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WITH YOU FROM BENCH TO BEDSIDE

Monthly Research Review

Table of Contents

Author Information

Jordan Feigenbaum, MD

@jordan_barbellmedicine

info@barbellmedicine.com

Winning the Losing Game: The Science of Maintaining Weight Loss

Physiological Predictors of Weight Regain at 1 - Year Follow - Up in Weight - Reduced Adults with Obesity by Nymo et al. 2019.

Key Points:

1. Clinically significant weight loss (e.g. 5-10% of body-weight) can be achieved relatively quickly using a very-low calorie diet.
2. Compensatory mechanisms such as decreased RMR, diminished EIEE, changes in subjective hunger ratings, or hunger-associated hormone levels do not correlate reliably with weight regain after weight loss.
3. Multidiciplinary teams, e.g. doctors, dieticians, and exercise professionals can help individuals achieve and maintain clinically significant weight loss in obese individuals.

Introduction

Obesity is a disease that is defined as excess adiposity (body fat) that affects approximately 650 million adults worldwide and 1 of 3 adults in America.[WHO 2018, Garvey 2016] The impact of obesity on morbidity, mortality, and health care costs is profound, with huge burdens on patient suffering. In light of these burdens and costs, significant resources have been dedicated to improving screening, diagnosis, and treatments for obesity. In this month's research review, I'll review some of the important screening tools and nuances in management of obesity.

Screening for obesity is important, as it identifies those who are at increased risk from carrying too much body fat. While direct measures of body fat are available, e.g. DEXA, hydrostatic weighing, skin-fold testing, etc., we typically use anthropometric data such as Body Mass Index (BMI) and waist circumference as *both* screening and diagnostic tests to identify those with excess adiposity.

At present, it is recommended that all adults undergo yearly screening for obesity. BMI scores of 25 and 30 are very *specific* for overweight and obese categories, respectively, identifying >96% of individuals who are carrying too much body fat. Conversely, BMI as a stand-alone tool is not very sensitive and misses approximately half of individuals who *are* carrying too much body fat, but who have normal BMI scores (20-25).

Subsequently, the present obesity guidelines recommend those with BMI scores of less than 35 to also have their waist circumference measured in order to improve the *sensitivity* of BMI as a screening tool.[Garvey 2016] On the other hand, BMI scores greater than 35 indicate high levels of body fat and do not require additional information (e.g. waist circumference).

When using waist circumference in conjunction with BMI to screen for obesity it is important to note there are ethnic and region-specific waist circumference cutoffs that indicate increased risk of obesity-related diseases. For example, in the United States and Canada the cutoffs indicating increased risk are 88cm (34.5”) and 102cm (40”) for women and men, respectively. In Asian populations however, we use cutoffs of 74cm (29”) and 85cm (33.4”) for women and men, respectively.

After diagnosing obesity in an individual, management should focus on body fat reduction to clinically significant levels. Said differently, we need to generate enough weight (and fat) loss in an individual so that their risk of obesity-related disease is reduced back to baseline. At present, it appears that losing and maintaining **5-10%** of an obese individual’s body weight is necessary to reduce the risk of obesity-related diseases such as diabetes, heart attacks, stroke, high blood pressure, abnormal cholesterol levels, female infertility, male hypogonadism, non-alcoholic fatty liver disease, sleep apnea, COPD, and other pathologies.[Garvey 2016]

Weight loss occurs secondary to a negative calorie balance, e.g. total daily energy expenditure is greater than total daily energy intake. This is the so-called energy balance equation:

Total Daily Energy Intake = Total Daily Energy Expenditure

Additionally, while total daily energy intake is synonymous with total calorie intake, total daily energy expenditure is made up of a number of components including resting metabolic rate, thermic effect of food, and physical activity.

Weight loss occurs when total daily energy expenditure is greater than total daily energy intake and a calorie deficit results. Conversely, weight gain occurs when total daily energy intake is less than the total daily energy expenditure and a calorie surplus is present.

From an obesity management perspective, we'd like to use both dietary and exercise interventions to obtain the recommended 5-10% weight loss. While a discussion of specific dietary and exercise interventions are outside the scope of this review, each can be summarized as follows:

1. **Nutrition** – It is recommended that obese individuals obtain a 500-750kCal/day deficit in order to achieve ~2.5% weight loss per month. At present, the data suggests that specific diet types, macronutrient intakes, or avoiding particular foods matter little with respect to outcomes. From a health perspective, the recommended diet centers around lean protein, 6-8 servings of fruits and vegetables per day (total), reduced refined sugar intake, and reducing saturated fat intake to <10% of total daily calories.

2. **Exercise** – It is recommended that adults engage in 75-150 or 150-300 minutes per week of vigorous or moderate intensity exercise, respectively. A combination of both moderate and vigorous intensity activity can be used to obtain these goals. Additionally, it is recommended that adults participate in resistance training twice per week. There also appears to be a dose-response relationship between exercise volume and improvements in obesity and obesity-related disease. Said differently, higher exercise volumes appear to outperform lower exercise volumes in this context whereas no reliable relationship between intensity and exercise has been noted in the literature.

Ideally, implementation of both diet and exercise interventions produces substantial weight loss by producing a negative calorie balance. However, weight loss can produce several changes on both sides of the energy balance equation:

1. **Calorie intake** is regulated by the brain. In particular, specific areas of the hypothalamus play a central role in integrating biological, psychological, and social inputs regarding food intake, energy balance, and body weight. For example, obesity-promoting environments and behavior patterns tend to increase calorie intake by ~20-30% in obese individuals compared to those with normal bodyweights.[Greenway 2015] This area of the brain also integrates signals from 'hedonic' reward pathways that are associated with the palatability (e.g. sight, smell and taste) of food, which can override the homoeostatic system and increase desire to consume energy-rich food, despite physiologic satiation and replete energy stores. A number of neurotransmitter systems in the brain, e.g dopamine, serotonin, and cannabinoid systems, have a major role in reward pathways and mediating the pleasure drive for eating.[Lenard 2008]

2. **Resting metabolic rate** is the amount of energy used while a fasted individual is awake and sitting quietly. Approximately 80% of an individual's RMR is

determined by the amount of lean body mass (LBM), e.g. the greater the LBM the greater the RMR. With that being said, there is substantial inter-individual variance (~20%) in RMR that cannot be explained by LBM, race, sex, age, measurement error, or environment. Currently, it is thought that the variance is due to genetic differences amongst individuals.[Ravussin 1992] [Buchholz 2001] In any event, weight loss typically reduces both LBM and fat mass, which reduces RMR in general. While the magnitude of RMR decrease varies based on the individual, it is estimated that for each kilogram of bodyweight lost RMR decreases by about 30kCal per day.[Clamp 2018]

3. **Physical activity** is made up of both exercise-induced energy expenditure and non-exercise activity thermogenesis (NEAT). In general, this typically **does not change** secondary to weight loss. However, the brain also integrates biological, psychological, and social inputs regarding physical activity and the brain's output can have a significant effect on how many calories are expended from physical activity during a given day. In controlled studies, the amount of calories burned during exercise in obese individuals who are losing or who have lost weight is the same as those who are not losing or who have not lost weight.[Herrmann 2015] Additionally, most individuals who have lost weight will have increased levels of physical activity. However, total daily energy expenditure from physical activity can actually decrease and prevent further weight loss and, in some cases, promote weight regain. This process is not well understood, but is thought to be influenced significantly by genetics and environmental inputs.

Overall, long-term maintenance of weight loss can be challenging, as the compensatory mechanisms described above, adherence difficulties, and others can all contribute to weight regain. With that being said, it is not clear how much (or how little) any of the aforementioned mechanisms contribute to weight regain in the long-term, if at all. Previous studies tended to be limited by short duration of follow up, however this month's article followed individuals up for 1 year *after* they finished losing weight- making the article potentially very useful.

Purpose

As described in the section above, there are a number of compensatory mechanisms that can promote weight-regain. However, these mechanisms' role in weight regain are largely speculative. At present, there isn't much evidence demonstrating a causal relationship between weight-loss associated reductions in energy expenditure and increased appetite that, subsequently, result in long-term weight regain.

This month's article aimed to determine whether changes in resting metabolic rate (RMR), exercise-induced energy expenditure (EIEE), subjective appetite feelings, and plasma concentration of appetite-related hormones observed with weight loss were associated with weight regain at 1 year in adults who had undergone diet-induced weight loss.

Subjects

In this study, 54 adults with an average age of 40 and an average BMI of 37 kg/m^2 were recruited from Norway's 3^{rd} largest city, Trondheim.

Prior to participation in this study, individuals had to be "weight stable", which means they had to have less than a 2 kg weight loss over the last 3 months, not be dieting to lose weight, and have a sedentary lifestyle.

Additionally, individuals could not be pregnant, breastfeeding, or have a clinically significant illness, e.g. cardiovascular disease or diabetes, have undergone previous weight loss surgery, and/or taking medication known to affect appetite/metabolism or induce weight loss.

In summary, the subjects had to be *medically-healthy obese* who weren't previously trying to lose weight via diet and/or medication or be physically active.

Methods

Subjects in this study underwent 8 weeks of a very-low-energy diet (VLED), followed by 4 weeks of refeeding and a 1-year maintenance program. The 8-week VLED was a liquid-based diet that contained 550 and 660 kcal/d for females and males, respectively (carbohydrates 42%, protein 36%, fat 18%, and fiber 4%), plus no-energy fluids and low-starch vegetables (maximum 100 g/d). Weight loss was measured via a calibrated scale and body composition was measured using air-plethysmography (BOD-POD) at baseline (week 0), week 13, and at 1 year.

At week 9, participants met with a dietician to develop a plan to gradually reintroduce "normal" foods while withdrawing from the VLED shakes. Calorie intakes were tailored to individual energy requirements, which were determined from each individual's directly-measured RMR and physical activity. RMR was measured using indirect calorimetry whereas physical activity was measured using a wearable armband tracking device. Per the study's report, individuals were advised to consume diets with 15% to 20% protein, 20% to 30% fat, and 50% to 60% carbohydrates, according to the Nordic nutritional guidelines. Additionally, participants were asked not to change their PA levels during this phase of the study.

At week 13, participants started their 1-year maintenance program that included regular individual and group-based education sessions, focusing on nutritional counseling, PA, and cognitive behavioral therapy.

As mentioned above, resting metabolic rate (RMR) was measured using indirect calorimetry.

Exercise-induced energy expenditure was measured while individuals cycled at specified intensities on an exercise bike.

Subjective appetite feelings, e.g. hunger, fullness, desire to eat, and prospective food consumption were measured with a 10-cm visual analogue scale.

Finally, plasma samples of appetite-related hormones, ghrelin, glucagon-like peptide 1 (GLP-1), total peptide YY (PYY), cholecystokinin (CCK), and insulin were analyzed using a specialized laboratory assay at the beginning of the study (week 0), week 13, and at 1 year.

Findings

Of the 54 individuals who started the study, 48 individuals provided data at 13 weeks and 36 subjects provided data at 1 year. Losing 33% of your original sample size is somewhat concerning so we'll have to keep this in mind when reviewing the data. In any event, the results are described below:

Weight Loss and Body Composition Changes

On average, the study participants lost 17% of their body weight (20.5 kg on average; range: 11.7 to 32.2 kg) at week 13. Specifically, fat mass was reduced by ~18 kg and fat-free mass was reduced by ~3 kg at week 13.

At 1-year follow-up, 30 out of the 36 participants had WL of at least 10% of baseline weight. Additionally, weight regain at 1-year follow up was 2.5kg ± 9.0, which was predominantly fat-free mass (muscle, bone, water, organ tissue), whereas fat mass regain did not reach statistical significance on average

RMR, and Energy Expenditure Changes

At 1 year, there were no statistically significant correlations between weight loss and changes in RMR or exercise-induced energy expenditure (EIEE).

Additionally, no clear evidence emerged that changes in RMR or EIEE following weight loss predict weight regain at 1 year.

Hunger

At 1 year, there were no statistically significant correlations between weight loss and changes in subjective ratings of appetite.

However, there was a statistically significant decrease in cholecystokinin, ghrelin, and insulin with weight loss at week 13. However, after adjusting for age, sex, and magnitude of weight loss no significant hormonal predictors of weight regain were found.

At 1 year however, there were statistically significant decreases in cholecystokinin and ghrelin levels that persisted after adjusting for age, sex, and magnitude of weight loss, which were associated with weight regain at 1 year.

Why does this article matter?

Overall, this study suggests that changes in RMR, EIEE, subjective ratings of hunger, or hunger-related hormone changes predict weight regain. However, we need to briefly explain the reported correlation between weight regain and decreases in cholecystokinin and ghrelin levels at 1 year.

To begin, cholecystokinin (CCK) is a hormone that is widely distributed throughout the gastrointestinal tract and the central nervous system. There are close to 100 types, classified by the number of amino acids they contain, i.e. CCK-5, CCK-8, etc. It has a number of physiological effects including the stimulation of gallbladder contraction, both pancreatic and gastric acid secretion, and it slows gastric (stomach) emptying. From an appetite standpoint, it has been shown to reduce hunger and suppress energy intake between meals. Said differently, CCK levels rise after a meal and are involved in promoting satiety between meals. However, the role of administering CCK exogenously (taking CCK) and the effect of CCK on total daily energy intake are less clear. Presently, the evidence to support a role for CCK in the long-term control of energy intake is weak.[Little 2005]

In this month's study, CCK levels decreased from baseline to week 13 and then increased from the lower level to higher than baseline levels between week 13 and the 1-year follow up. Despite the small correlation between CCK's increase and weight regain, I don't think this implicates CCK as a causative element. If anything increases in CCK should be associated with hunger suppression, yet this particular study found the opposite relationship. I find this to be interesting, yet unconvincing overall.

Next, this study found that ghrelin increased from baseline to week 13 and then decreased from week 13 to the 1-year follow up. Ghrelin is a hormone that is made and released from the stomach in response to fasting, which subsequently increases food-seeking behavior and appetite. Conversely, its synthesis and release are both downregulated by consuming a meal. In a meta analysis looking at the effect of ghrelin levels and weight regain, Strohacker *et al.* found that:

"None of the available studies support the hypothesis that higher levels of ghrelin predict weight regain. Three studies found no association between weight loss-induced

increases in ghrelin and weight regain. Taken together, almost no studies found that higher ghrelin measured at any time point during weight loss predicted more difficulty with weight loss maintenance."[Strohacker 2013]

Similar to CCK's relationship to weight regain in individuals in this study, I think this particular study's findings are interesting, yet unconvincing overall. In short, I don't think the relationship between CCK or ghrelin levels are important in predicting weight gain in individuals who have undergone weight loss.

With that being said, the current perception is that participants of a structured weight-loss program regain all of their weight loss within 5 years. However, Greenway *et al* performed a meta-analysis of twenty-nine studies looking at 5-year weight loss maintenance. They found that on average, obese individuals were able to maintain weight losses of 3.2% of their initial body weight when participating in structured weight-loss programs and thus, do not regain all of the weight lost at 5 years of follow-up.[Greenway 2015]

Nevertheless, achieving and maintaining weight loss of 5-10% should be the goal and Greenway's meta-analysis suggests that maintenance of clinically-significant weight loss can be very difficult. Indeed, the prevention of weight regain is the most clinically relevant challenge after achieving the initial diet-induced weight loss.

We need to better understand this issue in order to succeed in tackling the obesity epidemic. This month's study adds to the mounting evidence that changes in RMR, EIEE, and hunger *are not* the smoking guns with respect to weight regain, which ultimately contradict the "compensatory mechanism" theory. Rather, the findings of this month's article suggest that there may be other issues contributing to weight regain, i.e. genetic predispositions, non-hunger-related dietary adherence issues, other hormonal changes, etc.

Finally, the National Weight Loss Control Registry (NWLCR) suggests that many individuals can obtain clinically significant weight loss (5-10%) and keep it off for extended periods of time. At present, the average duration of weight loss maintenance in NWLCR subjects is just over 10 years. We need to continue researching this topic from new perspectives in order to reduce obesity's burden on our society.

Thanks for reading, folks. See you next month!

-Jordan Feigenbaum

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Author Information

Austin Baraki, MD

@austin_barbellmedicine

draustin@barbellmedicine.com

What factors promote participation and adherence to resistance training?

Factors associated with participation in resistance training: a systematic review by Rhodes et al. 2017.

Key Points:

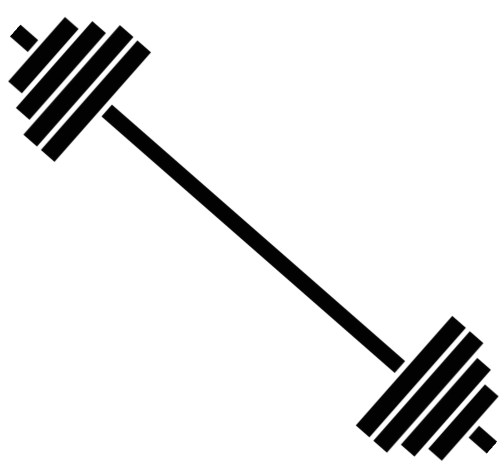
1. This review of the literature identified numerous biological, psychological, and social/contextual factors that have been studied for their association with participation in resistance training (RT).

2. The authors found that individuals' perceived health, affective judgements (i.e., beliefs, feelings, and expectations) towards RT, self-efficacy, and self-regulation behaviours, as well as interpersonal factors such as subjective norms and training program leadership are important for promoting RT participation. Evidence regarding the role of environmental factors is sparse, but transportation and access to facilities/equipment appear to be important.

3. Participation in RT was low among individuals with low education levels and poor health status. However, other factors such as race, sex, employment status, alcohol and tobacco use, and marital factors did not have consistent evidence indicating an association with RT participation.

Introduction

Promoting healthy behaviors is the primary thrust of most public health interventions. However, there is enormous variability in individual engagement with such behaviors, including meeting guideline recommendations for diet and physical activity.



According to the 2018 Physical Activity Guidelines for Americans, recommendations include [Piercy 2018].

1. Cardiorespiratory exercise:
    Moderate-intensity activity x 150-300 min/wk, OR
    Vigorous-intensity activity x 75-150 min/wk, OR
    A combination to expend **≥ 500-1000 MET-minutes/week***

2. On 2-3 days per week, adults should also perform resistance exercises of moderate or greater intensity for each of the major muscle groups.

**A metabolic equivalent, or MET, represents the ratio of the metabolic rate during an activity compared to the metabolic rate at rest. 1 MET is equivalent to 1 kilocalorie per kilogram bodyweight per hour, which is the approximate energy cost of sitting quietly. Therefore, a 5-MET activity uses 5 times the energy of sitting at rest, and a 5-MET activity performed for 20 minutes would achieve 100 MET-minutes of energy expenditure. The established public health target for energy expenditure, as noted above, is a total of 500-1,000 MET-minutes of moderate-to-vigorous activity per week.*

Specific resistance exercise recommendations from the American College of Sports Medicine include performing 8-10 exercises involving the major muscle groups for 8-12 repetitions each, using moderate- (5–6) to vigorous- (7–8) intensities using an effort scale (RPE) of 0 to 10. And as an aside, regardless of what anyone might think of such an initial programming recommendation, the key component of any program that drives long-term adaptation is *progressive overload* [ACSM 2009]. So even if one views this sort of initial programming recommendation as "sub-optimal" for whatever reason, our view is that if the program is progressively loaded over time, we can likely achieve equivalent long-term positive health outcomes.

Rates of guideline-concordant resistance training (RT) participation in nationally representative datasets is estimated to range from 10-30%. [Bennie 2016, CDC 2013, Loustalot 2013] While there is a large body of evidence on factors influencing people's engagement with general physical activity or with aerobic-type activity, there has been little synthesis of the evidence with respect to RT.[Bauman 2012] Similar to the nutrition front -- we can put out as many official guidelines as we'd like, but that has little influence on real-world behaviors that are influenced by a number of more complex biological, psychological, sociocultural, and economic contextual factors. **It is unproductive and unethical to dismiss people as being "non-compliant" or stigmatizing them for "not caring about their health" when there may be a number of complex modifiable and non-modifiable factors influencing the ultimate behavior.**

Purpose

This study aimed to review the literature and describe the demographic, behavioural, intrapersonal, interpersonal, and environmental factors associated with participation in resistance training.

Subjects

Upon initial screening of the literature, two independent reviewers identified a total of 77 articles that were potentially relevant for review. A total of 26 studies were ultimately excluded for reasons described in the paper; these included mixed-intervention studies (*e.g.*, combined RT and aerobic training) and other limitations. A total of 51 independent data sets from nine different countries were ultimately included, representing 164,378 subjects across nine countries. Thirty-eight studies included both men and women and the average study length was 7.3 months.

Methods

After initial screening, a total of 51 data sets were included in this systematic review (as described above). Risk of bias assessments were also performed by independent reviewers using standardized criteria and found that the overall dataset was at moderate risk of bias. The large degree of heterogeneity in study designs and resistance training interventions prevented meta-analysis of the data.

The authors analyzed all included studies for the association between specific factors and resistance exercise participation. They used a socioecological framework to identify themes and subthemes to “categorize” the factors.

If a particular factor showed a positive association with RT participation (including both statistical significance and clinically meaningful effect sizes) in greater than 59% of studies included, it was deemed to be a positive factor. If a positive correlation was found in 34-59% of studies, the overall association was deemed inconclusive. If < 34% of studies showed an association, no overall association was concluded. Similarly, a negative association in greater than 59% of studies included was required to define a negative factor, with the same percentage cutoffs for inconclusive results or no association.

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Findings

The authors identified five general themes among the included articles:

1. Demographics

There was little evidence that **race**, **sex,** or **employment status** had any reliable association with participation in RT. **Age**, **BMI**, and **income** showed inconsistent associations with RT participation, although suggested that older individuals and those with higher BMIs may be less likely to participate.

All of the large-scale studies showed a significant relationship between **education** and RT participation, with college graduates participating in RT with **1.7 to 2.5 times greater odds** than high school graduates.

Positive perceived health showed a medium- to large effect size on RT participation, with those reporting "superior" perceived health having 13.5 **times greater likelihood** of meeting RT frequency recommendations. Higher **perceived quality of life** and lower levels of **fatigue** showed small to medium effect sizes with respect to RT participation.

2. Health Behaviors

The evidence showed an inconsistent relationship between **alcohol use** or **smoking** and RT participation. There was also conflicting evidence on the association between **overall physical activity** levels and participation in RT.

3. Intrapersonal factors

There was consistent, strong evidence that **affective judgments** were positively associated with RT participation. Affective judgments are defined as "*judgements about the overall pleasure/displeasure, enjoyment, and feeling states expected from enacting an activity.*" [Nasuti and Rhodes 2013] In other words, general emotions and feelings towards physical activity, as well as *expectations* about what it is going to feel like (*e.g.*, whether it will be enjoyable or unpleasant), are predictive of participation. [Rhodes 2009]

There was also consistent evidence indicating a positive relationship between **self-efficacy** (*i.e.*, perceived behavioral control) and RT participation. However, the authors add the caveat: "*the effectiveness of interventions to increase RT participation by promoting self-efficacy is unclear.*"

Self-regulatory behaviors (e.g., self-monitoring, goal-setting, planning, and tracking) showed consistent positive association with RT participation, with medium to large effect sizes.

Other factors such as **perceived benefits of RT** and **perceived barriers to RT** had mixed evidence overall. Among 21 quantitative studies, ten studies showed a positive association between perceived benefits and participation, while eleven studies showed no relationship. Regarding barriers to RT participation, the evidence found lack of time to be the most commonly cited barrier, followed by poor health and financial costs of RT.

4. Interpersonal factors

There did not appear to be a consistent association between **marital status** and engagement in RT. The evidence regarding **social support** was mixed; out of fourteen total studies examined, six qualitative studies and two quantitative studies suggested social support as an important factor. For this reason, the relationship between social support and RT participation remains unclear.

There was consistent evidence that **subjective norms** -- i.e., *perceived social pressure or approval* for performing a behavior -- had a small, but positive effect on RT participation.

There was also consistent, strong evidence of RT **program leadership** and ongoing adherence to RT.

5. Environment

The authors only identified one study in the literature examining the role of environmental factors in RT participation, which they describe as a *"rather glaring omission in this literature."* Specifically, they found that:

> *"Built environment factors such as access to transport, access to shops, access to recreation facilities and having a vehicle were all related to participating in RT. In addition, people with home RT equipment were 4.5 times more likely to participate in RT."*

But given the large body of existing research on environmental correlates of *general* physical activity, more research is needed specifically for resistance training.

Why does this article matter?

This large study helps elucidate some of the factors promoting and hindering broader engagement with resistance training in the population. These factors provide potential targets for intervention in efforts to promote resistance training participation.

One strength of this study is the collection of a very large, multi-national data set that included both men and women, as well as healthy individuals and those with various medical conditions (e.g., multiple sclerosis, cancer, or chronic obstructive pulmonary disease). However, due to the broad heterogeneity among the included studies (e.g., variability in RT interventions), the authors could not perform meta-analysis on the data. Additionally, the bias assessment indicated that overall, the included studies were at moderate risk of bias. The authors also point out that restricting their systematic review to English publications may introduce components of publication bias and language bias, limiting the generalizability of the findings to non-English speaking populations. In other populations these same factors may have different effects, or there may be entirely different sociocultural/environmental factors that exert more significant influence on likelihood of participating in RT.

The authors identified numerous biological, psychological, and social/contextual factors that have been studied for their association with participation in resistance training. And, consistent with the broader literature on behavior change and physical activity, there are identifiable factors from each of these domains that appear to influence ultimate behavior.

As mentioned above (and as discussed in our recent podcast on nutrition from a public health perspective), simply providing guidelines for dietary or exercise recommendations remains a woefully inadequate intervention in order to actually change human behavior on a large scale. If we are to have any hope of successfully influencing large-scale behavior change, we must identify and target as many modifiable / intervenable factors as possible. For example, this study would suggest that specific interventions targeted towards sex, race, or employment-specific factors are less likely to be beneficial than interventions targeted towards education, self-effcacy and self-regulatory behavior, and providing program leadership. Similarly, as in other domains, identifying individuals' perceived barriers to participation such as lack of time or poor health may provide specific targets for improving participation and compliance on an individual level.

Affective judgments represent a particularly interesting area, given that these judgments can have strong social influences. In other words, our feelings towards RT and their expectations of how it will feel can be informed by what we observe and learn from others around us. For this reason, our choice of language and the way we discuss resistance training, as well as the culture we promote around resistance training, may be particularly important for RT promotion on a larger scale. For example, we have observed those who dramatize the experience of resistance training by describing it using violent or graphic language, talking about how training must be *brutally hard* or downright painful in order for it to be effective. These sorts of unnecessary and unhelpful dramatizations may be influencing the uninitiated and setting certain expectations or affective judgments that actually *hinder* their likelihood to initiate and adhere to long-term resistance training.

In addition to these considerations, the authors point out the severe lack of evidence with respect to environmental determinants of RT participation. Given our understanding of these factors with respect to dietary interventions (e.g., availability of and access to healthy food), it is plausible that these exert particularly potent effects on resistance training participation. Lack of transportation or access to resistance training facilities likely present a substantial barrier to participation for a large proportion of the population and may ultimately require interventions on the government and public policy level to effect large-scale change.

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Author Information

Michael Ray, MS, DC

@michael_barbellmedicine

mike@barbellmedicine.com

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Is High Intensity Exercise Appropriate For Those Dealing With Axial Spondyloarthritis (axSpA)?

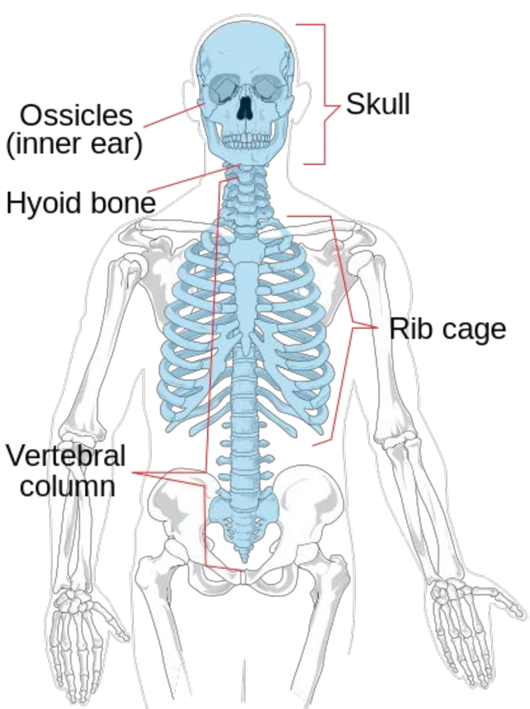
High intensity exercise for 3 months reduces disease activity in axial spondyloarthritis (axSpA): a multicentre randomised trial of 100 patients by Sveaas et al. 2019.

Key Points:

1. This article provides good quality evidential support for recommending high intensity exercise (cardiorespiratory- and resistance-based) for those dealing with axial spondyloarthritis (axSpA) while helping to dispel unfounded fear around such recommendations.

2. The exercise intervention resulted in improvement in disease activity and markers of cardiorespiratory fitness (VO2peak) with minimal adverse events.

3. The randomized control trial was clinician-conducted, demonstrating the effectiveness of such exercise based interventions in clinical practice.



Introduction

Axial spondyloarthritis (axSpA) is an umbrella phrase for chronic inflammatory issues affecting the axial spine (see blue structures in photo). Such disorders include:

- *Ankylosing Spondylitis*
- *Psoriatic arthritis*
- *Reactive arthritis, and*
- *Inflammatory bowel-related arthritides (Crohn's and Ulcerative Colitis)*

The prevalence of axSpA is between 0.32% and 1.4%.[Sieper 2017] *Although this is a low prevalence rate, this population still necessitates evidence based interventions to aid with disease activity and quality of life. Often, issues with low prevalence rates have a lack of research and thus evidence based information to aid with decision making; further intensifying the need for well conducted trials.*

Clinical Presentation:

Patients may report persistent spinal pain usually involving the low back & pelvis. Typical features include morning stiffness that is relieved with activity but not rest, as well as night pain. Admittedly, there is heterogeneity in subjective reporting from patients, and other issues may present with a similar history as well - making the diagnosis difficult.

Axial spondyloarthritis can present with changes to the sacroiliac (SI) joints and/or spine visible on X-ray (e.g., in ankylosing spondylitis) or without X-ray findings altogether. The latter situation is termed *non-radiographic* axial spondyloarthritis.[Sieper 2017]

The primary issue with axSpA is inflammation, which may result in spinal structural changes leading to decrements in mobility (defined as the ability to move).[Hoyer 2018]

Other common presentations include peripheral joint involvement via arthritis and/or enthesitis. Arthritis-based symptoms present in the lower extremities with inflammation of the joints (swelling) and possibly pain. *Enthesitis* describes inflammation at the sites where ligaments and tendons attach to bone. A common area for enthesitis is the Achilles tendon. Finally, another common extra-articular finding is uveitis (inflammation of the uvea, a part of the eyeball).

Purpose

Exercise has previously been demonstrated to have a small but beneficial effect on disease activity for this patient population.[Sveaas 2017] However, the dosage typically recommended to those dealing with axSpA is low. Many clinicians are fearful of recommending high-intensity exercise to this patient population for fear of eliciting a flare-up in symptoms and/or disease activity. Given that exercise appears to be under-dosed for these patients, perhaps the historically observed benefits of exercise could be improved with higher dosed exercise interventions. **The authors set out to determine the effects of a 12-week exercise intervention inclusive of high intensity cardiorespiratory and strength training on disease activity and cardiovascular health among participants with axSpA.**

Subjects

Participants were recruited from outpatient rheumatology departments and via social media advertisements in Norway and Sweden.

Study inclusion was based on the following:

- Meeting the Assessment of SpondyloArthritis International Society (ASAS) criteria for axSpA,
- Between the ages of 18 - 70 years old,

- No change in Tumor Necrosis Alpha (TNF)-inhibitor use during the previous 3 months
- Moderate - High disease activity at pre-screening based on a score greater than or equal to 3.5 on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and
- No regular engagement of cardiorespiratory and strength training in prior 6 months (no more than 1/week).

Study exclusion criteria were:
- Symptoms of Cardiovascular Disease (see table 1)
- Comorbidities resulting in reduction in exercise capacity and/or contraindications to exercise based on the American College of Sports Medicine guidelines
- Inability to participate in weekly exercise sessions
- Pregnancy

Table 1:

Cardiovascular Disease Exclusionary Screen		
1.Medical history for:		
Cerebral Stroke	Established Coronary Heart Disease (prior MI or angina pectoris)	Indication of ischemic heart disease
2.Patient's screened with the following questions at baseline:		
Relatives who have died suddenly and unexpected before the age of 40 years		
Indication of ischemic heart disease during physical activity such as chest pain, dizziness, or abnormal dyspnea		
First-degree relatives diagnosed with hypertrophic cardiomyopathy		
ECG signs of ischemic heart disease shown at a previous consultation		
3. Blood Pressure screened at baseline:		
If patients presented with either a systolic blood pressure > 200 mmHg or a diastolic blood pressure > 115 mmHg, then they were excluded due to contraindication for physical activity.		
4. Measured for atrial fibrillation at baseline:		
If A-fib was detected, then patients were excluded from the study.		

Methods

Originally 100 participants were part of a 3 month assessor-blinded two-armed multicentre randomised controlled trial comparing standard care (no intervention) and high intensity exercise. Three participants were lost to follow-up, leaving 97 included in the analyses. No significant baseline differences were identified between groups.

The exercise protocol followed ACSM guidelines for recommended cardiorespiratory and strength training (see Tables 2A & B). The exercise intervention group had 3 training sessions each week; 2 physiotherapist-supervised sessions inclusive of cardiorespiratory and strength training, and a single session of cardiorespiratory training on their own. To ensure exercise adherence, the physiotherapist maintained a record and participants kept an exercise diary.

Table 2A: Exercise Program (3 months)

Cardiorespiratory exercise (3 days / week)	
HRmax determined at the end of a maximal treadmill test	
High Intensity Interval Exercise	
Delivery	Supervised by a physiotherapist at the hospital or a fitness center.
Type	Walking or running on a treadmill/cycle ergometer.
Frequency	2 days per week.
Intensity	• 10 min warm up at 70% of HRmax. • 4 x 4 min interval exercise at 90-95% of HRmax with 3 min of active resting period at 70% of HRmax between each interval. • 3 min cool down at 70%. • The intensity was controlled by a Polar puls watch during each session.
Time	38 minutes
Home Session	
Delivery	Unsupervised individual training.
Type	Walking/running/cycling outdoor or at fitness center.
Frequency	1 day per week.
Intensity	≥70% of HRmax. The intensity was controlled by a Polar puls watch.
Time	≥40 minutes

Table 2B: Exercise Program (3 months)

Muscular Strength Exercises (2 days / week)	
Delivery	Supervised by a physiotherapist (performed after the high intensity interval exercise). Started with 2-3 weeks with gradually adaption before the work load was set to 8-10 repetitions maximum.
Type	Six exercises for major muscle groups, individually adapted. Preferably with external load. Examples of exercises: Squat, leg press, deadlifts, rows to chest, bench press, shoulder press, pull downs and sit-ups.
Pattern	Circle of exercises or switching between two exercises (no rest-intervals).
Frequency	2 days per week.
Intensity	8-10 repetitions maximum
Time	20 minutes
Repetitions	8-10 repetitions
Sets	2-3 sets
Progression	If the patient could perform more than 10 repetitions per sets, the workload was increased.

Of note, the participants were allowed to exercise with tolerable pain levels; defined as less than or equal to 5 on a scale of 0 to 10. If participants pain symptoms worsened the day after a training session, then adaptations were made to the exercises.

The control group was instructed to continue with their usual physical activity level and received "standard care". A retrospective questionnaire was administered to the control group to assess exercise habits during the intervention period.

Safety of participants was monitored by assessing disease flare-ups post-intervention. assessment was based on disease activity via the Ankylosing Spondylitis Disease Activity Score (ASDAS), BASDAI, and the blood inflammatory markers C-reactive protein and erythrocyte sedimentation rate (ESR). Physiotherapists were also tasked with reporting any adverse events.

Outcomes

Baseline outcome measurements were taken at the beginning of the study and again immediately following the intervention period. Outcomes assessed included: ASDAS, BASDAI, and a clinical examination by an assessor who was blinded to group randomization. The clinical examination consisted of resting HR, blood samples, flexibility tests, and a treadmill test.

The primary outcome of interest was disease activity based on the ASDAS and BASDAI.

The ASDAS includes a composite score from C-reactive protein plus 4 patient-reported variables measured on an 11-point numeric rating scale:

1) Neck/back/hip pain
2) Peripheral joint pain
3) Duration of morning stiffness
4) Patient global assessment

The ASDAS uses the following classification system:

- Inactive disease <1.3
- Low disease activity 1.3-2.1
- High disease activity 2.1-3.5
- Very high disease activity >3.50

The minimum clinically important difference (MCID) for ASDAS is 1.1 units for "clinically important improvement" and 2.0 units for "major improvement".[Magrey 2019]

Similar to the ASDAS, the BASDAI is a questionnaire consisting of 5 patient reported symptoms measured on an 11-point numeric rating scale:

1) Fatigue

2) Neck/back/hip pain
3) Peripheral joint pain
4) Tenderness
5) Degree/length of morning stiffness

Once the above variables were measured, a sum score from 0 to 10 was calculated (0 = no disease activity and 10 = very active disease). MCID for those reporting a BASDAI > 4 (potentially high disease activity) is 1.1 as well as a minimal 50% change.[Magrey 2019]

Secondary outcomes included assessment of physical function via the Bath AS Function Index (BASFI). The BASFI is a series of questions rated on an 11-point numeric rating scale (0 - 10, with 10 = worst) and a sum score calculated. Participants spinal mobility was also assessed via the Bath AS Metrology Index (BASMI), which consists of five measurements for spinal mobility rated on a numeric rating scale of 0 to 10.

1) tragus-to-wall distance,
2) cervical rotation,
3) modified Schober's test,
4) lateral spinal flexion and
5) intermalleolar distance.

A mean score is calculated from the five measurements equaling a final score of 0 to 10 (10 = worst).

Cardiorespiratory fitness was measured via a maximal treadmill test based on the Balke protocol (see online supplementary file 3 for explanation). At the end of the treadmill test, peak oxygen uptake (VO2peak mL/kg/min) was estimated.

Waist circumference, BMI, and lean body mass (via a dual-energy X-ray absorptiometry scan) were also assessed. Finally, blood samples were completed after 4 hours of fasting for measurement of CRP and ESR levels.

The authors defined improvement based on ASAS20/40:

> *"ASAS20 is defined as a relative improvement of ≥20% and an absolute improvement of ≥1 unit in at least three of the four following domains; patient global assessment, pain, physical function and morning stiffness, and no worsening of ≥20% and ≥1 unit in the remaining domains. ASAS40 response is defined as a relative improvement of ≥40% and an absolute improvement of ≥2 unit in at least three of the four domains that are defined for ASAS20, and no worsening at all in the fourth domain."*

The authors calculated a necessary sample size of 100 participants. The randomization process was computer generated and participants were allocated to a group after the physiotherapist assessment. The outcome assessor was blinded to group allocation, however participants and physiotherapist supervising exercise were not, and this likely wouldn't have been possible.

Results

Primary Outcomes

Table 2 – Primary outcomes. Effect of high intensity exercises on disease activity. Values are shown as mean with SD unless stated otherwise.						
	Exercise group (n=48)		Control group (n=49)		Estimated mean group difference (95% CI)*	P values
	Baseline	3 months	Baseline	3 months		
Primary Outcome						
Disease activity score ASDAS	2.6 (0.8)	1.9 (0.7)	2.7 (0.6)	2.6 (0.7)	-0.6 (-0.8 to 0.3)	<0.001
Disease activity score BASDAI †	4.9 (1.6)	3.3 (1.6)	5.3 (1.5)	4.8 (1.5)	-1.2 (-1.8 to 0.7)	<0.001
Inflammatory marker						
CRP (mg/L), median (range)	2 (1, 28)	2 (1, 29)	1 (1,13)	2 (1,14)		0.041‡

*Analyzed with Mann-Whitney U test.
†Measured with numeric rating scale (0-10, 10=worst)
‡Estimated mean group difference, analyzed with analysis of covariance with adjustments for baseline values and study center.
ASDAS, Ankylosing Spondylitis Disease Activity Score (higher score = worst); BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C reactive protein.

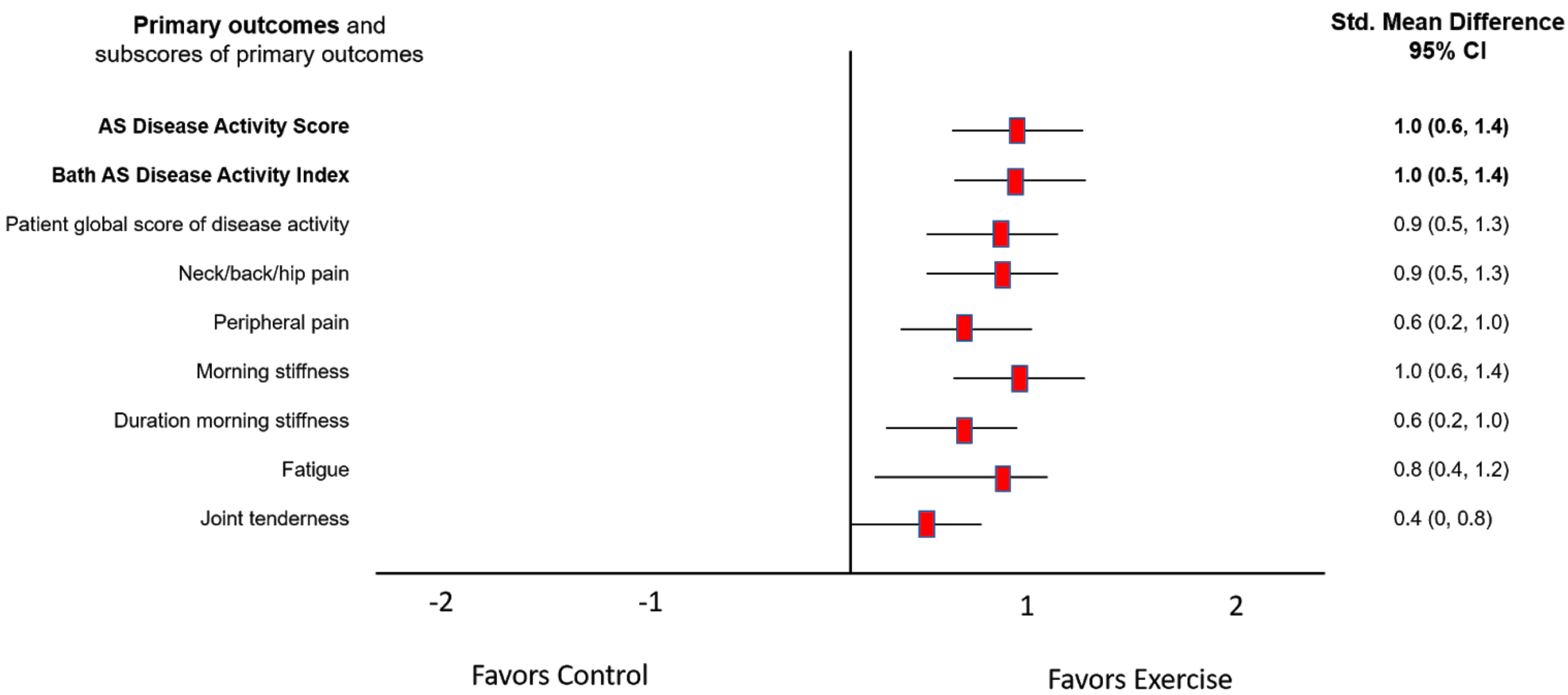
The ASDAS demonstrated a between group difference of 23% (see table 2). The exercise group had a 27% change from baseline to the end of the exercise intervention (3 months) vs a 4% change in the control group (2.7 to 2.6). The BASDAI demonstrated a 24% between group difference (see table 2) with a 33% difference between baseline and intervention for the exercise group vs 9% difference for the control group.

ASAS20/40 Improvements:

Absolute increased benefit (AIB) was 42% (95% CI, 25% to 58%) at the end of the intervention. AIB is the calculated difference between the proportion of participants having a 20% and 40% ASAS improvement due to the intervention. 25 patients (52%) in the exercise group and five patients (10%) in the control group achieved a 20% improvement. Additionally, the numbers needed to treat (NNT) for a positive benefit of the intervention for one additional patient was 3 (95% CI, 2 to 4).

AIB was 33% (95% CI, 19% to 48%) at the end of the intervention for 18 patients (38%) in the exercise intervention group vs 2 (4%) in the control group with 40% improvement. This improvement also demonstrates an NNT of 3 (95% CI, 2 to 5).

Figure 2 Forest plot of the effect of high intensity exercises on primary outcomes, the disease activity indexes with sub-scores.



The above Forest plot displays standardized mean difference (SMD, effect sizes) with 95% CI.

- 0.2 - 0.4 = small effect size
- 0.5 - 0.7 = medium effect size
- ≥0.8 = large effect size

Fatigue, morning stiffness, neck/back/hip pain, patient global score of disease activity, BASDAI, and ASDAS all demonstrated large effect sizes favoring the exercise intervention.

Secondary Outcomes

Secondary outcomes demonstrated further support for the exercise intervention. Cardiorespiratory fitness had an 8.2% between group difference in VO2peak; estimated mean group difference of 2.7 (95% CI, 1.6 to 3.8). Other variables showing improvement included physical function (BASFI) with a 27% between group difference (38% vs 11%), and flexibility with a 10% between group difference (14% vs 4%). See table 3 in the article for all secondary outcomes.

Adverse Events

One patient from the exercise group experienced chest pain and nausea during the intervention, prompting the person to switch to moderate intensity exercise under the guise of their cardiologist. Additionally, only two patients reported persistent pain during the exercise intervention.

Why does this article matter?

Physical activity (PA) is highly recommended for those dealing with axial spondyloarthritis. The 2018 European League Against Rheumatism recommends *"...physical activity should be an integral part of standard care for people with RA/SpA/HOA/KOA."*[Osthoff 2018] However, the authors listed a primary directive for future research "*to evaluate the long-term effectiveness of PA at different intensities and types and monitoring of adverse events (AE).*"

As mentioned earlier, Sveaas et al conducted a 2017 systematic review on the effects of cardiorespiratory and strength training for this patient population and found small, but beneficial effects for disease activity scores, joint damage, symptoms, and erythrocyte sedimentation rate with no effect on C-reactive protein.[Sveaas 2017] In the most recent Sveaas article, the authors argue perhaps only a small effect was seen due to the under dosing of exercise interventions.

Although many are advocating for exercise in this cohort, little is known about the appropriateness of higher intensity exercise and many healthcare professions shy away from recommending this type of exercise for fear of worsening disease activity and eliciting flare-ups - despite there appearing to be no strong evidence at this time to recommend against such activities.

In their most recent article, Sveaas *et al* effectively demonstrated the positive benefits of high intensity cardiovascular and strength training by observing improved disease activity in this patient population as well as improved cardiorespiratory fitness via improved VO2peak, potentially leading to a reduction Cardiovascular disease (CVD) risk.

CVD risk is something to consider for this population given prior research has demonstrated an increased risk of MI and stroke.[Mathieu 2018] According to Sveaas *et a*l, those dealing with axSpA have also been demonstrated to have lower cardiorespiratory fitness than the general population. The authors argue their study demonstrates an important effect on cardiorespiratory fitness and CVD risk, *"In the present study, the mean treatment effect of 2.7 mL in VO2peak indicates large health gain, as it has been reported that every 1 mL increase is associated with a 15% decrease in CV death."*

Additional strengths of this article include being a clinician conducted randomized control trial demonstrating the effectiveness of this intervention in clinical practice. The study also utilized well-supported subjective and objective outcome measurements. Adherence for this study is also considered good given thirty eight patients (76%) from the exercise intervention group maintained compliance with ≥80% of the exercise protocol. Only four patients stopped the exercise intervention. Activity in the control group was likely not a major confounder given only five (10%) patients in the control group completed cardiorespiratory or strength training (≥2/week) during the three month intervention. The study also had a low drop out rate. Finally, the NNT is considered low (3) demonstrating a minimal reach for future positive effects in patients.

Limitations

The exercise intervention didn't meet the recommended MCID of 1.1 for the ASDAS. However, the effect sizes for the intervention were large for both primary outcome measures (ASDAS and BASDAI).

Another limitation is that the study was only 3 months in duration. It would be interesting to see if the beneficial effects of higher intensity exercise were sustained, magnified, or attenuated with a longer duration, as well as being able to assess long term changes in disease activity. Furthermore, the authors appear to be arguing for a positive effect on the inflammatory process by affecting CRP. The measured CRP remained the same in the exercise intervention group but worsened by 1 unit in the control group. Whether this should be considered as evidence for positive effect on blood inflammatory markers is debatable, given that blood ESR remained the same for both groups. A longer study duration may provide more insight on the effects of higher intensity exercise on blood inflammatory markers.

The authors also bring up a good point about the potential confounding effects on reported outcome measures due to the increased contact time between clinician and patients for the exercise intervention compared to the control group. Continued interaction can likely play a role in positive psychological effects on the exterice intervention group and thus improved reported outcomes/symptoms.

Finally, resistance exercise dosage likely needs further study for this patient population. It is debatable whether the exercise guidelines outlined in Table 2B for muscular strength exercises should be considered of high intensity. The cardiovascular exercise recommendations have clear cut explanations based on heart rate for measuring intensity levels (as denoted by 4 x 4 intervals at 90-95% of maxHR), as well as an objective marker of improvement in cardiorespiratory fitness as measured by VO2peak. However, such standards are lacking in the muscular strength exercise guidelines and no strength based objective measurement was utilized. Of note the authors did utilize a DEXA scan to track lean body mass changes between groups, but examining table 3 below - there doesn't appear to be any significant effects in the exercise group vs the control group besides waist circumference (which this may be predisposed to a sampling bias given the inclusion criteria for data analysis for this variable). This likely speaks to the underdosing of the strength training protocol.

Table 3 – Effects of exercise on secondary outcomes. Values are shown as mean with SD unless stated otherwise.

	n	Exercise group (n=48)		n	Control group (n=49)		Estimated mean group difference (95% CI)*	P values
Secondary Outcomes		**Baseline**	**3 months**		**Baseline**	**3 months**		
Weight	48	82.2 (19.4)	82.2 (19.1)	48	84.3 (16.3)	84.1 (16.4)	0.2 (-0.8 to 1.1)	0.740
BMI	48	27.5 (5.1)	27.5 (5.0)	48	28.7 (6.4)	28.7 (6.4)	0.1 (-0.3 to 0.4)	0.677
Waist circumference‡	35	100.6 (13.3)	99.8 (12.5)	37	102.4 (13.5)	103.2 (13.6)	-1.7 (-3.2 to 0.2)	0.031

‡ Only patients with an increased waist circumference at baseline are included in the analyses (males >94 cm and females > 80 cm).

The authors appear to have utilized circuit training with no rest allowed between each resistance training exercise. The intensity appears capped at 8-10 repetition maximum and 20 minutes allotted for completion. Progression was based on the patient's ability to complete more than 10 reps with a particular weight. However, we are unsure of how these standards measure up to a percentage of the patient's estimated 1RM (e1RM) or internal perception of difficulty of the exercise, typically measured via Rate of Perceived Exertion (RPE). A recent article by Morton *et al* discusses current best practices for improving strength and hypertrophy. Although fully discussing this topic is beyond the scope of this article, the authors highlight several relevant factors when designing a resistance training protocol with the goals of improving strength and/or hypertrophy:

- *Changes in muscle mass and strength are mediated by the FITT principles*
    a. *Frequency: more sessions per week may mediate (volume-dependent) muscle size*
    b. *Intensity (effort): volitional fatigue and internal focus increase muscle size*
    c. *Type: exercise selection and high loads mediate muscle strength*
    d. *Time: performing more repetitions (volume) may mediate muscle size*
    e. *Other variables (e.g., inter-set rest, time under tension) have little influence on outcomes*[Morton 2019]

However, this study is a step in the right direction and a case can be made the protocol utilized is a sufficient first step in non-trained/minimally-trained individuals. Further long-term follow-up would help fine-tune the appropriate dosage recommendations to improve disease activity, quality of life, and performance markers in this population.

In closing Sveaas *et al* state,

> *"We conclude that high intensity exercise should be strongly considered as a part of treatment of axSpA. Future studies should examine the effects of longer exercise interventions with longer follow-up. It is also time to refine the high intensity exercise programme in clinical practice."*

Overall I'm in agreement with this conclusion and the authors did demonstrated positive effects with high intensity exercise training in those dealing with axial spondyloarthritis. Hopefully evidence such as this will continue to dispel fear based misinformation regarding exercise recommendations for those dealing with axial spondyloarthritis.

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Author Information

Derek Miles, PT, DPT

@derek_barbellmedicine

derek@barbellmedicine.com

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The Role of Strength Training in Improving Symptoms Related To Knee Osteoarthritis

The role of muscle strengthening in exercise therapy for knee osteoarthritis: A systematic review and meta-regression analysis of randomized trials by Bartholdy et al 2017

Key Points:

1. Different types of exercise, from aerobic exercise to strengthening exercises, have proven effective for symptom reduction and improving function in individuals with knee osteoarthritis.

2. Exercise interventions following American College of Sports Medicine (ACSM) guidelines provide superior outcomes for knee extensor strength but not pain or function in the setting of knee osteoarthritis.

3. A strength increase of at least 30% is needed to elicit clinically significant improvements in pain and disability.

Introduction

The prevalence of knee osteoarthritis (OA) has nearly doubled in the last 50 years.[Wallace 2017] While the base rate of OA on X-rays in the asymptomatic population over 40 years of age is 19-43%, the diagnosis is also associated with a high medical burden.[Culver 2018] [Vos 2012] As of 2010, approximately 4.7 million Americans (3.0 million women and 1.7 million men) were living with a total knee replacement.[Meredit Kramers 2015] With the physical, economic, and psychological burdens incurred by OA, we need to establish evidence-based approaches to stave off symptoms and increase function among these patients before resorting to costly, invasive interventions.

Exercise has long been advocated as a means of increasing physical function, yet Americans are becoming increasingly sedentary with the average teenager as active as the average 60 year old in some studies.[Varma 2017] The current ACSM recommendation for strength training exercise is 2-3x/week, yet only 18.6% of Americans meeting this recommendation.[Dankel 2016] Of those who did in the Dankel study, they were at a 23% reduction in all cause mortality. While this reduction is multifactorial in that individuals who resistance train likely have other advantageous behaviors, resistance training has also been correlated with reduced mortality in other longitudinal studies after controlling for other health behaviors as well.[Kraschnewski 2016] In a separate analysis, Dankel sought to determine whether the simple behavior of exercising was more important than the results of exercise (e.g., *actually getting stronger*). They found that individuals who were in the top quartile for meeting strengthening activity guidelines *and* top quartile for lower extremity strength had a reduction in all cause mortality of 72%.[Dankel 2016] Individuals who only met exercise recommendations had a risk reduction of 4%, but those in the top quartile of strength but not meeting the recommendations at 46%.[Dankel 2016] This is of course for all cause mortality and not specific to OA but it certainly makes a case for getting and being strong having a large influence on outcomes later in life.

Specific to knee OA, decreased strength of the knee extensors (i.e., quadriceps) has been shown to be a risk factor for developing symptoms and functional deterioration.[Culvenor 2017] Ruhdorfer *et al* took this one step further by demonstrating that while thigh muscle weakness was associated with symptoms, it was *not* related to radiographic disease (i.e., severity of X-ray appearance).[Ruhdorfer 2014] So, if being stronger can help individuals both feel and function better with knee OA, we need to know *how much* stronger we need to get them in order to obtain these benefits. While it could easily be argued that the proper answer is “no one has ever been too strong”, seeking objective measures to aim for with patients can be beneficial.

Purpose

The purpose of this study was to identify associations between changes in muscle strength, pain, and disability as well as analyze if exercise interventions following the ACSM criteria differ from other types of exercise.

Methods

This was a pre-registered systematic review with study selection, assessment of eligibility criteria, data extraction, and statistical analysis based off prior registration. The study included randomized or quasi-randomized controlled trials of at least one exercise intervention compared with no intervention, placebo, or waiting list. Knee OA needed to be diagnosed in one or both knees, and all studies needed to have a strength measurement of the lower limb and include outcome measures for pain and disability. No restrictions on BMI, gender, or age were applied.

Exercise interventions were classified as "ACSM interventions" if they met the criteria put forth by ACSM on resistance training:

> *"A voluntary contraction against an external resistance typically performed in especially designed equipment or with free weights. The external load should be above 40% of 1 repetition maximum (1RM) corresponding to very light to light intensity, and the exercises performed in 2-4 sets of 8-12 repetitions; preferably to contraction failure or muscular exhaustion. The exercise program should consist of at least 2-3 sessions per week."* [Garber 2011]

Eligibility was determined by two reviewers with data extraction performed in Excel. The Cochrane Collaboration Tool was used to assess risk of bias in the included studies.[Higgins 2011] Risk of bias was determined as adequate (low risk of bias), inadequate (high risk of bias), or unclear (insufficient information). The scoring was based on the Cochrane Handbook for judging different domains.[Higgins 2011]

The effect sizes on muscle strength and self-reported pain and disability were expressed at standardized mean difference (SMD). If necessary the authors approximated a mean score and standard deviation from figures in individual reports. The authors used I^2 as a measure of inconsistency, to be interpreted as the proportion of total variation in study estimates due to heterogeneity. The authors used random effects models fitted to a maximum likelihood (REML) model for evaluating the difference between studies using ACSM guidelines and those that did not for all 3 outcomes. A meta-regression analysis was used to determine the association between strength gains and pain and disability, with percent muscle strength gained as an independent variable and SMD for pain and disability as dependent.

Results

The literature search resulted in 4408 articles with 2251 being screened on title and abstract after removal of duplicates. Two-hundred and eight articles were reviewed in full text with 45 articles, and 56 comparisons included in the final analysis. The 56 comparisons included a total of 4699 subjects. The average age of the participants was 64 years (range 55-71) with the proportion of females to males ranging from 36% to

100%. The mean BMI of the participants was 29.6 kg/m^2 with a range from 22.4 to 33.9 kg/m^2.

Twenty-two of the interventions followed ACSM guidelines while 34 did not. Both the ACSM and non-ACSM studies had an average exercise period of 8 weeks with an average frequency of 3 sessions per week. Thirty-three comparisons had no intervention as their control group, 20 compared with a sham intervention, placebo, or attention control group, and 3 compared with a waiting control list.

Outcomes for Pain and Disability (ACSM Studies)

- Pain
  - WOMAC Pain (15 Studies)
  - Pain during walking (4 studies)
  - Brief Pain Inventory (1 study)
  - Pain During Motion (1 study)
  - Numeric Rating Scale (1 study)
- Function
  - WOMAC function (17 studies)
  - SF-36 Physical Component (1 study)
  - Lequesne Index (1 study)

Figure 1. Pain and functional outcomes distribution for studies meeting ACSM criteria for strengthening

Outcomes for Pain and Disability (non-ACSM Studies)

- Pain
  - WOMAC Pain (14 studies)
  - Pain during walking (5 studies)
  - Pain during standing (4 studies)
  - KOOS (4 studies)
  - Brief Pain Inventory (1 study)
  - AIMS2 arthritis pain (1 study)
  - VAS Pain (1 study)
  - VAS Pain during motion (1 study)
  - OASI Pain (1 study)
  - VAS Present Pain (1 study)
- Function
  - WOMAC function (16 studies)
  - KOOS function (3 studies)
  - Lequesne Index (4 studies)
  - Functional Incapacity score (1 study)
  - SF-36 Physical Component (1 study)
  - AIMS2 Mobility Level (1 study)
  - OASI Mobility Level (1 study)
  - Subjective rating of daily activity (1 study)
  - KOOS ADL (1 study)

Figure 2. Pain and functional outcomes distribution for studies not meeting ACSM criteria for strengthening

The benefits of exercise were seen in both groups for all outcomes across all studies. There was a statistically significant favor for ACSM exercise versus non-ACSM for increasing knee extensor strength (SMD: 0.448, 95% CI 0.091 to 0.805). No statistically significant difference was seen between ACSM and non-ACSM for effects on pain (SMD 0.106 95% CI -0.239 to 0.451) or disability (SMD 0.153 95% CI -0.239 to 0.549).

While there was a large degree of heterogeneity between studies (I^2=67.4%), a meta-regression of 53 studies demonstrated that a **gain of at least 30% in knee extensor strength is needed if a decrease in pain is to be expected.** For disability, meta-regression could be performed on 47 studies of which heterogeneity was also high (I^2=75.2%). Here, **a 40% increase in strength is necessary if a beneficial increase in function is to be expected.**

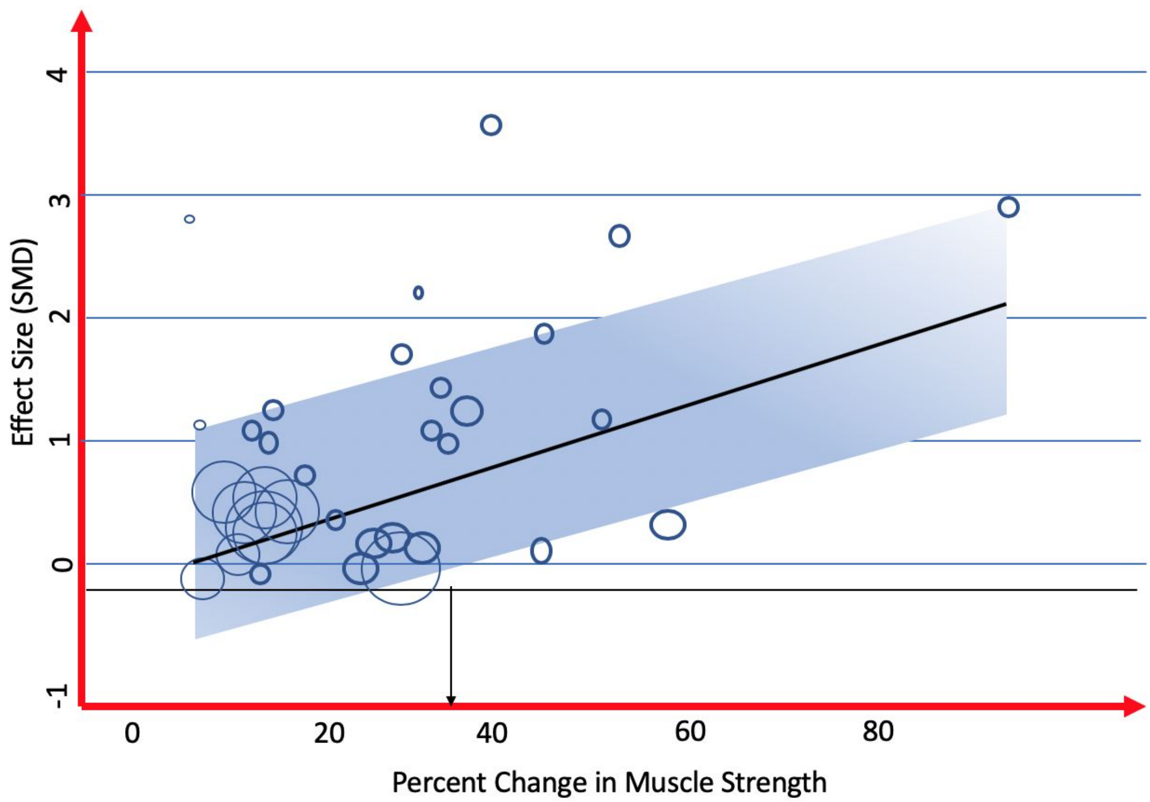

Figure 3. Meta regression with SMD of individual studies with respect to pain at different percentage changes of knee extensor strength

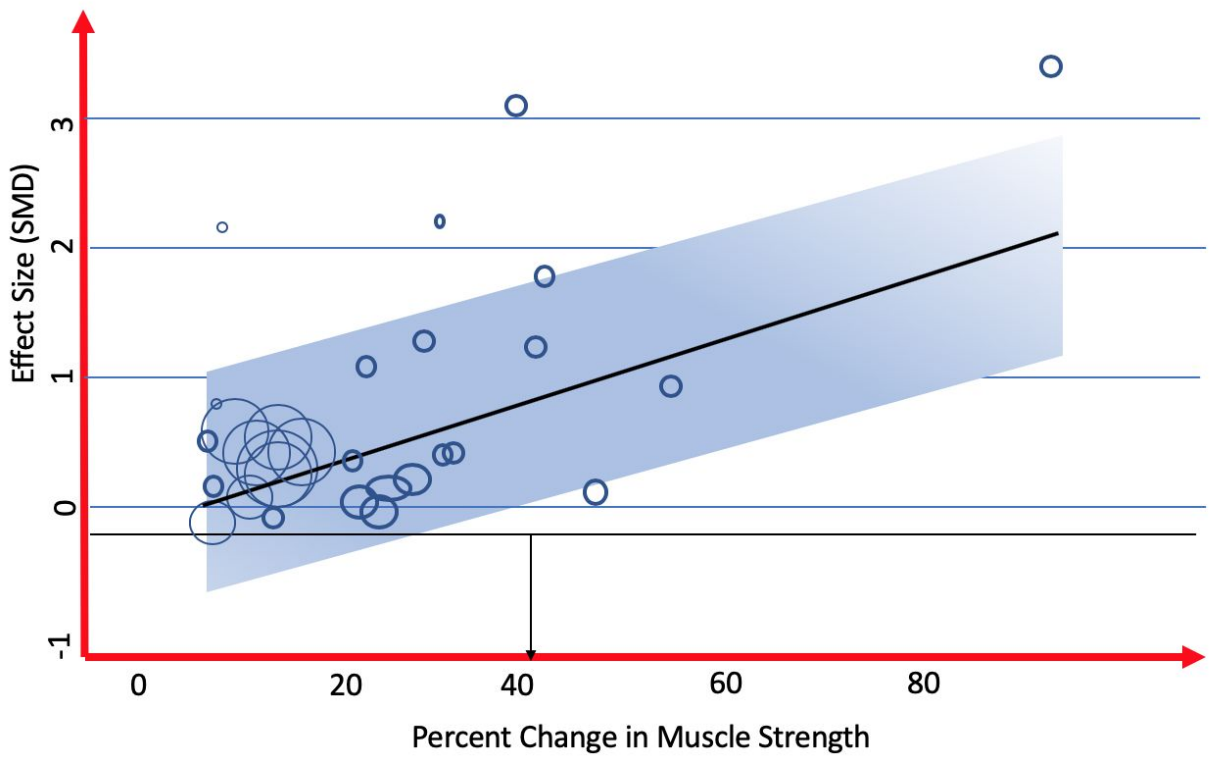

Figure 4. Meta regression with SMD of individual studies with respect to disability at different percentage changes of knee extensor strength

Why Does This Study Matter?

This study gives clinicians objective goals with which to aim when implementing exercise prescription for individuals with OA. Exercise is often prescribed haphazardly in rehabilitation environments without an emphasis on progressive overload or with a fear of incurring additional damage. From the Dankel study on exercise behavior versus strength outcomes influencing all cause mortality, actual strength wins out over behavior alone.[Dankel 2016] Evidence continues to mount that exercise is not only effective, but *necessary* for successful aging. The LIFTMOR trial has demonstrated ***heavy*** resistance training to be both safe and effective for older individuals, even among those with osteoporosis or a history of osteoporotic fracture.[Watson 2015] This trial showed increases in bone mineral density and function using the barbell squat, deadlift, and press in the 80-85% 1RM range. *Yellow theraband be damned*.

Highly trained individuals may look at the advocacy of a 30-40% improvement target as insurmountable, as typical training blocks yield less than 5% gains for them. Yet this is a demonstration of just how *under-trained* the individuals in this cohort are. If an individual begins on a leg press at 50 pounds and can progress to 75 pounds, that is a 50% increase with a weight that most would still consider very light. In barbell terms, if someone can barely squat an empty bar and a coach can get them to 65 pounds, that is a 50% improvement. We should arguably be asking what protocols the studies were running that could *not* achieve a 30% improvement in strength. If the protocol from Bennell *et al* 2005 is taken as an example, it can be seen.[Bennell 2005] Here 119 participants with OA were randomized to either receive "treatment" or "placebo." The treatment cohort completed a standardized treatment that consisted of "knee taping; exercises to retrain the quadriceps, hip, and back muscles; balance exercises; thoracic spine mobilization; and soft tissue massage." Unfortunately, this is not far from a "standard" treatment session in many clinics. The "exercises", if they can be called that, consisted of:

- Buttock Squeeze
  - 5 second hold for 5 repetitions
  - Isometric gluteal contraction in sitting with co-contraction of hip adductors
- Buttock Rock
  - 10 second hold for 5 repetitions each side
  - concentric contraction of the quadratus lumborum with isometric contraction of gluteus maximus in sitting
- Rock and Stand
  - 5 repetitions
  - sit to stand exercise with isometric contraction of hip adductors
- Half Squat
  - 3 sets of 5 repetitions
  - performed with co-contraction of the gluteals and hip adductors
- Step ups onto a 10cm step
  - **IF** able to complete 5 repetitions with <3/10 VAS pain 1 set of 5
  - Isometric contraction of gluteals muscles onto the supporting leg while stepping up with the other leg. Then lower back down to floor
- Standing balance
  - 5 repetitions each leg
  - with a piece of theraband around the ankles, standing on one leg while moving the other leg backwards on a diagonal

The primary strength outcome for this study was an isometric strength test performed on a dynamometer at 60 degrees. The authors had the participants perform three maximal 5 second contractions with 15s rest and normalized the peak force to bodyweight. The cohort in the experimental group initially produced 3.9 N/kg (3.5-4.3) which is a somewhat hard statistic for the lay reader to comprehend. If the subject weighed 78 kg (the average weight of the subjects in the PT group) that would mean they averaged 304 N of force. If that is converted into pounds (apologies to the readers using the metric system) that is 69.5 pounds for their isometric contraction. After the intervention the subjects produced 4.2 N/kg which converts to 73.6 pounds. I don't think any coach or therapist would be switching out the "s" for the "z" in terms of strength *Gains* for this cohort.

In order to achieve the 40% increase in strength to increase function and decrease pain the cohort would have to increase from 69.5 to 97.3 pounds. Nowhere in the Bennell study is there room for progressive overload to even remotely elicit this effect. This will influence any meta-analysis that includes such a study under the umbrella term of "exercise." Where Bartholdy *et al* improved upon this is dichotomizing between ACSM-adherent exercise and non-ACSM-adherent interventions. This still led the authors to conclude:

> "*The results of this meta-analysis are ambiguous: exercise interventions that follow ACSM guidelines for strength training results in significant increases in knee extensor strength compared to other interventions. However, changes in clinical outcomes seem unrelated to the choice of strengthening exercise or other types of exercise interventions. Yet, we found an association between changes in knee extensor strength and changes in pain and disability, which suggest that strength gain is beneficial."*

There is a lot to parse out in these conclusions. While ACSM exercise interventions did increase knee extensor strength, there was no ***specific*** exercise that was deemed superior to others. The ACSM exercises recommend an intensity above 40% 1RM. This is sub-threshold to the recommendations for intensity offered in the systematic review and meta-analysis by Borde *et al* that recommends the largest effect sizes for intensities between 70-79% 1RM.[Borde 2015] Granted, this study was suggested for "healthy" individuals, which raises the question of whether this intensity is appropriate for individuals experiencing pain. No one is advocating to train individuals through increasing pain, and symptoms should absolutely influence training intensity. However, the meta-analysis from Smith *et al* does offer some evidence that it is okay to experience pain while performing rehabilitation exercises.[Smith 2017]

Perhaps even the ACSM guidelines are underdosed, and if the authors are being honest, the likelihood of intensity truly being determined from 1RM is low. This is why we at Barbell Medicine prefer the proxy of rate of perceived exertion (RPE). This allows patients to determine the difficulty of the exercise based on both how *hard* the exercise is they are performing as well as how *much* their current symptoms are influencing their performance. If a patient is constantly reporting an RPE of 3/10, the exercise is most likely underdosed. In the same regard, if there is a report of a 10/10 and the patient is not actually failing their sets, there is likely a need to discuss perspective, reframe the situation, and consider whether alternative approaches may be a better fit for the individual. With that said, there are studies that actually do use one-repetition max (1RM) testing in the older population. A study by Wang *et al* from 2017 used a 1RM performed on a hack squat machine as a means of programming an 8 week strength block for individuals in their 70's. They then had participants perform 4 sets of 4 squats on the hack squat machine at 85-90% of 1RM, increasing 5 kilos if the individual was able to perform more than 5 repetitions. The individuals who completed this program has a **68% increase in strength.**[Wang 2017] This was from performing 1 exercise, for 4 sets, with 4 minutes rest, accounting only for intensity in progression.

It is also important to consider the *duration* of the training intervention. The average duration for both the ACSM and non-ACSM cohorts was only 8 weeks. While obtaining a 30-40% increase in strength in two months is certainly an excellent outcome, focus should also be on *maintaining* that outcome. If individuals stop the prescribed training, there is no reason to believe that the benefits will be maintained. According to the Borde meta-analysis, the most effective duration for maintaining strength was year-round training.

Overall, the Bartholdy *et al* study provides objective targets for resistance training programs among individuals with knee OA. It also demonstrates that it is okay to use heavier loads in individuals with OA. In fact, it is necessary to progressively load individuals with OA if improvements are to be seen. While no specific strength training modality proved superior to another, one that is underdosed will always be inferior.

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