm 1991, Manninen 1992, Adult Treatment Panel II 1993).

At this point it is important to note that these lipoprotein particles are NOT the same thing as cholesterol; they are the circulating particles that *carry* cholesterol and other lipid-based substances including fat-soluble vitamins, for example. The total mass of cholesterol carried on LDL particles is routinely measured as LDL-C on the standard lipid panel. This is a cheaper and more easily accessible -- though imperfect -- proxy measurement for total LDL particle concentration (LDL-P). It actually turns out that the strongest correlate for cardiovascular risk based off of the standard lipid panel alone (i.e., without specifically measuring particle concentrations, apolipoprotein B levels, or other more advanced testing) is the ***non-HDL cholesterol*** concentration, i.e., total cholesterol minus HDL cholesterol.

Atherosclerotic Cardiovascular Disease (ASCVD)

Evidence that high levels of these atherogenic apoB-containing lipoproteins (i.e., VLDL, IDL, LDL, and chylomicron particles) contribute to ASCVD comes from several sources: animal models, literature on individuals with genetic forms of hypercholesterolemia, epidemiological studies, mendelian randomization studies, genome-wide association studies, and controlled trials (Ference 2018, Ference 2017). At this point, we have over 200 studies with over 2 million participants with over 20 million person-years of follow up, and over

150,000 cardiovascular events demonstrating dose-dependent, log-linear association with absolute magnitude of vascular exposure to LDL and risk of ASCVD. Furthermore, we have over 30 randomized controlled trials with over 200,000 participants and 30,000 ASCVD events evaluating therapies designed to lower LDL particle concentrations showing a reduction in ASCVD event rates in proportional to the absolute reduction in blood LDL levels.

Historical data from U.S. population studies (Stamler 1986, Kannel 1971) suggest that optimal total blood cholesterol levels are about 150 mg/dL, which corresponds to an LDL-cholesterol level of about 100 mg/dL. As we'd expect, adult populations with cholesterol concentrations in this range manifest the lowest rates of ASCVD (Lawes 2004) -- however, it should be noted that cardiovascular disease is a complex pathophysiologic process where elevated blood lipids are not the *only* risk factor (Yusuf 2004), so it is common to find exceptions to these numbers as well. So while the LDL-cholesterol goal of 100 mg/dL is supported by the 2016 European Society of Cardiology guidelines for primary prevention of ASCVD, this isn't a universal rule and it gives us a chance to discuss the differences between primary and secondary prevention as well as the concept of risk reduction (Catapano 2016).

ASCVD Risk Reduction

Primary prevention of clinical ASCVD events (i.e., acute coronary syndromes, stroke, etc.) focuses on preventing the events from happening in the first place by targeting known risk factors for suffering a cardiovascular event. Thus, risk reduction in this context refers to how an intervention changes the probability of a first cardiovascular event from occurring. In order to estimate the risk of a cardiovascular event for a given individual, current guidelines recommend using a validated model such as the Pooled Cohort Equations (link) or Framingham model, which combines risk factors like age, sex, race, smoking status, presence of diabetes, cholesterol levels, and blood pressure and formulates a 10-year risk score given as a percentage. This score represents the risk of a first cardiovascular event in the next 10 years and is used to help make clinical decisions such as initiating statin therapy, based on risks and benefits of doing so for a particular individual.

The following are two patient examples for which the decision to start statin therapy may differ despite both patients having the same baseline LDL-C:

- A 45-year-old non-smoking woman with normal blood pressure and an LDL cholesterol of 180 mg/dL and a high-density lipoprotein cholesterol (HDL-C) of 40

mg/dL has an estimated 10-year risk of a cardiovascular event of approximately 1%. Given that statins generally confer a 20-30% relative risk reduction, this patient's risk could be reduced by a total of about 0.2 to 0.3 percentage points if she were treated with a statin daily for 10 years -- a trivial amount without clinical significance.

- A 60-year-old non-smoking man with normal blood pressure and an LDL-C of 180 mg/dL and an HDL-C of 40 mg/dL has an estimated 10-year risk of a cardiovascular event of approximately 12%. Use of a statin would reduce this risk by 3 to 4 points, down to approximately 8 to 9 percent -- representing a much more substantial risk reduction correlating to a number needed to treat (NNT) of approximately 25-33 patients to prevent one event.

The example above illustrates how a different baseline risk influences the potential for risk reduction by any intervention, including statins. With respect to primary prevention, the current guidelines stratify individuals into four different groups based on their 10-year ASCVD risk score:

- <5% or "Low Risk" should emphasize **lifestyle changes** to address risk factors, and these changes should also be recommended to **all subsequent higher-risk groups as well**.
- 5%-7.4% or "Borderline Risk" describes about **101 million adults** in the United States age 40 to 79 years who do not have cardiovascular disease. These individuals should be evaluated for ASCVD "risk enhancers" such as family history of premature ASCVD, elevated LDL > 160 mg/dL, chronic kidney disease, and other disease states. If present, these additional risk factors may favor initiation of statin therapy depending on the risk / benefit assessment.
- 7.5%-20% or "Intermediate Risk" describes about **33 million adults** in the United States who should also be assessed for risk enhancers and additional risk factors to determine if they're likely to benefit from a pharmaceutical intervention. If so, it is recommended that the LDL cholesterol should be reduced by 30-49%.
- >20% or "High Risk" are individuals where statins have a high potential for reducing risk and it is recommended that LDL cholesterol be reduced by >50% based on high-quality evidence.

It is important to note that the "risk discussion" occurring between patient and clinician reviews any cardiovascular *risk enhancers* that patient may have, the risks of any proposed interventions, and the expected benefits of the proposed interventions. *This expected benefit is directly related to the individual's baseline risk*, which can be

estimated using the current 10-year ASCVD risk calculator and assessing for other risk enhancers.

In individuals whose baseline risk is estimated to be very low, the benefits of statin therapy may indeed *not* outweigh the risk of adverse events, and statins would therefore not be recommended in this situation. Conversely, current guidelines recommend that individuals with a 10-year ASCVD risk of >10% be considered for initiation of statin therapy in addition to lifestyle modifications, as the risk / benefit balance in this cohort is more favorable. However, it should be noted based on the Cholesterol Treatment Trialists meta-analysis of 26 clinical trials and 170,000 patients, that treating **any** level of LDL cholesterol with statins shows at least *some* relative benefit with regards to reducing ASCVD risk (Baigent 2010). We aren't suggesting this, however, as these sorts of data points have led to ridiculous, overly cavalier comments about "putting statins in the water".

Finally, with respect to *non-cardiovascular* benefits of statins, He et al. performed an umbrella review of meta-analyses on the topic and found no convincing evidence of an association between statins and improvements in most non-cardiovascular disease outcomes (He 2018), so we generally do not recommend their use for non-cardiovascular conditions.

Statin risks

With respect to the risks of therapy, the commonly cited serious adverse events from long-term statin treatment include myopathy (muscle damage as evidenced by substantial elevations in blood levels of creatine kinase) or overt rhabdomyolysis, new-onset Type 2 Diabetes, and, potentially, hemorrhagic stroke (Collins 2016). While these are all obviously undesirable adverse effects, the rate at which they happen is quite low.

The incidence of simple muscle *pain* (i.e., myalgias) *without* objective evidence of muscle damage (i.e., myopathy) in statin users is a very interesting topic, as randomized placebo-controlled trials suggest that these symptoms are often misattributed to statins. In a blinded, randomized-controlled trial among patients who were considered to be **"statin intolerant"** due to a history of muscle pain from statins, muscle pain was reported in 25% of all subjects, *regardless* of whether they were receiving the statin or placebo. This is interesting because all (or at least a higher percentage) of the subjects getting the statin should have reported muscle pain if truly statin intolerant, and none (or a lower percentage) of the folks getting the placebo should have experienced muscle pain (Moriarty 2015, Moriarity 2015).

This is an example of the *nocebo effect*, where patients with *expectations* of adverse effects are more likely to experience them, and helps to explain the differences between rates of "statin intolerance" due to muscle pain in the community (8-12% in the US) compared to the rate observed in blinded, randomized-controlled trials (~5%, with no difference between those getting statins or placebo) (Tolbert 2016). What's even more interesting is that in English-speaking countries there are greater amounts of websites returned from a Google search on statin intolerance and this is itself strongly correlated (r = 0.868) with higher rates of statin intolerance (Khan 2018).

Finally, data from the cross-sectional Understanding Statin use in America and Gaps in Patient Education (USAGE) study suggests that muscle symptoms may occur in up to 29% of patients initiated on statin therapy and may be an important driver of statin discontinuation, statin switching, or other statin non-adherence (Wei. 2013). Given that there are large socio-cultural inputs constantly influencing patient's expectations, we should make sure that information being published on social media platforms by those in a position of perceived authority is accurate to ensure that we're not harming individuals who may stand to benefit from statin therapy. Additionally, simple social learning via peer-to-peer conversations about individual experiences may have similar harmful impacts via nocebo-type mechanisms.

In terms of real risk, if we took 10,000 patients with a history of cardiovascular disease treated with statins for 5 years, we'd predict about 5 total cases of myopathy, 50-100 new cases of diabetes and 5-10 hemorrhagic strokes (Chou 2016). Conversely, in those same 10,000 patients with pre-existing cardiovascular disease we would *prevent major vascular events in about 1,000 patients* over those 5 years (Chou 2016). If the patients didn't have any pre-existing vascular disease, we'd predict statin therapy to prevent a major vascular event from occurring in about 500 patients, with increasing benefits seen the longer therapy is continued (Collins 2016).

What About Lifestyle Interventions Alone?

Statin critics often assume that medical professionals fail to appreciate or recommend lifestyle interventions for managing cardiovascular risk, despite the strong recommendation for implementing lifestyle modifications at all levels of risk in all official clinical practical guidelines. Lifestyle modifications centering around exercise, diet, and weight loss have indeed been shown to significantly reduce ASCVD risk by improving cholesterol levels, blood pressure, preventing diabetes, and many other mechanisms.

That being said, sometimes lifestyle changes aren't effective enough to *maximally* reduce the risk of a cardiovascular event. Additionally, patients may not be able to adequately comply to the lifestyle interventions for numerous reasons ranging from genetic predispositions to other complex psychosocial factors such as socioeconomic status and mental health status, among others. Regardless, it's worth discussing what kind of benefits can be expected from diet and exercise and reconcile them with the target risk factor reductions based on the current evidence base.

To begin, the lay public generally considers obesity to be associated with cardiovascular disease, but the data are complicated on this topic. For instance, when we look at longitudinal data from young adults gaining weight in the CARDIA study, we see that dyslipidemia (defined as low HDL cholesterol and high triglycerides) is the first risk factor for ASCVD to appear over the subsequent 20 years, occurring **before** obesity, hypercholesterolemia, hypertension, or diabetes (Paynter 2015). Additionally, dyslipidemia is the *only* risk factor to occur first and be followed by clustering of the other risk factors more often than expected.

The relationship between BMI and circulating lipoproteins is also nuanced. For example, The Framingham Heart study showed an increase in HDL cholesterol and a decrease in triglycerides over 10 years in 1,666 subjects whose BMI increased during the same time frame (Ingelsson 2009). While LDL cholesterol levels are a major risk factor for ASCVD, elevated BMI doesn't necessarily have a direct effect on circulating LDL cholesterol levels, and elevations in LDL cholesterol as well as ASCVD can occur in patients with and without obesity (Garrison 1980). All this is to say that while excess body fat can certainly contribute to elevated LDL cholesterol and other risk factors for ASCVD, it isn't universally true, and we may need to use additional interventions (like statins) in order to reduce risk in patients when it is deemed appropriate.

Nevertheless, dietary interventions and weight loss can reduce risk of ASCVD by improving cholesterol levels in many patient populations. Regarding specific dietary interventions, a brief overview of the representative literature suggests that dietary sugars and refined carbohydrates should be minimized (Welsh 2010), increasing dietary fiber tends to lower triglycerides and LDL cholesterol (Erkkila 2006, Ylonen 2003, Anderson 2004), heavy alcohol intake should be avoided (Feinman 1999), dietary trans fats should be eliminated entirely (Kreisberg 2003, Mozaffarian 2010), reducing saturated fat intake to <10% of total daily calories is useful for decreasing LDL cholesterol (Eckel 2013) and cardiovascular risk provided those calories are not replaced with refined carbohydrates (Siri-Tarino 2010, Hooper 2015, Li 2015).

With respect to weight loss, a brief overview of the representative literature suggests that weight loss has a beneficial effect on lipids and lipoproteins (Bays 2013, Miller 2011, Viljoen 2012, Pasanisi 2001, Van Gaal 2005). Weight loss of 5 to 10% has been shown to produce a 20% decrease in triglycerides, a 15% reduction in LDL cholesterol, and an 8 to 10% increase in HDL cholesterol (Nordmann 2006). This "LDL cholesterol" effect was confirmed by a recent study that showed good adherence to nearly any LDL-lowering diet will reduce LDL cholesterol by 10% to >15% (Chiavaroli 2018).

It is important to draw the reader's attention to the data suggesting dietary interventions tend to reduce LDL cholesterol by 10-15%, whereas the current cholesterol guidelines recommend **much greater** LDL reductions for both primary and secondary prevention of ASCVD. For primary prevention of ASCVD in intermediate and high risk individuals, the American Heart Association guidelines recommends 30-49% and >50% LDL reduction, respectively (Grundy 2018). For secondary prevention of ASCVD, these same guidelines recommend a 50% reduction or more in LDL cholesterol in most cases.

While greater degrees of weight loss can achieve progressive improvements in dyslipidemia (Wing 2011), it seems irresponsible to suggest that statins are of no (or minimal) benefit for primary or secondary prevention of ASCVD.

Conclusions

Thankfully, there is an abundance of evidence from well-designed randomized controlled trials and meta-analyses suggesting that the use of statins to reduce blood lipid levels (and subsequently reduce ASCVD risk) is effective for primary prevention of cardiovascular events. A brief overview of the representative literature shows that statins can reduce the incidence of nonfatal heart attacks (Shepard 1995), fatal heart attacks and sudden cardiac death (Vallejo-Vaz 2017 and Ridker 2008), death from cardiovascular disease and nonfatal stroke (Yusuf 2016) in those who do not have pre-existing cardiac disease.

In contrast to primary prevention, *secondary* prevention focuses on interventions that reduce ASCVD events from happening again. Presently, the data on statins are even stronger for secondary prevention of cardiovascular events in those with preexisting ASCVD. Clinical ASCVD includes things like history of acute coronary syndrome, history of coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), peripheral artery disease (PAD) including aortic aneurysm, and other disease states. Furthermore, randomized controlled trials of lipid-lowering therapy in high-risk patients confirm that reducing blood lipid levels produces massive reductions in ASCVD

and supports the general principle that “lower is better” with respect to non-HDL cholesterol (Boekholdt 2014, Cannon 2015, Sabatine 2017).

Again, the overwhelming majority of available literature on the use of statins for secondary prevention of ASCVD suggests a favorable risk:benefit ratio. Five trials, one large meta-analysis (Baigent 2010 and Collins 2016) and 4 RCTs (Amarenco 2006, Athyros 2002, Kjekshus 2007, and The Lipid Study Group 1998) show a ~15% reduction in major ASCVD events on average when LDL-C is reduced by 50% or more due to either high-intensity statin therapy or moderate-intensity statin therapy in combination with other lipid lowering therapy.

With that information as our foundation, I agree with the 2018 American Heart Association /American College of Cardiology guidelines for statin consideration in those with elevated risk of ASCVD. Briefly, those who are most likely to benefit from statin therapy include:

- Individuals with a history of clinical atherosclerotic cardiovascular disease (ASCVD)
- Individuals with LDL cholesterol >190 mg/dL
- Individuals with type 2 diabetes and age between 40 and 75 years with LDL-C between 70 to 189 mg/dL
- Individuals with an estimated 10-year risk of ASCVD > 7.5% and age 40 to 75 years
- Others who may be eligible for statin therapy include those ages 0-19 years old with familial hypercholesterolemia (FH), as well as individuals aged 20-29 with family history of premature AVCSD and LDL cholesterol > 160 mg/dL.

Collectively, the contributing organizations have reviewed the relevant evidence base to date and I cannot disagree with them in good faith. Nevertheless, I frequently hear that people have, “done their own research” and come to their own contrary conclusions with respect to the role of statins in preventing cardiovascular events. I find this sentiment to usually mean someone has spent the better part of an hour reading someone else’s opinion on the topic and adopting it as their own. I also find it strange that an individual with no expertise in clinical medicine, epidemiology, physiology, biostatistics, or public health would think themselves capable of identifying and reviewing thousands of research articles to come up with “their own conclusions”.

Even if one person *did* possess expertise in all those fields, they wouldn’t be able to do a review of this magnitude alone. Rather, they’d have to rely on a team of experts that collectively could perform such a task and then collectively come to a general

consensus. In sum, I don't think it's reasonable to reject the guidelines or guidelines like them without an army of trained experts who, after a thorough review of the existing scientific literature, have come to a different conclusion that they have published in a reputable journal for other scientists to consider. Those who reject the current science are, at best, misguided, or worse, doing active harm in the community - especially if they happen to have a large soapbox to deliver their narratives to people who are likely to be influenced and either reject therapies that may benefit them, or experience nocebo-type effects from the therapies leading to non-adherence.

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Do biological sex and age reliably affect training responsiveness?

Heterogeneity in resistance training-induced muscle strength and mass responses in men and women of different ages by Ahtiainen et al. 2016.

Key Points:

1. This study showed that among untrained adults completing a 20-24 week standardized resistance training program, relative increases in 1RM were greater in females (~24%) compared to males (~19%), but showed no difference in relative strength increase across age within the sexes (<45 years vs. 45-60 years vs. >60 years). An approximate 5% increase in muscle size compared to baseline was observed on average, with no significant differences by sex or age.
2. Large inter-individual variation was observed in training response, with relative changes in 1RM varying from -8% to +60% in the training group, and relative changes in muscle size varying from -11% to +30% in the training group.
3. These findings suggest that sex and age do not drive the inter-individual variation in training response in a categorical fashion, and should thus not be used to predict or set expectations regarding training responsiveness prior to initiating resistance training.

Introduction

We are increasingly appreciating the wide range of inter-individual variability in responses to physical training interventions. However, significant controversy and confusion remains regarding whether (or to what degree) this responsiveness has inherent variability across demographic cohorts.

In other words, it is generally accepted that there will be a range of responses observed among a cohort of fifty 20 year old men performing the same program. But if we look across cohorts, do men always respond better to training than women? Do “old” people always respond more poorly to training than “young” people? Do the proportions of apparent “non-responders” vary between these different demographics?

Purpose

This study set out to examine the inter-individual variation among male and female subjects of different ages in response to a standardized resistance training program.

Subjects

A total of 359 healthy, untrained, Caucasian volunteers from ten resistance training studies performed by the same research group between the years 1996 - 2011. This population included 287 adults (men, *n* = 183; women, *n* = 104) who were assigned to "training" groups in these studies, and 72 adults (men, *n* = 53; women, *n* = 19) who were assigned to "control" groups. Ages ranged from 19 to 78 years.

Methods

Subjects assigned to the training groups all participated in a 20-24 week periodized resistance training (RT) program designed to increase muscle size and strength in accordance with American College of Sports Medicine recommendations. The RT program was nearly identical across all ten studies and involved two days per week of full-body training. Each training session involved 7-10 exercises of single- and multi-joint exercises performed through a full range of motion under supervision. The start of the program began with sets of 12-20 repetitions in the 40-60% 1RM range, then progressed to sets of 5-12 repetitions in the 60-80% 1RM range, and finished with sets of 5-8 repetitions up to 85% 1RM by the 20-24 week time point. Subjects also had a minimum of two days rest in between sessions.

The authors write that "*All training sessions were supervised by the research team to ensure that proper techniques and high loading effort were used in each exercise*." Subjects were also required to complete a minimum of 90% of training sessions in order to be included for analysis.

In contrast, control groups were specifically instructed to *avoid* resistance training during the study period, but to otherwise "*continue their normal low-frequency and low-intensity recreational physical activities".*

Researchers obtained measurements of quadriceps muscle size and leg strength in all subjects prior to and after the completion of training (with at least two days' rest prior to measurement). Depending on the methods available at the time, different techniques

were used to measure muscle size. Ultimately, measurements of 1) quadriceps cross-sectional area by ultrasound (US) or magnetic resonance imaging (MRI), 2) vastus lateralis thickness by US, or 3) overall leg lean mass by dual X-ray absorptiometry (DXA) were included for analysis.

Muscle strength was assessed on the same horizontal leg press machine, using a 1-repetition maximum concentric effort. Strength data were available for 283 out of 287 subjects in the training group, and for 66 out of 78 subjects from the control group.

Findings

Muscle strength was assessed via 1-repetition maximum performance on the same horizontal leg press machine across all studies — though this was a different machine than the one used for the training program in order to reduce confounding by learning effects specific to the machine used in training.

	Age (years, mean (SD))	1RM PRE (kg, mean (SD))	1RM post (kg, mean (SD))	1RM/body mass (PRE)	1RM/body mass (POST)
Men < 45 (n=61)	31.2 (7.3)	169.3 (29.5)	200.5* (32.2)	2.2 (0.4)	2.6* (0.4)
Men 45-60 (n=55)	53.8 (5.0)	161.7 (29.0)	192.2* (32.2)	2.0 (0.3)	2.4* (0.4)
Men > 60 (n=67)	66.1 (4.0)	140.4 (28.3)	167.0* (34.6)	1.8 (0.3)	2.1* (0.4)
Men control (n=53)	49.8 (16.9)	155.1 (28.3)	161.7* (29.5)	2.0 (0.4)	2.0* (0.5)

	Age (years, mean (SD))	1RM pre (kg, mean (SD))	1RM post (kg, mean (SD))	1RM/body mass (PRE)	1RM/body mass (POST)
Women < 45 (n=27)	38.7 (4.6)	107.1 (17.8)	135.2* (24.2)	1.7 (0.3)	2.1* (0.4)
Women 45-60 (n=41)	53.0 (4.5)	105.5 (21.7)	126.3* (27.4)	1.6 (0.3)	1.9* (0.4)
Women > 60 (n=36)	65.2 (3.1)	93.6 (18.2)	117.9* (21.2)	1.4 (0.3)	1.7* (0.3)
Women control (n=19)	52.3 (7.4)	91.6 (12.1)	92.8 (12.8)	1.4 (0.1)	1.4 (0.1)

* $p < 0.05$ compared to the value measured pre-training.

Table 1 shows the average age of each cohort (for further baseline characteristics such as height, weight, and BMI, see table 1 in the paper) as well as pre- and post-training leg press 1RM measurements, as well as ratios of 1RM adjusted for body mass. On average, younger cohorts had higher absolute 1RMs and 1RM/body mass ratios at baseline (i.e., *pre-training*) compared to older cohorts.

	Relative 1RM increase pre-to-post (%)	Relative muscle size increase pre-to-post (%)
Men	**19.4 +/- 9.5%**	**5.1 +/- 5.9**
<45	19.0 +/- 8.6	5.5 +/- 5.6
45-60	19.4 +/- 9.0	5.2 +/- 5.7
>60	19.7 +/- 10.8	4.7 +/- 6.4
Women	**24.2* +/- 13.8**	**4.2 +/- 6.3**
<45	26.7 +/- 13.9	3.3 +/- 8.6
45-60	20.0 +/- 12.7	4.9 +/- 4.6
>60	27.0 +/- 14.1	4.1 +/- 5.9

Table 2 shows relative changes in strength and muscle size outcomes. See attached Figure for graphical representation of these data. * indicates significant difference

Strength Outcomes: The *relative* increase in 1RM performance was greater in women (24.2 +/- 13.8%) compared to men (19.4 +/- 9.5%). Most men improved between 10% and 20% from baseline, while most women improved between 20% and 30% from baseline. Subgroup analysis showed no significant interactions between sex group, age group, or sex x age group with respect to 1RM strength responses. Relative changes in 1RM varied from -8% to +60% in the training group, compared to -10% to +18% in the control (non-training) group.

Hypertrophy Outcomes: The *relative* increase in muscle size was 5.1% +/- 5.9% among men and 4.2% +/- 6.3% among women, with no statistically significant difference between groups (p=0.21). Subgroup analysis showed no significant interactions between sex group, age group, or sex x age group and muscle size responses. Relative changes in muscle size varied from -11% to +30% in the training group, and from -11% to +17% in the control (non-training) group. Of note, 71% of all trainees showed responses between 0% and 10%.

Results also indicated a weak, but significant, correlation between increases in muscle size and increases in muscle strength (r = 0.157, p = <0.01). [*Note*: This particular finding will not be a focus of this review, but it is a finding that has been observed elsewhere, particularly among beginner trainees, and is attributed to neurological improvements (e.g., motor unit recruitment and coordination, movement skill, etc.) in the early stages of training.]

A total of 35 subjects were labeled as “high responders”, defined as a greater than 1-standard deviation increase compared to the mean. Of these, fifteen subjects (5 men and 10 women) were in the highest quintile of training responses, with >9.1% increases

in muscle size and >30.3% increases in muscle strength. Conversely, fifteen other subjects were in the lowest quintile of training responses, with <0.6% increases in muscle size and <11.7% increase in muscle strength. A total of 9 subjects were defined as low responders for both muscle mass and strength, with one man and one woman responding *negatively* in both parameters.

Strengths & Weaknesses

There are several notable strengths of this study. First is the relatively large number of untrained subjects included for study and a fairly standardized training intervention across all groups. A particular strength is the inclusion of a relatively large non-training control group. This allows for a more accurate interpretation of the *training group's outcomes*, because we can control for confounders like measurement error, natural biological variation (e.g., day-to-day differences in 1RM performance), and other methodological issues influencing observed outcomes that might lead us to over- or under-estimate outcomes.

The most substantial limitation of the current study was that the subject data was pooled from a series of multiple studies over 15 years, and as a result, the methods used for measurement of muscle size varied between studies (including ultrasound, DXA, and MRI). This introduces several layers of error into the data for muscle mass outcomes; however, relying on the *relative* (rather than focusing on the *absolute*) changes in muscle size, as well as interpreting in the context of changes observed in the control group can account for some of this error. With that said, the authors argue

> "*all methods to assess muscle size gave approximately similar ranges of responses during the intervention and demonstrate inter-individual adaptability to RT. Therefore, these methods are considered to be comparable between each other enabling present data pooling and retrospective analyses."*

Fortunately, the methods used to measure muscle strength were identical across studies, and even used the same leg press machine. A final limitation is the generalizability of this study, as subjects were restricted to healthy, untrained, Caucasian adults recruited from one geographical region.

****Continued on next page****

Discussion

This relatively large study provides useful insights into the inter-individual variability of muscle strength and size responses to resistance training, and the interaction between the two in beginner trainees. While it is generally well-appreciated that different individuals will achieve different outcomes when using the same training program, the *nature* and *drivers* of this difference remain unclear and controversial.

For example, one common theory in the lifting world is related to the general concept of "hormones" and their differences with age and across sexes. For example, it is argued that because 1) blood testosterone levels tend to decrease with age, younger individuals will exhibit a greater training response compared to older individuals. It is similarly argued that because men tend to have higher blood testosterone levels compared to women, that men will exhibit a greater training response compared to women. Those familiar with our work will recognize this as a *reductionist* approach to a complex problem.

In other words, if this "hormone hypothesis" were true, we would expect to see the largest training responses in young individuals compared to older individuals, and greater responses among males in general compared to women. And while men tend to have greater *baseline* (i.e., *pre-training*) strength than women in real-world settings (though not when controlled for lean body mass), the *relative (i.e.,* percentage) strength increase from training actually tends to be greater among women — which is further supported by the findings of this study [Hubal 2005].

Similarly, while younger individuals tend to have greater *absolute* strength improvements compared to older individuals, they actually show similar *relative* increases on average compared to baseline levels. This is further supported by this study where *no significant differences in relative strength or hypertrophy outcomes were observed across age cohorts within sexes*. While we anticipate some traditional strength coaches will argue that the training program applied in this study was clearly "sub-optimal" (compared to their preferred programs), that is irrelevant to the outcomes observed in the study. This is because, according to traditional theories of training responsiveness (like the "hormone hypothesis" described above), the pattern of responsiveness should be the same *regardless* of training intervention. In other words, the young men "should" have the greatest response, even on a "sub-optimal" program … but this isn't what we observe here.

Now, despite the evidence suggesting little to no differences in relative training responses *on average*, we should still note the *enormous* inter-individual variability in training response that is observed in this study and in real world practice.

For example, consider the 15 individuals in the highest quintile of training response for both strength and muscle size — these are the folks who are generally viewed as athletic "freaks" and elite athletes, people who get a *huge* response with relatively little training compared to others. Conversely, there were a number of individuals with little to no (or even *negative*) responses to the training program, a finding which has been observed elsewhere as well.

However, there were no other *categorical differences* between these groups that might *predict* such differences in training response prior to starting the training program. In other words, the "freak" responders were *not* all young men, and the "poor" or negative responders were not all elderly women (as might be expected by the "hormone hypothesis"). And in fact, **we do not have any reliable metrics that we can apply in practice to predict such training responsiveness — including sex, age, or even blood testosterone level** (as discussed in BMR February 2019). **This suggests that we should not be changing our "default" approach to prescribing training interventions to untrained indvidiauls based on age or sex alone.**

Furthermore, the observation that someone responded poorly (or even negatively) to the specific training intervention administered in this study does *not* imply that these individuals are doomed to be poor responders for life. In fact, we have evidence questioning the concept of "exercise non-responders", arguing that poor- or non-response may be overcome by increasing the dose of stimulus when appropriate or by substantially *altering* the stimulus [Churchward-Venne 2015, Pickering 2019, Montero 2017, Jones 2016].

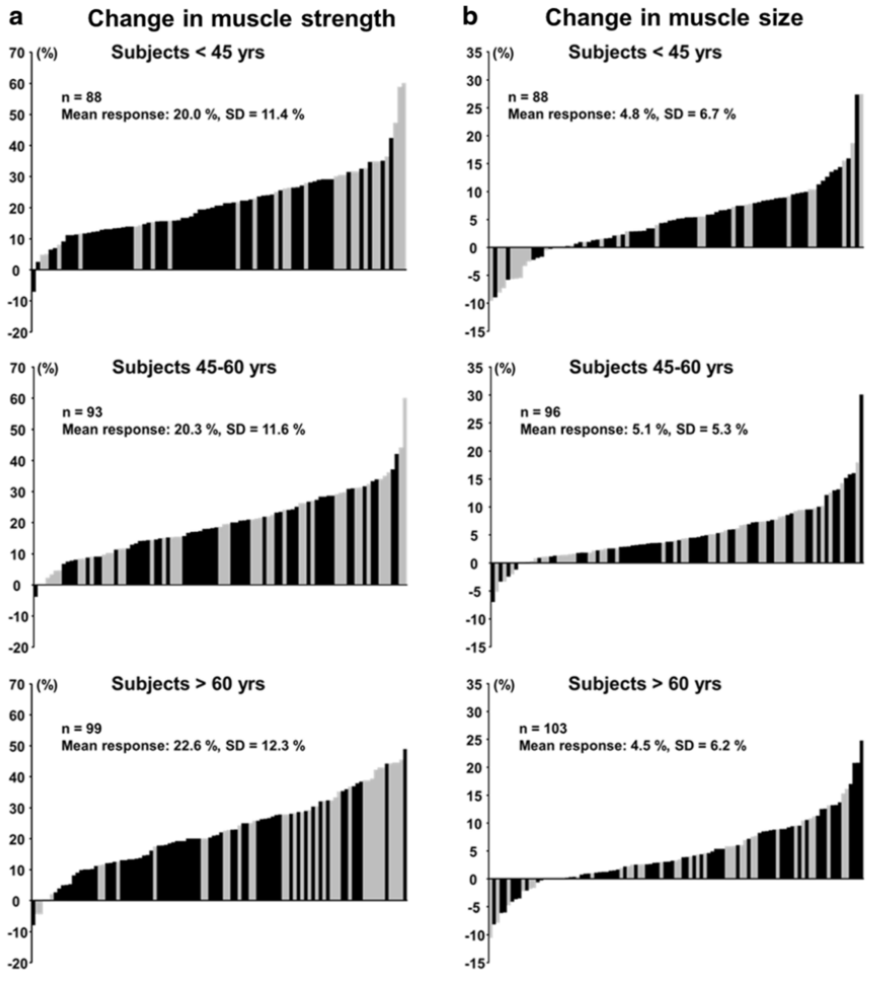
In other words, if a program doesn't appear to be working for you (and assuming that recovery variables are being managed reasonably), it is worth considering whether you need *more* training stimulus, or simply a *different program altogether*. **Simply put: there is no training program that works optimally for all trainees under all circumstances.**

Finally, we've previously discussed the interaction between psychology and physiology with respect to pain, performance, and other processes (see BMR January 2019). For these reasons, we choose to avoid delivering unsupported narratives about the significance of sex, age, testosterone levels, or any other baseline characteristic / metric with respect to training outcomes.

Although we recognize that there will be a wide inter-individual variability in training responses, we should *assume* that the individual will be a normal (or potentially even a *high*) responder until proven otherwise. This is because inducing the belief or expectation that characteristics such as female sex, older age, lower blood testosterone levels, etc. will inherently impair or limit training outcomes may cause harm by generating a “self-fulfilling prophecy”. If they *do* ultimately demonstrate a poor response, the next steps should include changing the “dose” or “formulation” of the training stimulus. It should also be noted that the overall proportion of low responders to both strength and hypertrophy was very low (~2%) — so statistically, any individual trainee is unlikely to be such a low responder and should thus not hold such expectations when initiating a training program.

Ideally, a similarly-sized prospective study can be performed in the future using one cohort with the same measurement methods across all subjects in order to strengthen our confidence in these results. Additionally, similar studies using other health metrics would be useful in elucidating the inter-individual variability and dose-response of exercise with respect to blood pressure reduction among patients with hypertension, or blood sugar reduction among patients with diabetes.

Figure 3.



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IASTM - Scraping the Bottom of the Barrel for Supportive Evidence

The Effectiveness of Instrument-Assisted Soft Tissue Mobilization in Athletes, Healthy Participants and Individuals with Upper/Lower Extremity and Spinal Conditions. A Systematic Review by Nazari et al 2019.

Key Points:

1. The effectiveness of Instrument Assisted Soft Tissue Manipulation was examined for the following populations: healthy, athletes, and those reporting spinal and/or extremity issues.
2. Articles were included in the review, overall the quality of the evidence was very low with a high risk of bias.
3. Primary finding: the current evidence does not support IASTM for any studied population for any of the usual supplied narratives (pain, function, or range of motion).

Introduction

Instrument Assisted Soft Tissue Manipulation (IASTM) is a popular intervention in the pain & rehab field that involves placing an external instrument (often metallic) on the skin of a patient and repeatedly scraping the area of tissue. IASTM isn't new and has roots in East Asian medicine with the technique known as Gua Sha. Although the implements have been updated over the years, the premise remains the same: expel blood "stasis". The traditional thinking is to treat perceived issues caused by "bad blood" by inducing petechiae and ecchymosis, improving blood "stasis" and bringing in "new blood". Early on, Gua Sha was advertised to treat a variety of issues from pain, colds/flu, respiratory problems (asthma, bronchitis), musculoskeletal issues, and other internal organ-related problems.

More recently, the focus has shifted to musculoskeletal issues and pain. The narratives to validate IASTM continue to be pseudoscientific explanations surrounding the inflammatory process. Often the claims are made IASTM will free “adhesions” and “scar tissue” left behind by a faulty post-traumatic inflammatory process. Proponents argue IASTM *“...increases blood and nutrient supply, and migration of fibroblasts to the site of injury. New collagen synthesis and realignment would assist with regeneration of the injured tissue.”* Although such claims sound physiologically plausible, the evidence needs to be assessed to see a) whether adhesions and scar tissue actually exist in the scenarios being described, b) if so, whether these are problematic and c) if so, whether they can be affected by IASTM in a clinically meaningful way. Furthermore, IASTM has become popular amongst athletes as a performance and “recovery” aid pre/post training sessions with little regard whether the evidence is supportive for such uses. There exist two previous reviews on this topic:

In 2016, Cheatham et al. stated IASTM lacked efficacy for certain musculoskeletal issues. The authors discussed the gap between current research and clinical practice, stating: *“The current evidence seems to lack the methodological rigours necessary to validate the efficacy of IASTM itself or any of the IASTM protocols.”*[Cheatham 2016]

In 2017, Lambert et al released a more recent review which included some of the same articles from Cheatham et al’s review. Oddly, Lambert concluded, *“The results of the studies included in this review suggest that IASTM is an effective treatment intervention for reducing pain and improving function in less than a three-month period.”*[Lambert 2017]

Purpose

Nazari et al. argue that these two previous reviews, although adding to the body of evidence (or lack thereof) regarding IASTM, have limitations:

1) Over reliance on *p*-values leading to the lack of assessment of the magnitude of treatment effects (clinical significance)
2) Lack of assessment for risk of bias
3) No grading of the quality of evidence
4) No included studies on healthy or athletic populations

The authors conducted the recent review in hopes of solving some of these prior methodological issues and determine the validity of IASTM for patients and healthy populations.

Methods

The authors compiled articles that met the following inclusion criteria:

1) Randomized controlled trials

2) Included subjects: healthy, athletes, and those dealing with spinal and extremity conditions
3) Interventions: any IASTM compared to sham/placebo, control (no treatment), or active treatment

A total of six outcome areas were assessed: pain, disability/function, ROM, muscle strength, pressure sensitivity, and muscle performance. The authors also established Minimally Clinically Important Differences (MCID) for each outcome assessment (see table). Recall that MCID is different from statistical significance in that it tells us the **smallest change in a treatment outcome that a patient would view as meaningful in their case management.** So if an intervention produces an effect below the MCID, it would be considered *not* clinically significant.

Finally, the GRADE system and Cochrane Risk of Bias tool were used to assess the quality and bias of each included study respectively.

Outcome Assessments

Title of Outcome Assessment	Minimal Clinical Important Differences (MCID)
Pain	21 points
Disabilities of the Arm, Shoulder, & Hand (DASH)	11 points
Patient-rated Tennis Elbow Evaluation (PRTEE)	11 points
Foot & Ankle Ability Measure (FAAM)	8 points
Modified Oswestry Disability Index (ODI)	11 points
Grip Strength (wrist and elbow)	6.5-7.0 kg
Range of Motion (ROM) & Patient-Report Outcome Measures lacking MCIDs	15% or SD (effect size) of 0.5 points

Findings

20 RCTs, published between 2000 - 2018, were included in the review. A variety of IASTM tools were studied: Graston, SASTM, HawkGrip, Ergon, FAT, Técnica, Gavilán, Astym, EDGE, and AdvantEDGE.

Risk of Bias of Included Studies

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bailey 2015	?	-	-	?	+	-	+
Blanchette 2011	?	?	-	-	-	-	+
Burke 2007	+	-	-	+	-	-	+
Crothers 2016	+	+	-	+	-	+	+
Fousekis 2016	-	-	-	+	+	-	-
Gulick 2014	+	-	-	+	+	-	+
Gulick 2017	+	-	-	-	-	-	+
Laudner 2014	-	-	-	?	+	-	+
Lee 2016	-	-	-	-	+	-	-
MacDonald 2016	-	-	-	+	+	-	+
Markovic 2015	-	-	-	-	+	-	+
McCormack 2016	+	+	-	-	+	+	+
Moon 2017	-	-	-	+	+	-	-
Palmer 2017	+	-	-	+	+	-	+
Rowlett 2018	-	-	-	+	+	-	+
Schaefer & Sandrey 2012	-	?	-	-	-	-	+
Sevier & Stegink-Jansen 2015	+	-	-	+	-	?	+
Stanek 2018	?	-	-	+	+	-	+
Vardiman 2014	-	-	-	-	+	-	+
Wilson 2000	-	-	-	?	-	-	+

- High Risk of Bias
+ Low Risk of Bias
? Unclear Risk of Bias

Examining the risk of bias of the included studies (see Risk of Bias table), overall the included studies were all considered at **high risk of bias**.

Two of the 20 trials were actually pre-registered. Pre-registration of trials is important because it helps mitigate publication bias, where the outcome of a study influences whether the study is published.

Fourteen of the 20 studies failed to assess for adverse events due to the intervention. Assessing adverse events is important in order to adequately weight risk vs benefits for treatment selection and its effects on prognosis of a patient case.

Three of the 20 studies were published in predatory journals. These journals often lack the same standard and prestige of other journals by lacking the

rigors of usual peer-review and merely requiring a financial payment to entry for publication.

Twelve studies failed to disclose funding sources which means the research could be biased for positive findings in order to promote the person/company/product providing financial aid.

Finally, nine trials didn't disclose whether there were any sources of conflicts.

Recruitment

10 trials compared IASTM plus other treatment vs other treatment
8 trials compared IASTM with control (no treatment)
5 trials compared IASTM with other treatment
2 trials compared IASTM plus other treatment with placebo/sham other treatment

Other treatments included exercise (stretching, strengthening, and balance), manual soft tissue mobilization, foam rolling, rehab programs, education, cycling/treadmill walking, or compressive myofascial release.

Problems Included in Review

Problem	# of Studies
Posterior Rotator Cuff "stiffness"	1
Elbow conditions (lateral epicondylitis and tendinopathy)	2
Carpal Tunnel Syndrome (CTS)	1
Non-specific Thoracic Spine Pain	1
Upper Back "Myofascial Trigger Points"	2
Low-Back "Myofascial Trigger Points"	1

The overall quality of included studies is very low with high risk of bias.

Outcomes

From the 20 included RCTS, 86 outcomes were reported; 73 of those outcomes showed no difference between the groups with or without IASTM.

Put another way: IASTM was not demonstrated as beneficial for these 73 outcomes.

The other 13 outcomes are questionable at best or in favor of other treatment(s).

Three outcomes favored IASTM (two range of motion and one function) by a clinically meaningful difference, however, the authors conclude more data is needed due to the following:

"...given the predefined MCID scores, the 95% CIs did not exclude the MCID scores, therefore, more data is required to make a definitive conclusion."

Eight outcomes (pain, range of motion, and pressure sensitivity) supported IASTM but the studies were published in suspected predatory journals and rated as very low-quality evidence with high risk of bias.

Two outcomes (range of motion and function) showed clinically meaningful support for **other** treatment groups (lacking IASTM).

The following forest plots display standardized means of the data. Forest plots are a great way to observe review results from included studies in a graphical representation. Standardized means are utilized when the same outcome variable is assessed with various tools across studies.

Figure 4. Forest plot of comparison: Instrument-assisted Soft Tissue Mobilisation (ISTM) plus other treatment (tx) vs other treatment (tx). Standardized mean differences. Outcomes: Function (0 – 100), Pain (0 – 100), Range of Motion (¡) and Grip strength (kg).

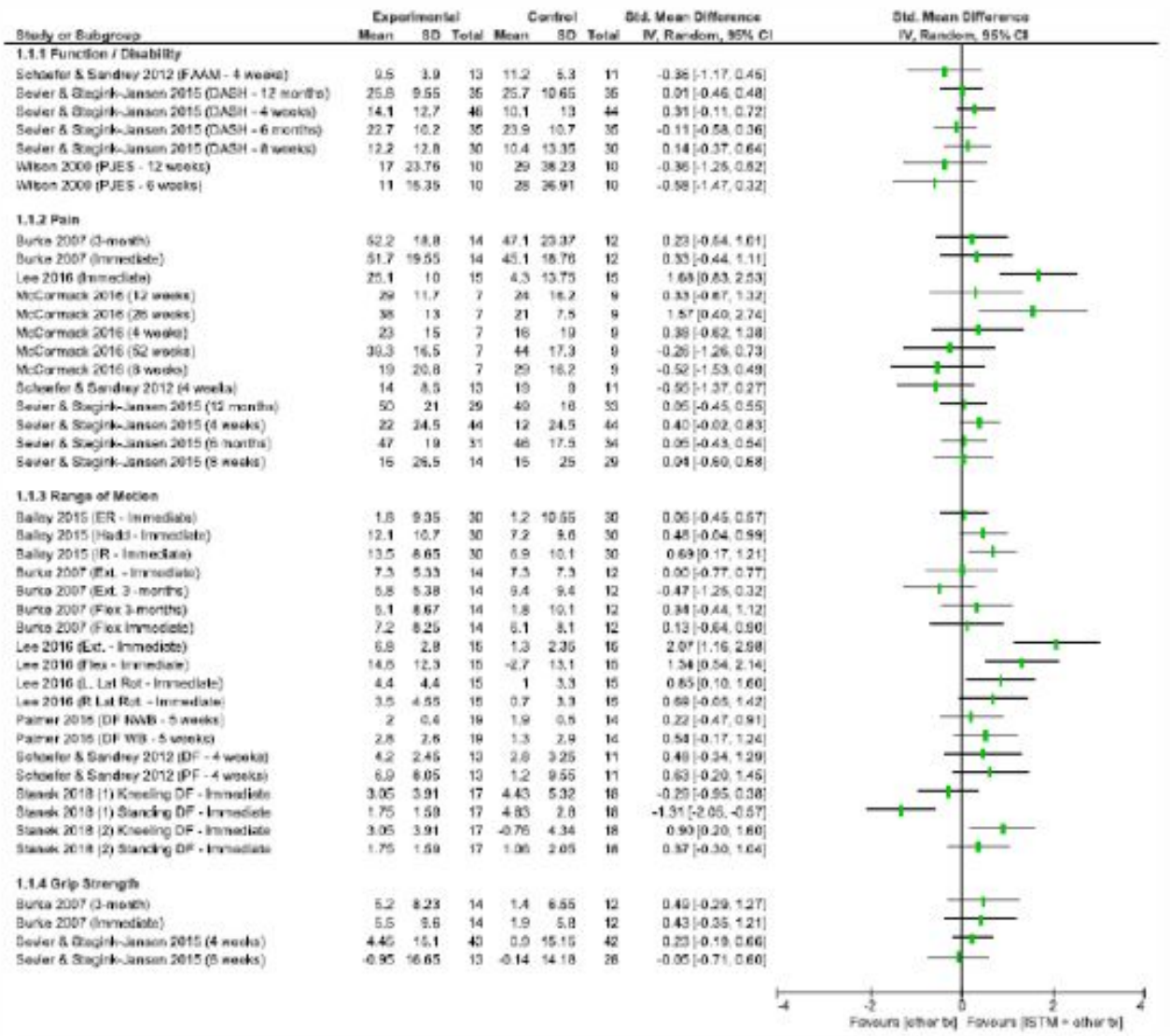


Figure 6. Forest plot of comparison: Instrument-assisted Soft Tissue Mobilisation (ISTM) vs no treatment (tx). Standardized mean differences. Outcomes: Pressure sensitivity (kg/cm2), Pain (0 – 100), Range of Motion (°) and Muscle performance (cm, Watts, m/sec).

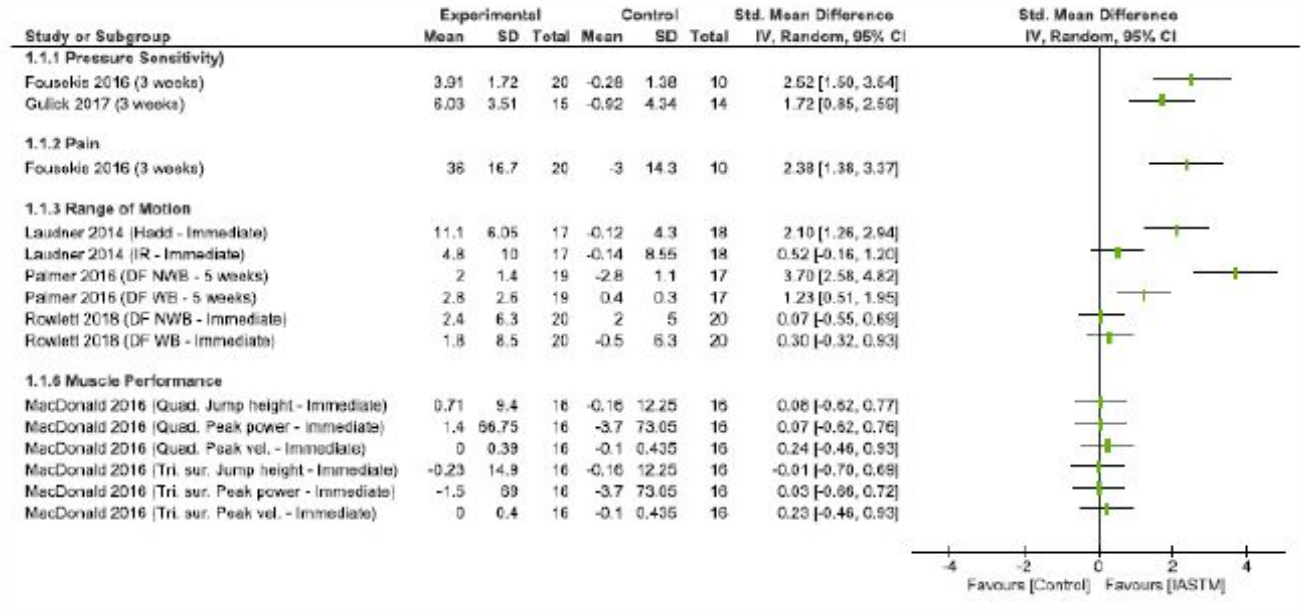


Figure 8. Forest plot of comparison: Instrument-assisted Soft Tissue Mobilisation (ISTM) vs other treatment (tx). Standardized mean differences. Outcomes: Function (0 – 100), Pain, Range of Motion (°) and Grip strength (kg).

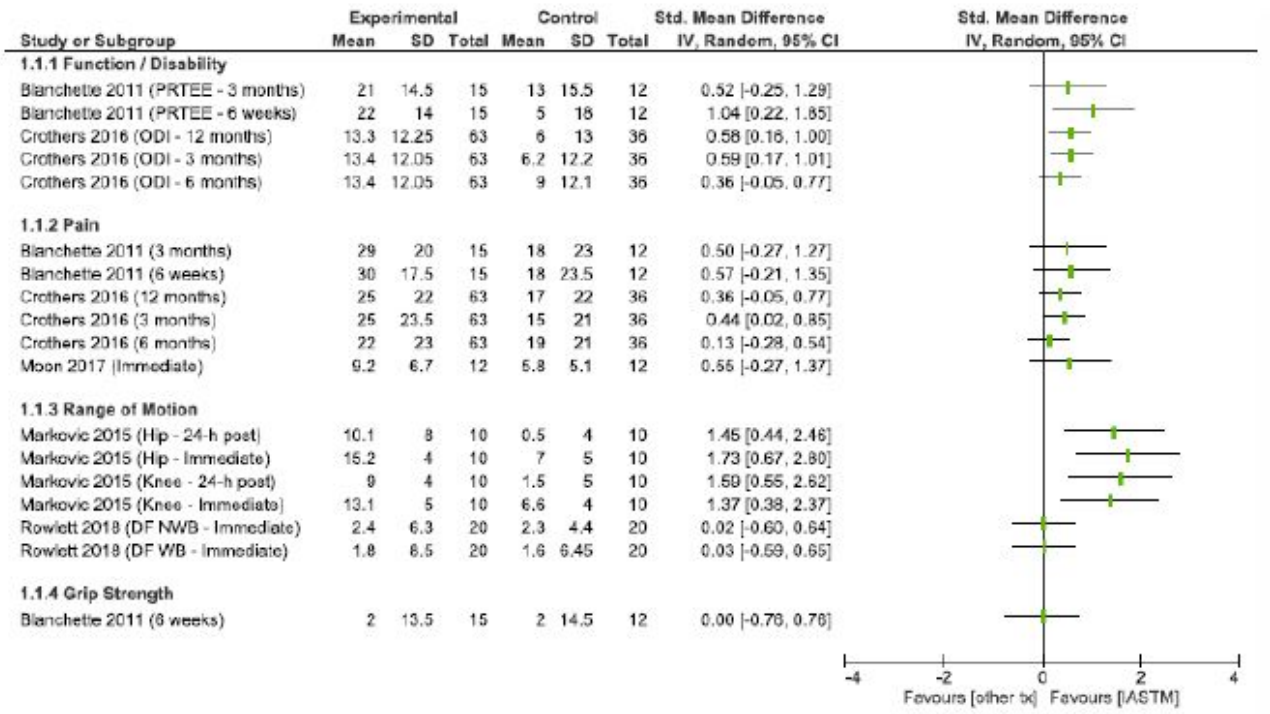
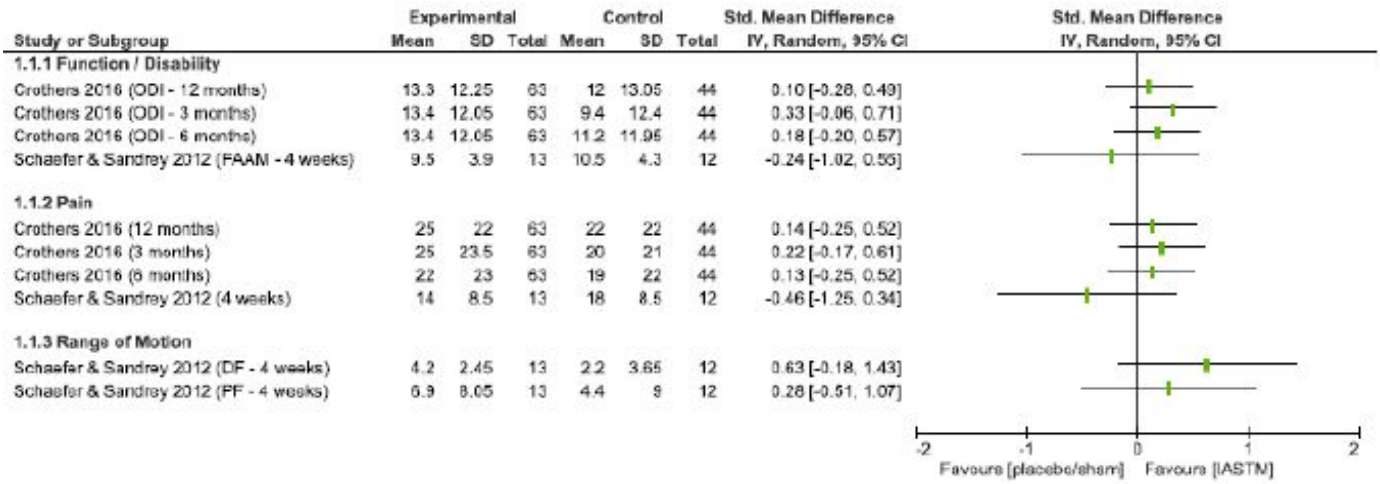


Figure 10. Forest plot of comparison: Instrument-assisted Soft Tissue Mobilisation (ISTM) with/without other treatment vs placebo/sham. Standardized mean differences. Outcomes: Function (0 – 100), Pain (0 – 100) and Range of Motion (°).



Based on the above, there is an underwhelming show of support for IASTM. This information, coupled with the other 73 outcomes showing no benefit via IASTM - support at this time is greatly lacking to utilize the intervention for patients, healthy populations, or athletes. The authors state [emphasis ours]:

> ***"The current evidence does not support the use of IASTM as an effective treatment to improve participant/patient outcomes, since all the included trials were very low quality, and three trials were published in suspected predatory journals."***

Why does this matter?

Often the popularity of an intervention rapidly grows and becomes accepted as the "norm" for usage in clinical practice well before research has been conducted, or in this case - despite what the evidence is demonstrating. To this point the authors state,

> *"The evidence is in conflict with the uptake of the intervention in practice. For example, the Graston website reports that more than 30,000 clinicians have been trained, 14,000 instrument sets have been sold and 2,500+ workshops have been provided. Since this represents the uptake form only one of the instrument providers, the potential gap between evidence and implementation is high."*

Even the narratives supplied to validate IASTM are not well supported. Clinicians cite the use of IASTM for pain, performance, myofascial trigger points, scar tissue, adhesions, and inflammation. However, these explanations of physiological effects and

proposed mechanisms for improving function while decreasing pain remain unsubstantiated in the research literature, as demonstrated by this recent review.

The way this process should work in clinical practice -

- Step 1 - **Conjecture** - does an issue actually exist beyond conjecture (example: myofascial trigger points). If existence can't be established then there is little need to assess the effectiveness or efficacy of an intervention.
- Step 2 - **Define Terms** - once we've agreed an issue exists, we need to define the issue (diagnostic criteria). More importantly, we need to determine the existence of the issue is pathological and warrants intervention otherwise prognosis will be negatively affected.
- Step 3 - **Quality & Justification** - after we've agreed the issue exists and is pathological, then we need to assess if we can make an impact. If we are capable of affecting the issue, then the risks vs. benefits of treatment(s) needs to be weighted.

And yet, the usage of IASTM has already jumped to the final step before the narratives given for its use have been validated. Regardless, Nazari has demonstrated IASTM greatly lacks support based on the totality of evidence at this time.

Reviews such as this are paramount for guiding clinical decision making and ensuring we are not unnecessarily conditioning patients to false narratives and treatments. We need to move on from this intervention and cease trying to scrape the bottom of the barrel for supportive evidence - it doesn't exist at this time.

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What Actually Reduces the Risk of Low Back Pain (Spoiler: It's Not Mobility Work)

Prevention of Low Back Pain A Systematic Review and Meta-Analysis by Steffen et al. 2016

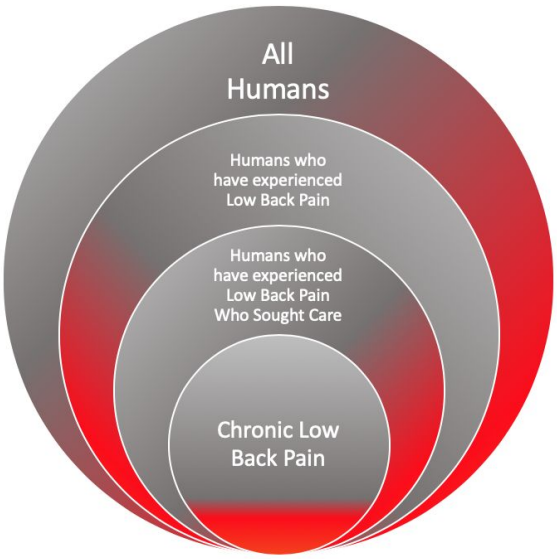
Key Points:

1. There is moderate-level evidence showing that compared to individuals who did not participate in exercise and were not educated on low back pain, those who did had a 45% decreased risk of low back pain.
2. Individuals who stopped the exercise program had a smaller overall risk reduction at one year. This suggests that for exercise to be effective in reducing the risk of low back pain, it needs to be continuous over the long-term.
3. Exercise alone was effective for reducing the incidence of low back pain, but only in the short term.

Introduction

Low back pain continues to be one of the most costly ailments society is faced with from both a monetary and loss of activity standpoint. GBD Collaborators 2016, Hoy 2010 A cursory internet search reveals countless ways to prevent an episode of low back pain, including massage, "detoxes", orthotics, or trips to see a specialist who can cure the back pain epidemic with just three magic exercises! Unfortunately, all of these sorts of claims lack scientific backing. Aiming to prevent low back pain is probably a misguided pursuit. While the terms "prevention" and "risk reduction" are often used interchangeably, the two have drastically different implications. We will likely never reduce the incidence of low back pain to zero, and therefore never globally eliminate or prevent low back pain. However, if specific variables are found to reduce the incidence of low back pain (either in isolation or combination), then we would be remiss not to incorporate them in our treatment approach.

The overall point-prevalence of low back pain (i.e., the number of people experiencing low back pain at any one time) has been estimated at 7.3%.[Hartvigsen 2018] This means *half a billion* people are experiencing low back pain at any given time, and a proportion of these individuals eventually progress to chronic low pain. If we are going to shift the aim towards *risk reduction* for low back pain, we need good evidence upon which to base our methods.



It is highly likely that the vast majority of individuals reading this piece have experienced an episode of low back pain at some point in their lives. It is less likely that *all* readers who have experienced an episode of low back pain ultimately sought medical care. This means that some individuals' symptoms self-resolve without ever seeking care. This information would likely push the point-prevalence of low back pain even higher, since these individuals may be unaccounted for in population estimates. Granted, some of these individuals likely achieved that resolution due to negative situations such as insurance constraints or lack of access to healthcare, but others were able to manage their symptoms and return to their usual state of health without any medical intervention required.

An internet search for "low back pain prevention" yields a cacophony of suggestions from "top 10" lists, to postural positioning suggestions and movements you should NEVER do, to whatever the bodywork *du jour* of professional athletes is at the time. None of these suggestions have supporting evidence. Indeed, what a professional athlete is doing for prevention is often the *exact opposite* of what the evidence would suggest. If the methods employed by professional athletes really did reduce the risk of injury, we would see ever-decreasing rates of injury in professional sports.

Unfortunately, what *does* tend to work is boring, and often not worthy of attention on social media. There is ample evidence that exercise is beneficial for a variety of health related outcomes. [Colberg 2016], [Dutheil 2013] Current research however shows we are falling fall short of proper utilization with studies showing the average 16 year old is as active as the average 60 year old.[Varma 2017] Before advocating for modalities,

supplements, braces, or orthotics, we should focus on methods that have substantial evidence, and substantial return on investment.

Purpose

The purpose of this review is to evaluate the evidence on the effectiveness of interventions for prevention of low back pain and use of sick leave for low back pain.

Methods

This was a systematic review based from the PRISMA guidelines. Moher 2009 The search strategies were based on the guidelines from the Cochrane Back Review Group with an emphasis on randomized controlled trials, back pain, and prevention. Furlan 2009 Two reviewers examined the full text article to decide if it met the inclusion criteria. To be included in the review, the following criteria needed to be met:

- The study included participants *without* low back pain at entry, or at least 1 outcome was not present at baseline (*e.g.,* some had mild low back pain, but were not out of work)
- Intervention was aimed at preventing future episodes of low back pain
- Compared intervention groups with groups that received no intervention, placebo, or minimal intervention
- Reported a measurement of a new episode of low back pain

Studies were excluded if they used a quasi-randomized format comparing two interventions against each other. The quality of the trial was assessed using the PEDro scale. De Morton 2009 Outcomes were extracted by the authors to calculate treatment effects using the methods laid out by the Cochrane Back Review Group. Furlan 2009 The overall quality of the evidence was determined by the GRADE scale Atkins 2004 with a downgrade from high quality for each of the following criteria:

- Design limitations (>25% of studies from a low methodological quality: PEDro <7
- Inconsistency of results or large heterogeneity between trials
- Imprecision (<400 participants)

The quality of the evidence was graded as:

High: Further evidence is unlikely to change conclusions
Moderate: Further evidence is likely to influence the magnitude of the conclusions

Low: Further evidence is likely to influence the magnitude of the effect and could change the direction of the effect
Very Low: No definitive claims can be made

Outcomes were dichotomized into short (<12 months) and long (>12 months) duration. If studies had multiple outcomes within the 12 month period, the longest duration was used. With this information, the authors calculated relative risks and 95% confidence intervals. From there, random effects models were used to pool estimates for each analysis.

Results

The initial search revealed a possible 6133 articles that were then screened by title and abstract down to 159 potential studies. After selecting for inclusion and exclusion criteria, 23 publications inclusive of 21 randomized controlled trials (RCTs) and 30,850 participants were selected. The trials focused on 6 different interventions: **exercise, exercise and education, education, back belts, shoe insoles, and "other prevention strategies"**. Trials were grouped according to strategy and time frame (short or long term).

Table 1- Effect of interventions on risk reduction of low back pain

	Short Term (Quality)	Long Term (Quality)
Exercise Vs Control	0.65 (Low)	1.04 (Very Low)
Exercise and Education Vs Control	0.55 (Moderate)	0.73 (Low)
Education Vs Control	1.03 (Moderate)	0.86 (Moderate)
Back Belts Vs Control	1.01 (Very Low)	0.85 (Moderate)
Insoles Vs Control	1.01 (Low)	N/A

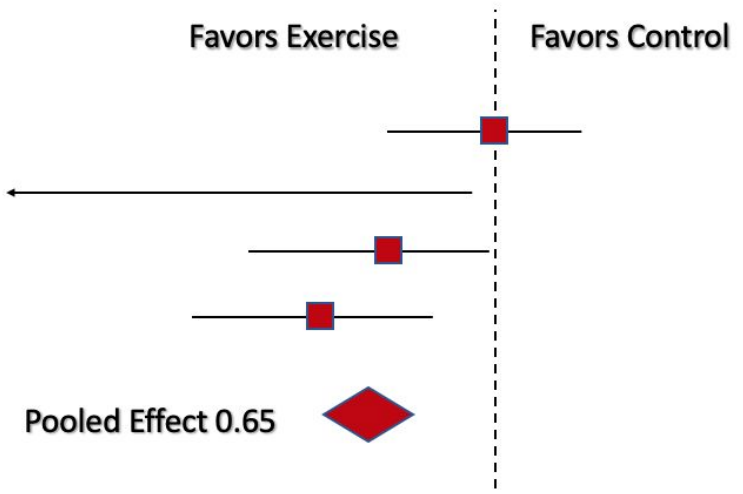


Figure 1- Forest plot of exercise interventions versus control for short term reduction in low back pain

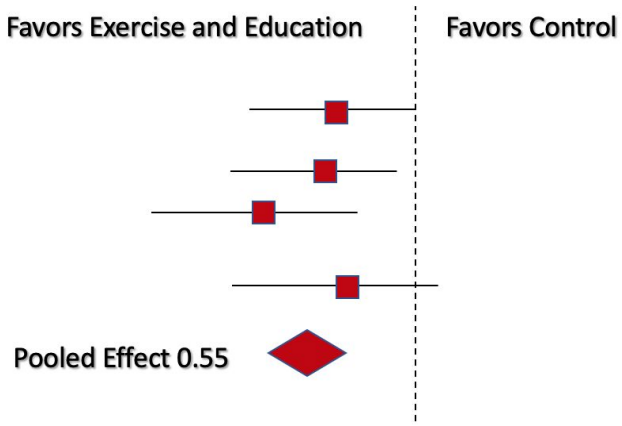


Figure 2- Forest Plot of exercise and education versus control for short term reduction of low back pain risk

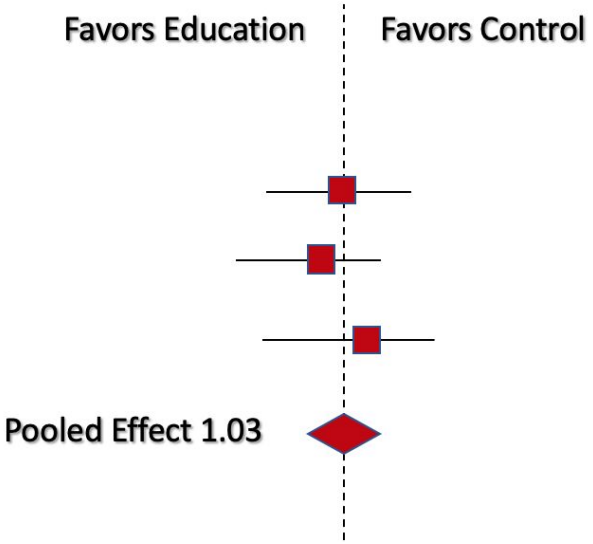


Figure 3- Forest Plot of Education Versus Control for risk reduction of low back pain in the short term

Why Does This Study Matter

With low back pain as a leading cause of disability and pain worldwide, we should employ any strategy we can to reduce its incidence, provided it is backed by evidence. Increased physical activity has been shown to have numerous positive health benefits, but if exercise alone were enough to reduce the risk of low back pain, we would not observe it in athletes. A cursory search of the literature or any stop on the internet would confirm that athletes do, in fact, experience low back pain. In the same regard, there has been a recent movement suggesting that individuals can be “educated

out of pain" because it is a subjective experience. The most recent systematic review by Watson *et al* on pain neuroscience education (PNE) would suggest that education alone is insufficient to treat individuals with low back pain.[Watson 2019] So it appears that when applied in isolation, neither exercise nor education alone significantly reduce the risk of low back pain in this meta-analysis either.

When combined, however, the two were able to reduce the risk of low back pain by 45%. If the rate of low back pain incidence could be almost halved with exercise and education, we would be remiss as a society to not incorporate these two interventions. However, what specifically constitutes "exercise" and "education" can be hotly debated. There are no shortage of well-meaning clinicians and trainers who promote exercise and education that ultimately does little to reduce the risk of low back pain. In specific studies looking at exercise, the exercise dose was likely homeopathic for what practitioners should prescribe. Moore *et al.* used 6 exercises for 15 minutes per day involving two isometric exercises and no external load whatsoever. [Moore 2012] While this was an underpowered pilot study, the group of workers participating in the exercise group experienced no episodes of low back pain over the course of a year. The subjects of this study were sedentary office workers, so the threshold for what constitutes a "*dose"* of physical activity was likely quite low. There is, however, evidence that the *perception* of what constitutes physical activity matters as well. In 2007, Crum and Langer studied a group of hotel room attendants for their mindset towards physical activity. The workers did not perceive themselves to be active despite the physical demands of their job. Crum *et al* took part of the cohort and informed them their job actually *did* meet the Surgeon General's recommendations for physical activity. Despite no change in activity levels, after 4 weeks those informed of meeting the criteria showed a decrease in weight, blood pressure, and other measures of health compared to their uninformed peers. [Crum 2007] This scenario demonstrates how exercise and education might work together for a positive influence on health.

Obviously those of us at Barbell Medicine have a predisposition for utilizing resistance training in reducing the risk of pain and injury, and this has been supported in the literature as well. [Lauresen 2018] Specific to the treatment of low back pain, there is also moderate- to high-level evidence that resistance training is effective in the short term for treatment of *chronic* low back pain. [Searle 2015] With that said, there is also low-level evidence for yoga, pilates, "motor control" exercise (whatever that is), and aerobic activity. [Saragiotto 2016], [Meng 2015], [Yamato 2015], [Weiland 2017] **The key seems to be to do *something*, do it *often*, and understand/accept that aches and pains are a natural part of life that often get better on their own.**

We recognize that not every individual is going to have the desire (or resources) to train with a barbell, and this is **okay**. This systematic review shows that even low levels of exercise can have a beneficial effect with respect to risk reduction of low back

pain. Meeting individuals where they are at and facilitating a desire to be more active likely supersedes the specificity of the modality with which they train. That being said, if low level isometrics can have an effect on the incidence of low back pain, an increased magnitude of external load would likely have an increased effect. The question should not be "*are you strong enough*" but rather "*are you strong enough to do what you want to do?*" And, if not, what steps do we need to take to get you there?

Current recommendations for resistance training are 2-3x/week, yet only 18.6% of individuals met this criteria. Dankel 2016 Society is spending hundreds of billions of dollars on the treatment for any real efficacy. Gaskin 2012 If over 80% of the population is not meeting the current recommendations for physical activity, then we are wasting money on numerous other treatment methods with far less efficacy. In addition, those treatment methods are often steeped in a biomedical explanation of their effects, whether it be that an individual's body is "broken", that they have "trigger points", or they have "adhesions". None of these claims have been substantiated and send the wrong message to patients. **Exercise and Education have an additive effect that can be more powerful than either alone, provided they are framed through a positive message that individuals are resilient, that they can improve, and most of all, that they will get better.**

The other reason this study matters is that it lends increased evidence to orthotics and back braces *not* having an influence on low back pain. The evidence is low on both accounts, but this matches data from other trials. Chuter 2017, van Duijvenbode 2008 Instead of focusing on a structuralist explanation of low back pain that can be fixed by an orthotic, brace, or tape we continue to accrue evidence that the best line of risk reduction is through an active approach that focuses on movement coupled with education.

This study is important as it highlights the effects of education and exercise in reducing the risk of low back pain. Thinking that education alone can prevent low back pain is farcical. That is akin to thinking that listening to every rock ballad is going to teach you how to love. Eventually, it has to be coupled with getting out and actually *doing something*.

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Research Methodology Spotlight

A Word on Forest Plots and Risk Ratios by Dr. Derek Miles

For those unfamiliar, forest plots are graphical representations of the results of either randomized controlled trials or meta-analysis. They often calculate the relative risk or risk ratio of the effect of an intervention. Risk ratio is the probability of an outcome in an exposed group to an intervention versus an unexposed group. There are three interpretations of a risk ratio:

- Risk ratio=1 means exposure to the intervention does not effect the outcome
- Risk ratio <1 means exposure to the intervention decreases risk of the outcome
- Risk ratio >1 means exposure to the intervention increases risk of the outcome

For the purposes of BMR the plot was displayed mainly to emphasize the pooled effect of the risk ratio of studied interventions. This is the average effect of the intervention on the risk with a confidence interval attached. These effects are typically what are seen in press releases such as Moran et al giving an odds ratio of 1.47 (95% confidence interval 1.22-1.77) for the ability of the functional movement screen (FMS) to predict injuries in military recruits. This could be interpreted as “recruits with an FMS score <14 are 47% more likely to sustain an injury than individuals who scored >14” and does make it appear than the FMS can, in fact, identify individuals at an increased risk of injury. Moran 2017 For a full interpretation of this data however, we need to know the base rate of injuries in this cohort. If I created a screen that could increase your chances of winning the lottery 47% it would still not be in your best interest to purchase a powerball ticket because the overall odds of winning are still so low. In the instance of the Moran study, the rate of injury in the military recruits, according to Knapik et al is 1.35 to 2.6 per 1,000 training hours. Knapik 2015 A 47% increase brings the risk of injury to 1.98 to 3.8 injuries per 1,000 hours. This does not sound nearly as useful as identifying an almost fifty percent increase in injury.

Forest plots are excellent ways of visualizing the data for a meta-analysis in that they can display the overall effect of a treatment as well as let the reader easily see studies that would function as outliers. If the sample size of the included studies are not close, the size of the box will also change as the study with a higher sample size would be heavier *weighted*. If the confidence interval for a study is larger, the *whisker* or confidence interval will also be larger. This can clue the reader to a larger heterogeneity of findings in that study's cohort. Visually, this would look like Figure 1A.

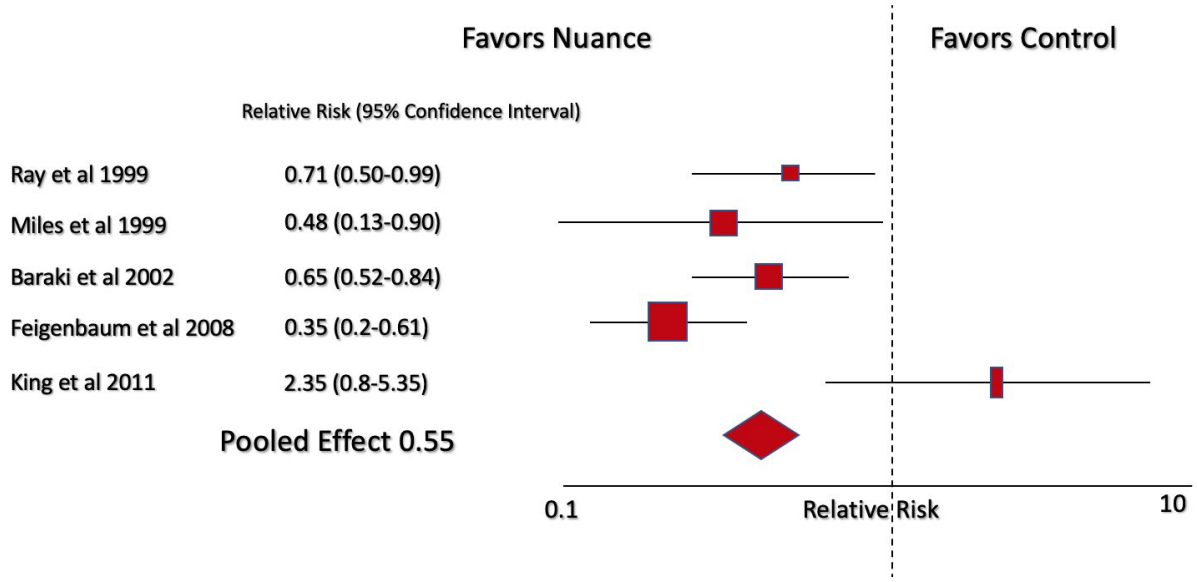

Figure 1A- Forest of the effect of nuance on the ability to achieve and maintain gainz

The study from Feigenbaum *et al* would have a larger number of subjects (n) and the small whisker (confidence interval) would warrant higher weighting of that study to the determination of the overall pooled effect. The study by Miles *et al* has a large whisker meaning it had a larger heterogeneity in findings. While the box of Baraki *et al* is the same size as the study by Miles, a smaller n could contribute to its equal weighting. The outlier here is the study by King *et al*. This would typically warrant further investigation as the findings are discongruent with all other studies. This could mean that the study was not well designed, or the author's definition of "nuance" was flawed. The authors of the King study could have also published their results in a pay to publish journal and further diluted the effects of well designed studies. This is why meta-analysis typically include the PRISMA, GRADE, and PEDro criteria. This tends to remove lower quality studies that would confound actual results.

For pooled data, a full fleshed out figure 2 from the main piece would instead look like Figure 2A below. Here, you can see the individual studies included in the meta-analysis, their authors, and the individual relative risks for each. This is useful when interpreting the data as the reader can visually see if there is an overall trend (as in the figure) or if there are outlier studies that confound the data. If these are present, it is often worth reading those studies to differentiate how their methods may have differed from other included studies.

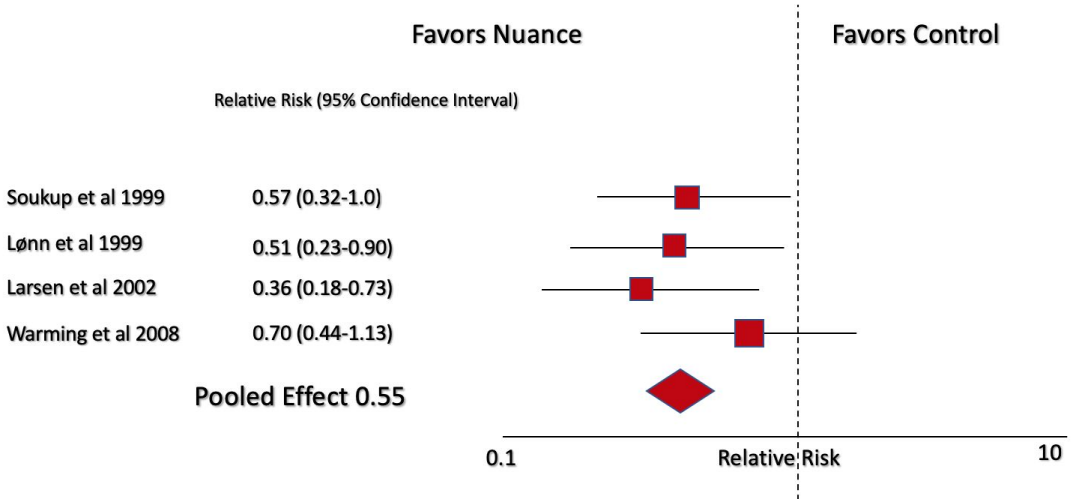

Figure 2A- Full forest plot of exercise and education versus control for risk reduction of low back pain.

To apply the principles discussed above, if the point prevalence of low back pain is 7.3% and the current world population is 7.7 billion people meaning 560,000,000 individuals are experiencing low back pain. With education and exercise that number could be dropped to 252,000,000 people. The cost savings of this effect alone would be enormous.

For the IASTM systematic reviewed included in this month's BMR there are also forest plots associated with data. This found no utility for IASTM for improving function, pain, or range of motion. Here, the authors did not pool the data, but visually a trend can still be seen in figure 3A.

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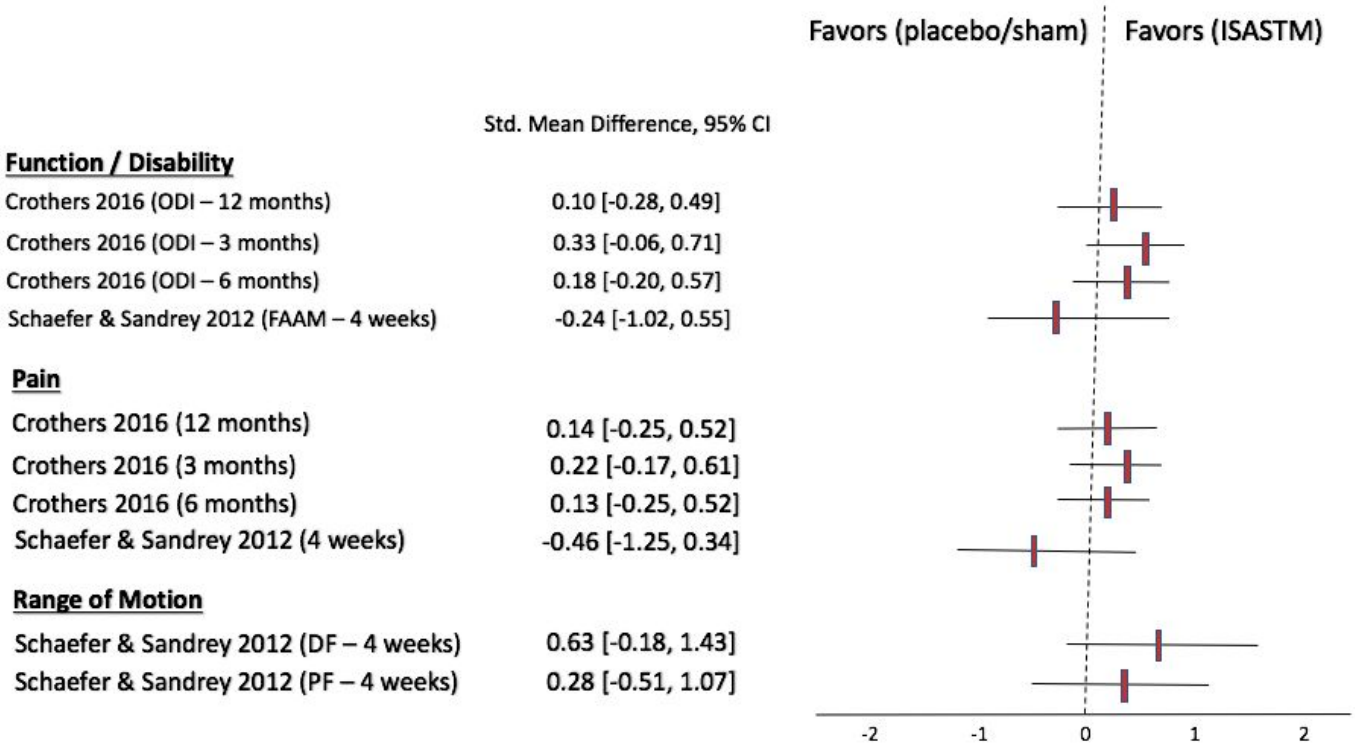

Figure 3A- Forest Plot for IASTM versus placebo/sham for function/disability, pain, and range of motion.

Even without the pooled data, every study included crosses the zero threshold. There is no clear trend either in favor of IASTM, or for control/sham. In this instance the data does not favor the use of the technique. Worth noting here is that many outcomes are from the same study. While this does give different points with which to measure outcomes, it all does come from the same cohort of individuals. When reading forest plots, there is nuance to the interpretation, but the more aware the reader is of the variables contributing to the data, the more informed decisions they can make.

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