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WITH YOU FROM BENCH TO BEDSIDE

Monthly Research Review

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A Step In The Right Direction: Daily Steps and Health Outcome

Daily Step Counts for Measuring Physical Activity Exposure and Its Relation to Health by Kraus et al 2019.

Key Points:

1. Steps per day offer a practical way to objectively monitor and assess physical activity. Smartphone applications and wearable devices can do this accurately.

2. Achieving a baseline level of steps of approximately 5000 steps per day may have some benefit at reducing all-cause mortality risk. Additionally, increasing steps by 2000 steps per day appears to have further health benefits by reducing the risk of cardiovascular events and type II diabetes.

3. We still have much to learn regarding the relationship between steps and health outcomes, however these initial findings show some promise for steps per day recommendations and health promotion.

Introduction

In this month's review, I want to take a step back from barbells, nutrition, and getting swole for the summer to talk about something less sexy, the role of daily steps in promoting health. To do this, we'll need to define what constitutes a step, cover some history, and look at what the most current research has to say about this topic.

To begin, how do we define a step? Interestingly, neither le Système International d'Unités (SI units) nor the Imperial system has a unit of measurement for the step, as the step is a behavior and not an object or event.[Basset 2017]

Rather, steps are a sort of “anthropometric” unit of measurement with the following characteristics:[Hatano 1993]

- Using a self-selected pace, the length of a typical step is approximately 42% of an individual’s height.
- Using a self-selected pace, the amount of energy expended per step is roughly proportional to a person’s body weight in kilos, e.g. (cal/kg/step).
- The intensity of steps tend to vary with one’s level of aerobic fitness, with frail, elderly individuals taking slower, shorter steps and younger, more fit individuals taking faster, longer steps.

Leonardo da Vinci, the Italian artist who painted *The Last Supper*, is credited with inventing the first step counter. It was mounted at the waist and had a long lever arm that was tied to the thigh. When the thigh moved back and forth during walking, the gears rotated and the resulting steps were counted.[Gibbs-Smith 1978]
Fortunately, this has been supplanted by smartphone apps (e.g. Apple Health) and wearable technology like the Fitbit, which cost $300.00 when it was first released in October, 2017. Based on a 2018 review of the relevant literature, these devices and applications tend to be fairly accurate at reporting step counts, with the authors stating:

“A total of 27 studies (191 accuracy comparisons) examined Fitbit device step measurements compared with a reference-standard criterion of direct observation and counting of steps in a controlled setting. Fitbit devices were worn on the torso, wrist, or ankle. Across the 191 accuracy comparisons examining step count in controlled settings, 46% (n=88) were within a ±3% measurement error, 51% (n=97) were below a –3% measurement error, and 3% (n=6) were above a 3% measurement error, with an overall tendency for Fitbit devices to underestimate steps by a difference of –9%”.[Feehan 2018]

Additionally, researchers have proposed a classification scheme to categorize individuals’ activity levels based on their daily steps as seen in Figure 1:
[Tudor-Locke 2004]

Steps per day	Classification
<5000	Sedentary lifestyle
5000–7499	Physically inactive
7500–9999	Moderately active
≥10,000	Physically active
≥12,500	Very active

Figure 1: Proposed classification scheme to categorize activity levels based on accelerometer-measured steps per day.

Up until recently however, it has been difficult to determine the relationship between varying levels of activity, as measured by steps per day, and health outcomes. In other words, does reaching a threshold of steps per day improve health or prevent specific diseases by any objective metric? Additionally, does increasing the amount of steps per day reduce the risk of any bad health outcome, e.g. heart attack, stroke, or diabetes.

This month, let's try to answer these questions using the latest systematic review and meta-analysis on the topic.

Purpose

This month's study set out to explicitly answer the following questions:

1. What is the relationship between step counts per day and all-cause and cardiovascular disease (CVD) mortality, CVD events, and type 2 diabetes?
2. Is there a dose–response relationship, and if there is, what is the shape of the relationship?
3. Does the relationship vary by age, sex, race/ethnicity, socioeconomic status, or weight status?

In short, the authors of the article first wanted to see if there was a correlation between steps per day and death from cardiovascular disease, prevention of cardiovascular events, and type 2 diabetes. Then, if they found a correlation they wanted to better characterize it. Let's see how they went about this and what they found.

Subjects/Methods

The authors of this paper used online databases to search for literature by asking members of the committee who wrote the 2018 Physical Activity Guidelines for Americans to provide additional articles identified through their familiarity with the literature.

I know what you're thinking, "They just asked the experts for articles?! Why?" As I alluded to earlier in this review, it's not like there was an existing consensus that had been published on this topic. In fact, the authors originally tried to search for articles themselves using a number of different search terms, criteria, and databases, but they weren't able to identify enough papers on the topic to come up with a new (and much-needed) consensus. So, they asked the experts.

The experts identified a total of 11 articles:

- 4 used a cross-sectional design, a type of observational study that analyzes data from a population, or a representative subset, at a specific point in time. Because it is likely that individuals with undiagnosed disease(s) may take

fewer steps per day than healthy individuals, the reviewed cross-sectional studies were used only to understand usual step counts per day across sample populations and not for primary evidence for relationships between step counts and disease.
- 6 used a prospective design, which looks for outcomes, such as the development of a disease, during the study period and relates this to other factors such as suspected risk or protection factor(s) in a group of subjects that are watched over time. These studies reported health outcomes including all-cause mortality, composite of CVD incidence (e.g. cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke), metabolic syndrome, and blood glucose concentrations.
- 1 used a randomized controlled design where control and intervention groups were compared.

Of note, 4 of the 11 articles were generated from the The NAVIGATOR study, a multicenter trial of 9306 individuals with impaired glucose recruited from 40 countries.

The subjects in all 11 reviewed studies were **all** middle-age or older and had equal representation between men and women. Individuals with existing CVD or high-performance athletes were excluded.

Findings

The baseline number of steps per day varied across studies but the median was approximately 5,000 steps per day. The samples of older adults showed that they accumulated fewer daily steps than did younger middle-aged adults, which corroborates what was discussed in the introduction. Of note, one of the studies included looked at Tasmanian adults living in Australia (not Barbell Medicine coach, Joe Pemberton, a native Tasmanian) accumulated nearly twice as many daily steps at baseline, e.g. 10,000 steps per day. Nevertheless, most studies showed that on average, non-sedentary individuals take about 5,000 steps per day.

Regarding the question posed about step counts per day and both all-cause and cardiovascular mortality, there were no studies identified that addressed this relationship. Subsequently, the authors felt compelled to say, "*we were unable to draw a conclusion about this relationship*."

However, there were a number of studies that directly provided data regarding the question posed about step counts per day and cardiovascular events and diabetes. **In each study analyzed, there was an inverse relationship shown between step counts and cardiovascular events and type 2 diabetes.**

Two of these studies stand out:

1. Ponsonby et al found that for any average daily step count, an additional 2,000 steps would be associated with a 25% reduction in developing type 2 diabetes in the next 5 years.[Ponsonby 2011]
2. Yates et al found that when individuals with impaired glucose tolerance ("pre-diabetic") increased their steps per day by 2,000, their rate of cardiovascular events per year decreased by 8 percent. Additionally, at baseline each additional 2,000 steps per day increment was associated with a 10% lower cardiovascular event rate.[Yates 2014]

Additionally, increasing the number of steps per day reduced the risk of cardiovascular events and type 2 diabetes development independent of the individual's weight, sex, age, geographic location, or baseline level of steps per day. That being said, the strength of this evidence is fairly limited due to the small number of studies on this topic and the available studies' designs.

Why does this article matter?

Daily step counts are a readily accessible means by which to monitor and set physical activity goals that are often claimed to have positive impacts on health outcomes, such as reducing the risk of cardiovascular disease and type 2 diabetes. What's more, the results reported in this review suggest a "dose-response" relationship, meaning that with increasing doses (steps per day) there were increasing responses (reduction of cardiovascular events and diabetes risk). Another recent study found a similar dose-response relationship, where mortality rates were reduced in older women as their daily step counts increased from 4400 steps per day to 7500 steps per day.[Lee 2019] Lee *et al* also found that stepping intensity was not clearly related to lower mortality rates after accounting for total steps per day. **The fact that stepping volume was associated with mortality reduction independent of intensity should not be overlooked.**

Additionally, there were no available consensus statements prior to this systematic review. With respect to steps per day goals and health outcomes the Scientific Report for the 2018 Physical Activity Guidelines has been updated to say the following regarding step counts:

1. Limited evidence suggests that step count per day is associated with reduced incidence of cardiovascular disease events and risk of type 2 diabetes. PAGAC Grade: **Limited**.

2. Limited evidence suggests a dose-response relationship between the measure of steps per day and cardiovascular disease events and type 2 diabetes risk. PAGAC Grade: **Limited**

Limited, in this context, is due to both the small number of total studies looking at the aforementioned questions and the lack of RCTs. Additionally, a single data set- The

NAVIGATOR Study- provided 4 of the 11 studies reviewed by the authors, which limits their (and mine) confidence in the results provided.

So, on the one hand I don't think that we have an overwhelming amount of well-controlled evidence suggesting that meeting a particular step count or increasing the amount of steps per day definitively reduces all-cause mortality, cardiovascular events, or diabetes rates. We just need more studies to come out to add to the body of research on this topic.

However, on the other hand I *do* think the existing evidence makes a pretty compelling case for encouraging sedentary individuals to increase their step counts to first achieve the average baseline seen in active populations, e.g. 5000 steps per day. Next, I think the existing data makes a pretty good case for trying to increase a person's baseline number of steps by 2000 steps per day in order to potentially reduce the risk of cardiometabolic disease.

You might ask, "But Jordan, you just said the data wasn't definitive. How can you make that recommendation?" The way I look at it is that increasing the number of steps per day has a relatively large potential benefit compared to the potential risks. Additionally, most individuals have a device (e.g. a Fitbit, Apple Watch, or smartphone app) that they can use for objective self-monitoring to encourage increased levels of physical activity.[Wang 2015]

Overall, I think that we'll know more about this topic as well as how daily steps correlate to other health outcomes in the near future, but for now I think the aforementioned recommendations are reasonable.

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Strength & Cancer-related Mortality: Is it enough to exercise, or do you actually need to get strong?

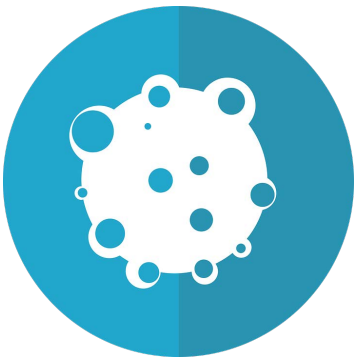
Cancer-specific Mortality Relative to Engagement in Muscle Strengthening Activities and Lower Extremity Strength by Dankel et al. 2018

Key Points:

1. Among patients with cancer, sarcopenia is prevalent at all stages of disease. It is a strong independent predictor of both cancer-related and all-cause mortality, independently increases the risk of treatment complications, and is associated with cancer-related fatigue, pain, and quality of life.

2. In this study of a nationally-representative sample of 2,773 adults, being in the top quartile for knee extensor strength was associated with an approximately 50% risk reduction for cancer-specific mortality after controlling for co-variates. These data suggested that approximately 20% of deaths due to cancer were attributable to not being in the top quartile for knee extension strength.

3. In contrast, simply engaging in muscle-strengthening activities was not associated with significant reduction in cancer-specific mortality. In other words, it appears that it is not enough to simply exercise, but rather that in order to enjoy maximal risk reduction, one must actually get strong.



Introduction

Cancer is among the leading causes of disease and death in the U.S. and contributes to a substantial burden of disease in the world.CDC,WHO Enormous amounts of resources are spent on treatment as well as research into new treatment approaches (e.g., chemotherapeutics, immunotherapies, and other emerging treatments) that often provide small, incremental survival benefits over existing therapies at great cost.Prasad 2015

Among physicians and oncologists, the end-stages of cancer-related wasting syndromes (known as *cachexia*) are well-recognized as poor prognostic factors associated with increased risk of treatment complications and mortality.[Tisdale 2002] However, the prevalence and significance of sarcopenia in earlier-stage disease is under-recognized.[Christensen 2014] It is also less appreciated whether inexpensive, accessible lifestyle interventions to counteract this progressive loss of muscle mass can attenuate cancer-related risks.

Purpose

The authors sought to use a nationally representative sample of U.S. adults to analyze the effects of 1) skeletal muscle strength and 2) engagement in muscle-strengthening activities on the overall risk of death due to cancer.

Subjects

Data were obtained from the 1999-2002 National Health and Nutrition Examination Survey (NHANES), which specifically included measures of knee extensor strength. This included a total of 2,773 individuals aged ≥ 50 years, 50.4% female, and 58% non-Hispanic whites.

Methods

Analysis used 1) measures of lower extremity strength, 2) rates of engagement in muscle-strengthening activities, and 3) cancer-specific mortality, as well as numerous co-variates that were used for adjustment. These data were obtained as follows:

1) **Lower extremity strength** was measured using an isokinetic dynamometer. Participants performed 3 warm-up repetitions followed by 3 maximal isokinetic contractions at a speed of 60 degrees per second. The peak force produced over the three repetitions was measured and corrected for gravity. [Validity]

2) **Engagement in muscle-strengthening activities** was measured via individual self-report in response to the following questions: "*During the past 30 days, did you do any physical activities specifically designed to strengthen your muscles, such as weight lifting, push-ups, or sit-ups?*" and, if so, "*During the past 30 days, how many times did you do these muscle strengthening activities (e.g., weight lifting, push-ups, or sit-ups)?*". Individuals reporting performance of at least 8 sessions within the prior month (*i.e.*, an average of two sessions per week) were classified as engaging in muscle-strengthening activities. [Validity]

3) **Cancer-specific mortality** was determined by matching personal identification information with the National Death Index (NDI), followed by manual examination

of medical records and associated International Classification of Disease (ICD) coding.

Co-variate data obtained and used for adjustment purposes included self-reported aerobic activity, age, race, total blood cholesterol, mean arterial blood pressure, body mass index, serum C-reactive protein, reported smoking status, and reported use of ambulatory devices (e.g., a cane), statin medications, arthritis, congestive heart failure, coronary artery disease, cancer, diabetes, and stroke.

The data were analyzed using knee extensor strength (dichotomized to the 75th percentile and above vs. below this cutoff) and engagement in muscle-strengthening activities (dichotomized to 8+ sessions per month vs. less than 8 sessions per month) as the independent variables of interest.

The authors then performed three analyses: a minimally-adjusted model (using only age, sex, race, and aerobic activity as co-variates), an extended adjusted model (using all of the above-listed co-variates), and an additional adjusted model comparing the bottom quartile (*i.e.*, 25th percentile) versus the upper three quartiles, rather than the upper quartile (*i.e.*, 75th percentile) versus the bottom three quartiles.

Findings

The authors reported the following findings:

1) Lower extremity strength

Individuals in the 75th percentile had an average knee extensor strength of 516 N (95% CI: 511-521), whereas those below this cutoff had an average strength of 295 N (95% CI: 291-298).

2) Engagement in muscle-strengthening activities

Overall, 382 individuals (13.8%) of the sampled population met sufficient engagement in muscle-strengthening activities (i.e., 8+ sessions per month), while 1009 (36.4%) met aerobic physical activity guidelines.

3) Cancer-specific mortality

Of the 699 individuals in the 75th percentile for knee extensor strength, 32 (4.5%) died of cancer, compared to 130 (6.6%) of the 1,944 individuals below this cutoff. Being in the top quartile for knee extensor strength was associated with a 53% risk reduction for cancer-specific mortality in the minimally-adjusted model, and a 50% risk reduction in the extended adjusted model.

Analyzing the data by sex showed that for every 15 N increase in knee extension strength, men had a 5% and women had an 8% reduced risk of cancer-specific mortality (Men, HR 0.95, 95% CI 0.91-0.99, P=0.01; Women, HR 0.92, 95% CI. 0.86-0.91, P=0.01).

There was no evidence of interaction effects between strength and age, sex, baseline history of cancer, body mass, or aerobic activity. In fact, excluding the 394 individuals who had ever been diagnosed with cancer from the study cohort, strength maintained a strong inverse association with cancer-specific mortality (HR 0.43, 95% CI 0.22-0.84, p=0.01).

Interestingly, when "flipping" the analysis to examine the bottom 25th percentile versus the upper three quartiles, the results were no longer significant (discussed further below).

In comparison to these data on knee extension strength, engagement in muscle-strengthening activities was associated with a 6% risk reduction for cancer-specific mortality in the minimally-adjusted model, and an 8% risk reduction in the extended adjusted model. However, neither of these findings were statistically significant.

A final analysis computed a statistic known as the *Population Attributable Fraction*, which aims to describe the proportion of cancer-specific mortality that can be attributed to a specific variable; in this case, strength. The PAF for those in the 75th percentile versus below was estimated at 20.9%, suggesting that approximately 20.9% of deaths due to cancer are attributable to *not* being in the top quartile for strength. **Theoretically, this means that about one out of every five cancer deaths could have been averted if the individuals had been in the top quartile for strength.**

Why does this article matter?

Cancer is known to have profoundly catabolic effects and leads to a generalized cancer-related wasting syndrome known as *cachexia* in its end stages. Sarcopenia (the loss of muscle mass and strength), however, can be present at *all* stages of disease and often goes unrecognized in earlier stages. For example, Burden *et al* found that 54% of newly diagnosed early-stage colorectal cancer patients had a handgrip strength below 85% of the reference range for healthy age-matched controls.[Burden 2010] Similarly, a study of 714 newly diagnosed patients with a variety of cancers found that they carried an average of 0.9 kg less muscle mass compared with healthy controls prior to the initiation of any treatment.[Cao 2010]

This decrease in muscle mass and strength occurs early and progresses over time through multiple complex mechanisms. These include things like tumor-derived systemic inflammation, chemotherapy and other drug-related effects, and

lifestyle-related factors such as physical inactivity and malnutrition. These collectively induce a state of *anabolic resistance*, whereby an individual demonstrates a blunted (or absent) response to a given dose of anabolic stimulus. Practically speaking, this means they are less "sensitive" to a given dose of protein or exercise. Additionally, these complex mechanisms promote catabolism of lean body mass.

There has been increasing research examining the role of skeletal muscle strength and function in cancer-related outcomes.[Christensen 2014] For example, skeletal muscle mass and function are strong independent predictors of both cancer-related and all-cause mortality.[Ruiz 2010] Additionally, sarcopenia independently increases the risk of treatment complications such as dose-limiting toxicity from chemotherapy and surgical complications (including death). Finally, there are strong associations between sarcopenia and patient-reported outcomes such as cancer-related fatigue, pain, and quality of life.

This study was the first to use a nationally representative sample of U.S. adults to analyze the effects of skeletal muscle strength and engagement in muscle-strengthening activities on the overall risk of death due to cancer. Limitations include the retrospective design, self-report of engagement rates in strength and aerobic exercise, and the relatively low mortality rate in the studied population (160 of 2,773 adults). Additionally, while the authors performed adjusted analyses using a number of co-variates (as described above), there may be additional unmeasured variables that were unaccounted for in the present analysis.

The authors found that being in the top quartile for knee extensor strength was associated with a 50% reduced risk for cancer-specific mortality after adjustment for a number of co-variates. However, there was *no* significant risk reduction associated with engagement in muscle-strengthening activities alone. **This means that simply *participating* in these sorts of activities alone is not sufficient to earn the mortality benefit – one must *actually get strong* in order to enjoy these benefits**.

Furthermore, when authors "flipped" their analysis to examine the bottom quartile (i.e., 25th percentile) versus the upper three quartiles, the results were no longer significant. This suggests that simply *avoiding being in the bottom quartile* is not enough to achieve maximal risk reduction; **again**, **one must *actually get strong***.

Notably, this presents a challenge given the wide inter-individual variability in baseline strength and in *response* to strength training interventions (see April 2019 BMR).[Ahtiainen et al. 2016] For an individual with low baseline strength and with a poor response to a particular strength training intervention, they could plausibly be at an increased risk of cancer-specific and/or all-cause mortality.

It is therefore important to recognize those with low physical strength and provide appropriately-dosed interventions to improve muscle mass and muscle function. We have evidence suggesting that resistance training can attenuate or reverse cancer-induced anabolic resistance.[Montalvo 2018] However, this anabolic resistance can be progressive, and end-stage cachexia represents a stage where patients may become nearly refractory to such anabolic stimuli.[Antoun 2018] Therefore, resistance training and nutrition interventions should occur as early as possible. Additionally, the "dose" of these interventions likely require titration on an individual basis over time in order to continue generating the desired adaptations.

While we have a good understanding of how resistance exercise and nutrition interventions can generate improvements in skeletal muscle mass and function, the specific mechanisms by which such interventions exert their beneficial effects on cancer outcomes are likely complex and multifactorial, and as of now remain poorly understood. Similarly, exactly *how strong is strong enough* for these health outcomes remains unknown as well, and may ultimately prove to be a highly individual threshold. While all of this will require additional research to clarify, we can still feel confident in recommending strength training interventions to patients with cancer to reduce their risk of mortality.

To summarize, clinicians and patients should understand:

1. the significance of sarcopenia with respect to cancer-related outcomes,
2. that simply *engaging* in activity (or "being active") is not enough to obtain maximal risk reduction, and
3. **that *one should actually get stronger* to maximize benefit.**

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Exercise for Persistent Pain Populations: Highly recommended but do we know the dosage?

Exercise-induced hypoalgesia: A meta-analysis of exercise dosing for the treatment of chronic pain. by Polaski et al. 2019.

Key Points:

1. Education and exercise are two mainstays for the treatment of persistent pain. However little is known about appropriate dosage of exercise (type, frequency, intensity, time, and duration) for particular pain states.

2. The authors re-examined data from a 2017 Cochrane review to see if a specific exercise dosage led to enhanced effects on pain analgesia.

3. Overall - the authors were unable to find specific exercise dosage effects on pain analgesia.

4. The findings from this review should encourage clinicians to work collaboratively with patients dealing with persistent pain by creating an exercise prescription specific to their goals and based on recent activity history.

Chronic pain has broadly been defined as persistent or recurrent pain lasting longer than 3 months and is estimated to affect approximately 1.5 billion people worldwide.[Treede 2015,Polaski 2019] Education and exercise are two commonly recommended interventions for the treatment of chronic pain. However, little is known about the appropriate dosage of exercise prescription for this population.

In the US, we have physical activity guidelines in place for the general population for overall health benefits (mortality, comorbidities, quality of life, etc), which recommend adults complete aerobic and muscle-strengthening activities each week as follows:

US Physical Activity Weekly Guidelines
Aerobic Physical Activity – Weekly
150 – 300 minutes of moderate-intensity aerobic activity, or
75 – 150 minutes of vigorous-intensity aerobic activity, or
Some combination of the above.
Muscle-Strengthening – 2 days or more per week
Moderate or greater intensity for all major muscle groups

However, since these guidelines are designed for the general population, it is unclear whether they can be generalized to those dealing with persistent pain. If they are not appropriate for this population, how should we alter the dosage?

Purpose

Polaski *et al.* sought to answer these questions and more as they relate to the appropriate dosage of exercise prescription for those dealing with persistent pain. The authors re-examined data from a prior 2017 Cochrane review by Geneen *et al*, which provided the following clinical implications for practice:

> *"The evidence in this overview suggests that the broad spectrum of physical activity and exercise interventions assessed here (aerobic, strength, flexibility, range of motion, and core or balance training programmes, as well as yoga, Pilates, and tai chi) are potentially beneficial, though the evidence for benefit is low quality and inconsistent. The most commonly reported adverse events were increased soreness or muscle pain, which subsided after several weeks of the intervention. Physical activity and exercise may improve pain severity as well as physical function and quality of life."*

It appears there was not exactly an overwhelming amount of evidential support for the recommendation of exercise or a particular dosage for individuals with persistent pain.

In this new review article, the authors sought to understand how altering the *dose* of exercise might affect pain. Their primary objective was to "*...test the hypothesis that the dose of exercise would impact the efficacy of exercise and physical movement-based therapy to reduce chronic pain.*"

Methods

The authors reviewed each included article from the 2017 Cochrane review, which was a comprehensive review of 21 papers from the Cochrane Library Meta-Analyses (381 individual studies) examining the effects of physical activity and exercise interventions on eight pain-based conditions. The included articles met the following criteria:

1. Randomized, controlled trials
2. Adult patients (18+ years of age)
3. Chronic non-cancer pain (≥ 3 months in duration)
4. Meta-analysis reporting post-intervention Effect Sizes (ES) for pain
5. Published in peer-reviewed journals

Studies were *excluded* for the following reasons:

1. Not in English-language
2. Multi-modal interventions (exercise A plus exercise B - this would confound the data on exercise dosage, specifically type, effects on pain)
3. Individualized exercise prescription for each participant in the study (this would diminish the external validity of the review's findings)
4. Intervention failed to meet World Health Organization definition of exercise - "*Exercise is a subcategory of physical activity that is planned, structured, repetitive, and purposeful in the sense that the improvement or maintenance of one or more components of physical fitness is the objective.*"

Pain states were classified into eight categories as follows:

- Rheumatoid arthritis (RA)
- Osteoarthritis (OA)
- Fibromyalgia (FMS)
- Low Back Pain (LBP)
- Intermittent Claudication (IC)
- Neck Pain (NP)
- Spinal Cord Injury (SCI)
- Patellofemoral Pain (PFPS)

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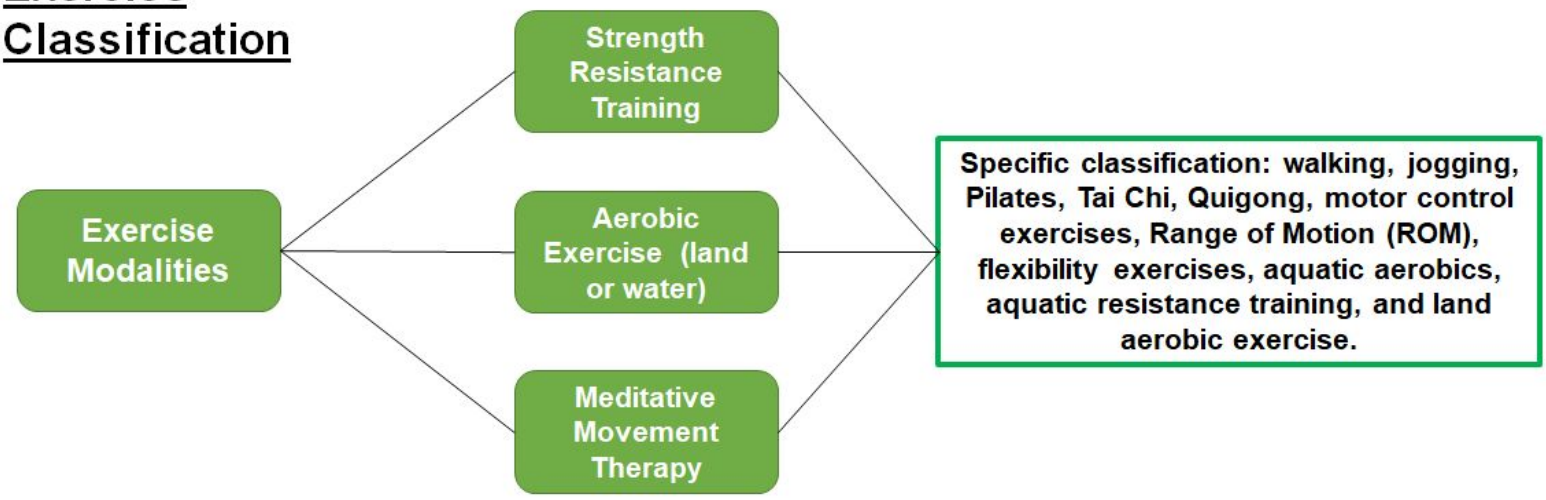
Exercise Classification

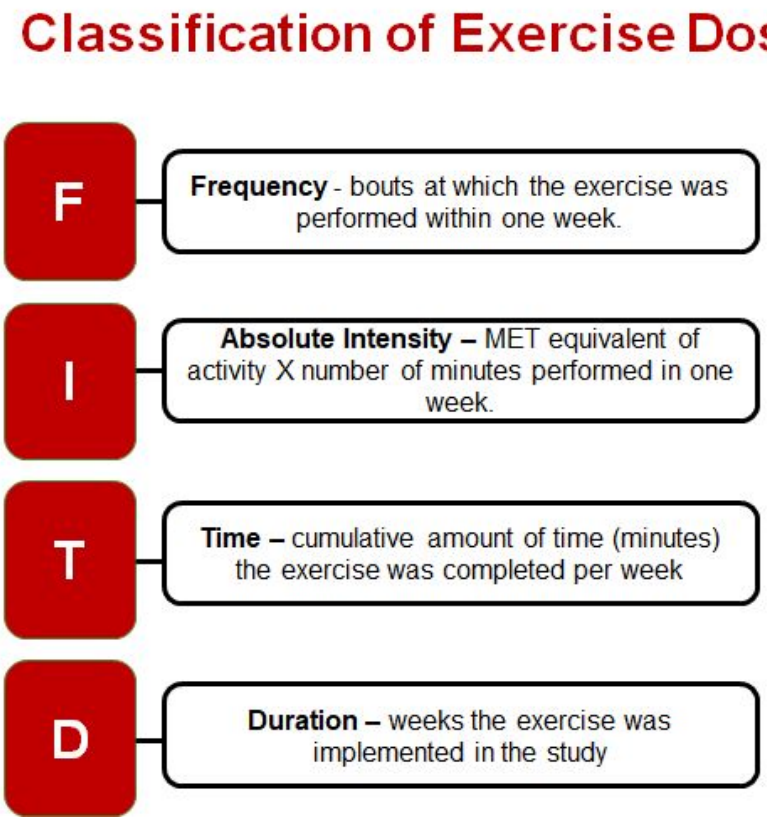


The authors took the data from included studies in Geneen *et al* and extracted effect sizes, means, standard deviations, and 95% confidence intervals strictly for the pain outcomes measured immediately post-intervention. The effect sizes demonstrated comparative changes between the exercise and control groups. The authors then converted the effect sizes from mean differences (effect size for each group) or standardized mean differences (experimental vs control groups) to just standardized mean differences (Cohen's D - which demonstrates the size of an effect exercise dosage has on pain analgesia). The standardized effect sizes were then converted to denote a positive effect value when a reduction in pain occurred.

Data analyses were based on two factors: 1) Pain outcome measures and 2) Exercise Dosage.

1) **Pain outcome measures**
    - Visual Analog Scale (VAS)
    - Numerical Rating Scale (NRS)
    - McGill Pain Questionnaire (MPQ)
    - Arthritis Impact Measurement Scale 2 (AIMS2)
    - Western Ontario McMaster Osteoarthritis index (WOMAC)
    - Short Form-36 Health Survey (SF-36, for bodily pain)
    - Health Assessment Questionnaire (HAQ)
    - West-Haven Yale Multidimensional Pain Inventory (WHYMPI)
      *Authors stated they calculated pain effect sizes based on pain specific sections or subscales from these questionnaires.

2) **Exercise Dosage**



The authors classified exercise dosage according to frequency, time, and duration. See outline (left) for descriptions. The authors gave the following example:

Prescribed exercise intervention = 3 x / week, 30 minutes a session for 4 weeks

- Frequency = 3
- Time = 90 minutes
- Duration = 4 weeks

Note: Intensity of exercise was recorded via a separate analysis and was based on *metabolic equivalent of task* (MET). MET for each activity was taken from the 2011 Compendium of Physical Activities: a second update of codes and MET values.

Univariate analyses were initially completed and then multivariate modeling was completed based on trends found from the univariate analyses.

For univariate analyses, the authors ran linear regressions with Pearson's Correlation Coefficients based on the standardized pain effect size and dose of exercise for all recorded disease states. Statistical significance was set at $p < 0.05$.

Three univariate analyses were completed:

1) **Pain state** - between-study comparisons for the same cohort of pain classification, data were combined across types of exercise interventions.

2) **Exercise type** - between-study comparisons for the same cohort of exercise type, data were combined across pain states.

3) **Intensity** - assessed after the above analyses were completed, using a "*Dose Intensity x Time*" analysis. The authors assessed for interactions between exercise intensity and standardized pain effect size.

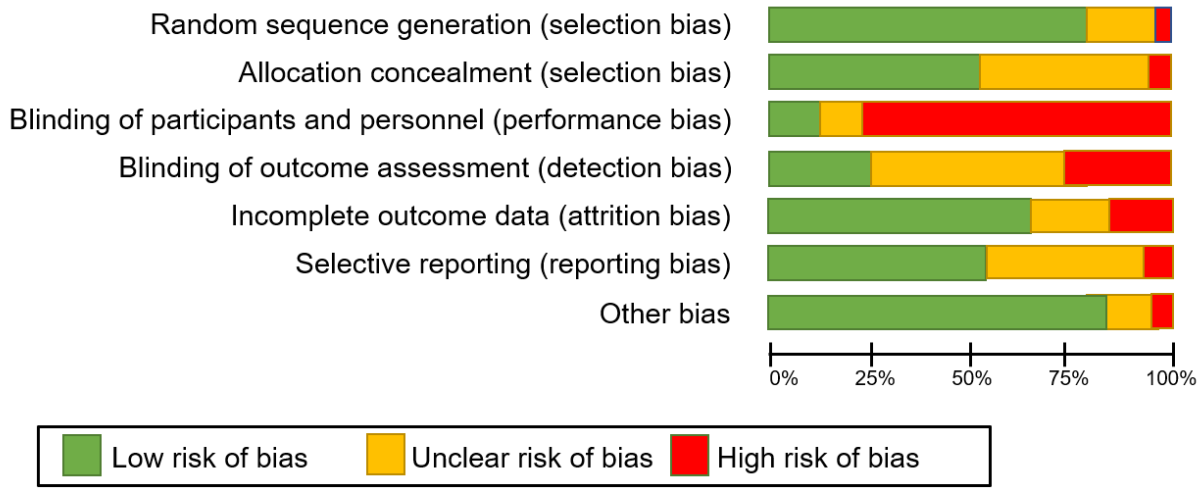
Multivariate analysis

For multivariate analysis, significant results were assessed based on exercise dosage via time, frequency, and duration. The authors explain how they arrived at their multivariate model,

"In order to control for studies that produced significant effect sizes and to model the effects of the three time-related dose measurements simultaneously, multivariate linear regression modeling was fit using a dummy variable for whether the study showed a significant ($p<0.05$) pain effect or not plus adding the three main effects of measured dose as TIME, FREQUENCY, and DURATION. Two-way interactions between the three measured dose effects were also added to the model. Selection of the best model fit was determined by significant main effects and interaction effects providing an overall significant model F-statistic ($p<0.05$) and adjusted R2."

Risk of bias

Figure 2. "Risk of bias" graph.



Risk of bias was assessed via the Review Manager assessment tool from the Cochrane Collaboration. See Figure 2 (above) for a breakdown of the risk of bias for each assessed category. Some assessment categories, like "Blinding of participants and personnel (performance bias)", are listed as high risk but this was inevitable given the type of interventions utilized and probably could not have been mitigated.

Findings

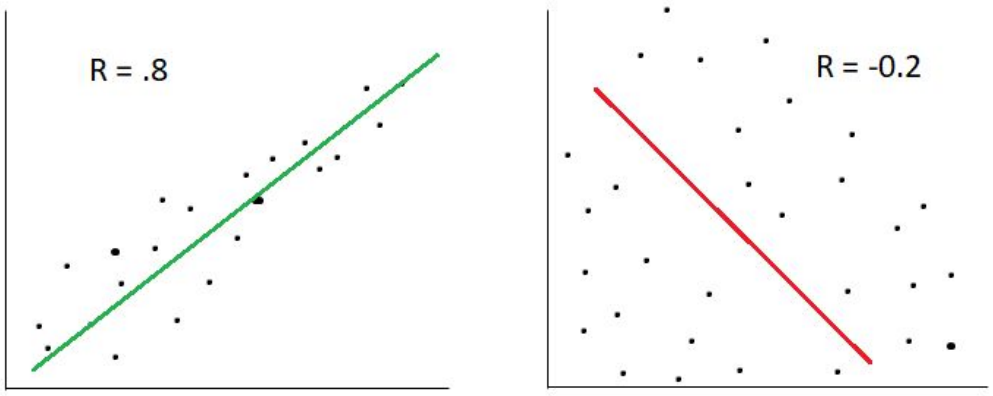
The authors included 75 of the original 381 studies from the 2017 Cochrane Review. The primary reasons cited for excluding studies were: not reporting an effect size for a pain related outcome, not reporting the effect size immediately post-intervention, and/or not reflecting the relationship for control vs. exercise group comparison. Overall - the authors found the following:

> ***"Most of the studies included in this review demonstrated some positive benefits of exercise on pain outcomes (69 of 75 studies); of which 30 were statistically significant. Of the statistically non-significant studies, 39 of 45 described positive trending benefits of exercise while only six studies reported worse pain with exercise."***

Granted, "trending towards statistically significant" is voodoo word trickery that isn't really meaningful beyond trying to support a bias. However, 30 studies of the included 75 did demonstrate statistically significant effect on pain outcomes.

Before diving into the data - a brief overview of Pearson's Correlation Coefficients.

If you are not familiar with Pearson's Correlation Coefficient, the measurement is denoted by *"r"* and describes the strength of a linear relationship between two variables.



When a line of best fit is applied to data, the closer *r* is to +1.0 or -1.0, the more clustered the data points are around the line of best fit with minimal variation, denoting a stronger relationship. Positive numbers represent a direct, or "upward" trend in the data, and negative numbers represent an inverse, or "downward" trend.

Guidelines have been recommended:

Understanding Pearson's Correlation Coefficient (r)		
	Coefficient, r	
Strength of Association	**Positive**	**Negative**
Small	.1 to .3	-0.1 to -0.3
Medium	.3 to .5	-0.3 to -0.5
Large	.5 to 1.0	-0.5 to -1.0

Back to the Polaski *et al* article:

Univariate Analyses:

1) **Pain state analysis** - The authors combined the data from all exercise modalities and examined how the dosage affected individual pain states (only NP, FMS, OA, and LBP were included). See table 2 (below).

Table 2. Comprehensive list of results for all univariate correlation analyses performed for pain effect size versus dose of exercise intervention.			
	R (N)		
Analyses	**Frequency**	**Time**	**Duration**
Neck Pain (NP)	-0.6969 (6)	0.3035 (4)	**0.8619 (8)
Fibromyalgia (FMS)	-0.2894 (12)	0.3739 (8)	-0.1541 (13)
Osteoarthritis (OA)	-0.1540 (23)	0.3703 (16)	0.0165 (27)
Low back pain (LBP)	-0.1979 (10)	0.1519 (9)	0.3819 (13)
Aquatic exercise	0.0948 (12)	0.3519 (10)	-0.0458 (12)
Aerobic exercise	-0.0585 (35)	0.2633 (26)	-0.1002 (36)
Strength training	-0.1254 (41)	0.1202 (27)	0.1181 (49)
Meditative movement	0.3453 (10)	0.5610 (10)	-0.2183 (12)
Pilates-only	0.5624 (6)	0.6718 (6)	-0.3286 (6)
Walking/jogging	-0.0074 (8)	-0.0725 (7)	-0.0392 (9)
Aquatic aerobic	0.0194 (7)	0.0088 (7)	-0.2308 (7)
Analysis grouping is shown in the left column. R represents value of Pearson's correlation coefficient. (N) represents the number of individual studies included in the analysis. **P<0.01.			

Examining table 2 reveals a statistically significant positive correlation for ONLY neck pain as it relates to exercise *duration* (r = 0.8619, p = 0.0059, n = 8).

2) **Exercise type analysis** - The authors assessed exercise dose effect on pain states. Each exercise type was classified and combined across studies, then effects assessed for pain conditions. The authors then ran a secondary analysis with more specific exercise categories (see table 2).

Surprisingly, the authors found **no** statistically significant correlations for either analysis as it relates to exercise type and dosage for effects on pain states.

3) **Intensity analysis** - Recall, this analysis was based on METs. METs was combined with exercise time (Intensity x Time) to assess the effect of exercise intensity on pain states (n = 43). Again, the authors found **no** statistically significant relationship in this analysis.

Multivariate Analysis:

The authors sought to better understand dose effects of exercise (frequency, time, and duration) on pain states by conducting a multivariate analysis. This modeling allows the authors to predict how dose might affect pain outcomes (*n* = 43).

The authors found their model accounted for 55.2% of the variation (R^2 = .552) in standardized effect size observed. R^2 demonstrates the model's ability to explain variation in the data's mean for the dependent variable (pain analgesia).

The model demonstrated that changing dosage of exercise influenced pain outcomes, even for studies not showing a significant effect size. Overall, increasing time of exercise dose **decreased** analgesic effects and increasing frequency **enhanced** analgesic effects on pain outcomes. However, it's important to note that the pain outcomes observed in this model are heavily dependent on the dosage of the other exercise variables and associated interactions.

An example will help illustrate the nuanced interactions of exercise dose variables:

The studies used to develop the model had an average exercise time of 120 minutes/week, average frequency 3 x / week, and average duration of ~15 weeks. Based on the authors' model, this exercise dosage predicts an effect size of 0.8 for studies demonstrating a significant effect, and 0.04 for those studies failing to demonstrate a significant effect. Although this can be debated, the authors argue that any effect greater than 0 should be considered a positive analgesic effect.

Based on the model, if a single variable of exercise dosage is altered while keeping the other variables consistent to the model - the varying pain effects can be assessed.

The model suggests that increasing frequency from 3 x / week to 6 x / week increases the pain effect from 0.8 to 1.5 for those studies which already found a significant effect, and from 0.04 to 0.8 for those studies that didn't find a significant effect. This is an interesting prediction because it increases studies originally not finding a significant effect to the predicted average for studies that did find a significant effect.

However, the opposite can be seen when adjusting the time variable of exercise dosage. The authors predictive model found increasing time from the average of 120 minutes/week to 210 minutes/week had a detrimental effect on pain outcomes reducing the effect to 0.3 in studies that found a significant effect and -0.4 in studies that didn't find a significant effect. Oddly, if time were decreased to 30 minutes/week the predictive effect was enhanced to 1.2 for significant studies and 0.5 for non-significant studies. If you are interested in further examining the predictive effects of the model by varying exercise dosage, see table 4 in the paper.

Why does this article matter?

Exercise is regularly recommended for many persistent pain states.[Skelly 2018] However, we continue to struggle to find appropriate dosage of exercise. The authors of this recent review state "*The lack of dosing studies for exercise means that patients may not be receiving the optimal therapy and/or be receiving a therapy that actually increases pain.*"

Even this most current review, building on the 2017 Cochrane Review, was unable to demonstrate strong correlation of a particular exercise dosage on a pain state. The only positive finding was with a single variable of exercise dosage, duration, on patients dealing with persistent neck pain. The multivariate linear regression model the authors utilized to predict exercise dosage effects on pain outcomes demonstrated how each individual exercise dosage variable can alter outcomes but didn't elucidate appropriate dosage. In the authors defense - the model does appear to demonstrate analgesic effects on pain states with manipulation of exercise dosage variables, but this is likely to be highly variable to pain states or even between individual patients. **In other words, appropriate exercise dosage may not be generalizable beyond the individual patient given their goals and prior activity levels.**

We do know that it's ok to allow patients dealing with persistent pain to exercise with pain and there may be some short-term benefits in allowing such an approach by decreasing kinesiophobia, instilling self-efficacy, and teaching that pain doesn't equal tissue damage necessitating avoidance for protection. [Smith 2018] [Luque-Suarez A 2019] **Perhaps it isn't necessary (or even realistic) to find an optimal, generalizable dosage of exercise for pain states, but rather to find appropriate exercise dosage for the individual based on their desired goals**.

Similar to recommended national physical activity guidelines, it would be nice to have a *starting point* that we can confidently state confers some benefit for the patient. Unfortunately, at this time such information isn't available and we will need further studies on exercise dosage and their associated effects on particular pain states. Until then, I recommend working collaboratively with patients to find exercises they enjoy to meet their goals while eliciting long-term adherence. The authors share this sentiment by advocating for a "***low and slow***" approach for patients with persistent pain. This suggests that it is likely better to err on the side of caution with patients dealing with persistent pain by starting conservatively with exercise dosage that is likely below their current abilities and progressing from there, rather than risking "overdosing" from the start. Such an approach allows for the accumulation of small "wins" over time, building the patient's confidence in their abilities and allowing the clinician to gradually titrate dosage to tolerance.

In conclusion, the authors state,

> *"Overall, this analysis of the existing literature demonstrated insufficient evidence for the presence of dose effects of exercise in relation to analgesia.* ***Ultimately, the major problem in this area is that no studies identified in this analysis individually account for the dose of exercise in the trial.*** *Specific randomized controlled studies with larger n's, done in specific patient populations, and multiple doses are necessary to determine the effects of exercise dose on the efficacy of exercise for chronic pain conditions."*

The lack of specified dosage for exercise interventions is a major limitation to better understanding the effects of exercise on pain. A specific example is utilizing METs for tracking exercise dosage for resistance training. The authors and myself are aware this isn't the best metric to utilize. However, the authors cite lacking data on load, volume, rest periods, etc from the primary included studies. This is an important limitation of the included studies as it relates to appropriate exercise dosage of resistance training for those dealing with persistent pain.

We need future studies to be specific in their exercise dosage, reporting:

1) Type of exercise (aerobic, resistance, etc)
2) Frequency (how many sessions per week)
3) Intensity (subjective and objective measurements specific to the type of exercise)
4) Time (how long a single session lasts in minutes)
5) Duration (total time for length of exercise prescription i.e. weeks, months, years)

The accurate tracking and reporting of the above information would likely help with the generalizability of research findings as it relates to this topic. Either way. hopefully the findings from this review help stifle claims that one must do a particular exercise dosage

(type, frequency, intensity, time, and duration) to “get themselves out of pain” and rather reframe focus onto finding the patient’s preferred exercise dosage based on activity history and individual goals.

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OxyRBX is a proven, safe performance enhancing drug to increase running performance.

Effects of an Injected Placebo on Endurance Running Performance by Ross et al. 2015.

Key Points:

1. Trained runners given a placebo that they perceived as an active drug were able to improve their 3 km running performance by almost 10 seconds versus a control group only improving 2 seconds.

2. The placebo, according to participants, reduced the qualitative perception of effort and increased motivation without changing the quantitative perception of effort via rate of perceived exertion.

3. An inert substance was able to increase performance without changing heart rate, rate of perceived exertion, or hematological variables, alluding to the role that beliefs play in performance.

Introduction

OxyRBX is a placebo. The efficacy of placebo in enhancing performance is as well established as it is multifactorial.[Geers 2014] This presents a paradox of a placebo being an inert substance, yet still having an effect on performance. A movement has recently transpired to move away from the term “placebo effect” and toward “contextual factors” to address apparent paradox.[Rossetini 2018] Contextual factors have been implicated in the effects of ergogenic aids, anabolic steroids, creatine monohydrate, and a variety of other substances and devices.[Beedie 2009] Oral placebos have consistently shown approximately 2% increases in moderately trained endurance athletes.[Beedie 2006,McClung 2007] The effect of the placebo has shown even greater effects when administered by an injection/needle.[Zhang 2008]

Athletes are constantly in search of anything that will give them a competitive edge, with the complementary health industry in American generating $30 billion dollars/year.[Nahin 2012] The vast majority of those supplements, treatments, and advice completely lack evidence of efficacy, and of those that do, most are illegal in higher levels of competition. Over the past two decades, the use of performance enhancing drugs (PEDs) has been on the rise.[Carpenter 2007, Stano Rossi 2011] Specific to endurance athletes, one of the most popular drugs is recombinant Human Erythropoietin (r-HuEPO) which has been shown to increase hematocrit (Hct).[Durussel 2013]
Even here, the effect on physiological changes translating to increased performance is in question, but the drug is now synonymous with the sport of cycling.[Heuberger 2013]

The association of r-HuEPO with increased performance can serve as an anchor with which to prime athlete expectations.[Tversky 1974] The expectation being that taking a substance with the same effects of r-HuEPO should increase performance as well. This study aimed to explore the magnitude of those effects on performance, as well as biochemical markers in a competitive environment.

Purpose

The purpose of this study was to quantify the effect of a placebo injection purported to have the same level of effect as a proven drug (r-HuEPO) on endurance running performance in a field based, head-to-head competition.

Methods

This was a randomized cross-over design, with participants undergoing tests before and after a 7-day “control” phase during which no intervention was given, and a 7-day “placebo” phase during which individuals were administered daily subcutaneous saline injections (0.5mL of 0.9% NaCl) that they thought to be OxyRBX. The study recruited 19 endurance-trained males, with three dropping out prior to the study due to concerns of possible complications. One additional participant dropped out without giving a reason. This left 15 well-trained club level athletes who engaged in 213 +/- 129 minutes of endurance training and 50 +/- 58 minutes of resistance training per week. Their personal record (PR) in a 10-km race was 39.3 +/- 4.4 minutes.

Participants were given an informed written consent that they were taking a “legal erythropoietin-like substance, OxyRBX,” to enhance the deception. After the study all participants were debriefed that they had taken a placebo. Prior to the study all participants were informed of the effects of r-HuEPO on exercise performance on an individual basis. They were provided information on the effects, dosage, and safety of

OxyRBX as well as the benefits on performance. OxyRBX was described as a legal r-HuEPO-like substance shown in animal studies to induce benefits similar to r-HuEPO and was safe for use in humans.

Athletes performed a 3-km familiarization time trial which was used to handicap the 3-km competition runs in the main study. Handicapping means if an individual ran 5 seconds faster than another on their time trial, the slower individual would get a 5 second head start in the actual race. Then participants followed a randomized crossover design with testing before and after a 7 day "control" phase and before and after a 7 day "placebo" phase with 14 days in between. The 14 day gap was sold as a "wash out" phase for individuals who received the OxyRBX. Eight participants underwent the control phase first with the other seven undergoing placebo first.

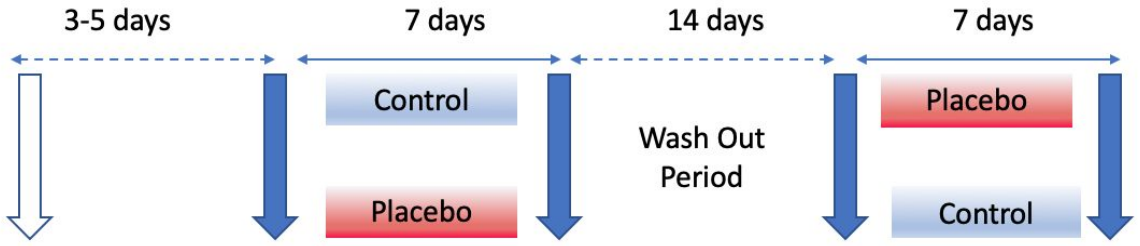


Figure 1: Representation of trial design with the solid arrows constituting blood tests and a 3km time trial and the hollow arrow only a 3km time trial.

The primary outcome was participant's 3-km race time with quantitative variables of mean heart rate, rate of perceived exertion [RPE], hemoglobin (g/dL), Hct (%), red blood cell count ($x10^9$/L), mean cell volume (fL), and mean corpuscular volume (pg). RPE in this instance was based on the Borg scale from 6 to 20 where 6 = no effort and 20 = maximum effort. Participants were also queried when attending their sessions for daily placebo injections on whether they noticed any changes while taking OxyRBX. Specifically, they were asked if they felt different while "taking" the substance; how they felt during training and races; whether they felt that their recovery was different, and whether they noticed any side effects.

There was also a qualitative arm to the study *after* the race with research team members asking participants questions pertaining to their experience taking OxyRBX during the trial, whether they thought it would improve their performance, whether they felt different "taking" the substance, how they felt during training and races, whether they felt their recovery was different, and whether they experienced any positive or negative side effects. After individuals had seen their race times they were also asked

the extent to which the substance allowed them to work harder. All subjects were debriefed to the nature of the study after completion of the post-race interview.

Results

When believing they had taken the placebo drug, individuals demonstrated significantly improved performance in their 3-km races than when exposed to control (9.73 s faster, 95% Confidence Interval (CI), 5.14-14.33 s faster vs. 1.82 s, 95% CI 2.77 s slower-6.41 s faster). Eleven participants improved more in response to placebo than control, one had no change, and three participants had greater performances in response to control.

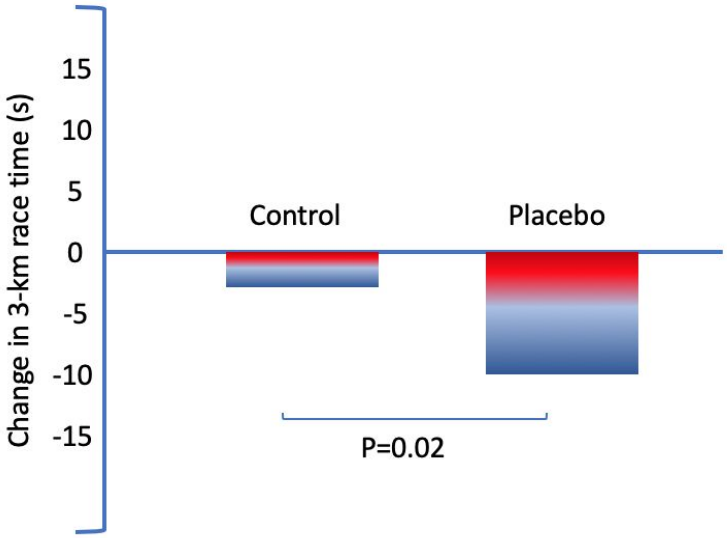


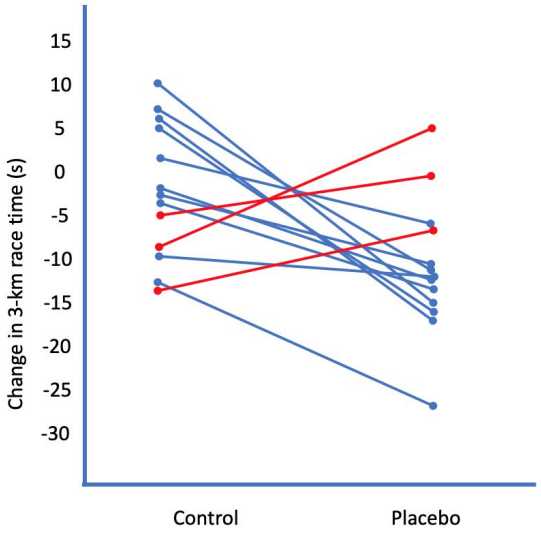
Figure 2: 3-km time differences between placebo and control group pre- to post-test

Figure 2 demonstrates the difference in individual race times in 3-km times between the control group and placebo.. The placebo group amounts to a 1.2% improvement in time compared to the control group. For perspective, in the 2018 men's 5-km race the difference between 1st and 8th place was 5.27 seconds.

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

On an individual participant level, figure 3 demonstrates the changes in time for 13 participants, 10 of whom improved their times with the introduction of placebo. There were, however, 3 individuals whose time increased with the introduction of placebo. Those individuals, in the qualitative aspect of the study expressed statements such as “I felt like my legs were really heavy, felt like it was working against me, particularly the drug week.” While the total cohort did improve, it is important to note that some individuals did not, with some times worsening. This is where the qualitative portion of the study can offer insight as to why these results were present.

Figure 3: Individual responses in running time to control or placebo.



Athletes were questioned post-study regarding their beliefs with almost all reporting they believed they were taking a real drug. The magnitude of their expectations demonstrated a loose association with the magnitude of their performance.

An individual who experienced a positive response reported *“I wanted to kind of count down until I was going to take it”* while another who did not experience any improvement reported *“I didn’t think taking the drug would have any effect at all…”* The authors attribute the overall effect to *motivational intensity theory,* which states that maximal exercise tolerance increases when either perception of effort is reduced or “potential motivation” is increased. Marcora 2010

There was no reported difference in hematological variables in either group. Table 1 shows these results. Also, there was no difference in RPE rating between pre and post conditions in either group.

	Control		Placebo	
	Preintervention	Post intervention	Preintervention	Post intervention
3-km race time (s)	665.9 +/- 13.8	664.0 +/- 13.6	665.9 +/- 13.8	665.9 +/- 13.8
Mean Heart Rate (bpm)	174 +/- 4.2	174.3 +/- 4.3	174 +/- 4.2	174 +/- 4.2
RPE	18.5 +/- 0.4	19.3 +/- 0.2	18.5 +/- 0.4	18.5 +/- 0.4
Hemoglobin (g/dL)	14.3 +/- 0.2	14.5 +/- 0.2	14.3 +/- 0.2	14.3 +/- 0.2
Hematocrit (%)	43.2 +/- 0.5	43.9 +/- 0.6	43.2 +/- 0.5	43.2 +/- 0.5
Red Blood Cell Count ($x10^9$/L)	4.8 +/- 0.1	4.9 +/- 0.1	4.8 +/- 0.1	4.8 +/- 0.1
Mean Cell Volume (fL)	90.8 +/- 0.8	90.3 +/- 0.7	90.8 +/- 0.8	90.8 +/- 0.8
Mean Corpuscular Volume (pg)	30.0 +/- 0.3	29.9 +/- 0.3	30.0 +/- 0.3	30.0 +/- 0.3

Table 1: Hematological and performance variables between the control and placebo group.

Why does this study matter?

There is a lot to unpack with this study, and it was chosen to expand upon those commentaries. First, my selection for the title of this piece “OxyRBC is a proven, safe performance enhancing drug to increase running performance” was intentional. Even though this study was a trial of placebo, and did exhibit positive results, the *framing* of those results could easily convey the message that this substance *caused* a real effect on performance. There are numerous supplements on the market that show increased performance attributable to some biochemical change that likely do not fair better than a placebo. Randomized, controlled trials are designed, and often necessary, to pick up any difference between an inert and actual substance. Demonstrating that a substance increases performance in an uncontrolled study does not give good information as to the actual utility of the substance versus the *meaning response* associated with it.

Unless the reader has seen this study prior, the first inclination upon seeing the title was likely a curiosity to see what this “OxyRBX” is, and what it can offer to athletic performance. The choice of a placebo study on endurance performance for this month’s BMR was also intentional. The large cohort of readers subscribing here have an inclination towards strength sport. It is easier to look at an outgroup and see the flaws in their reasoning. If the reader does not think these same effects are prevalent in strength sports, let me refer them to Ariel *et al* 1972 and Maganaris *et al* 2000. Ariel 1972, Maganaris 2000 The first study, from 47 years ago, is a testament to the power of beliefs in training for strength sports. Fifteen athletes with at least two years training experience were instructed they were going to participate in a study on the effects of Dianabol (an anabolic steroid) but only those who demonstrated the best gainz in the first 7 weeks of the study would be selected. During those 7 weeks, the selected cohort of 6 individuals for the placebo arm of the study put 11kg on their total for squat, bench press, and seated military press. These six individuals then completed an additional 4 weeks of training while taking a placebo pill that they were informed contained 10mg of Dianabol. I want to reiterate here that these individuals had reported training for at least two years and that they were taking a placebo. How much did their total improve? **45 kilos**. This was after 11kg improvement in the prior 7 weeks.

The astute reader will also notice there is a contradiction in key points 2 and 3 at the beginning of this pieceThere was no difference in reported RPE between groups in the pre and post interventions but there was a qualitative reporting of the race *feeling* easier. Table 1 shows the RPE ratings with the low end being an 18.5 in both groups. A basic conversion to the RPE most readers are familiar with would be approximately RPE 9. This means the athletes were competing near maximum effort which is, in effect, where anyone should be for a competition. Races are judged on the distance they are ran (stating the obvious) and in this case a 3-km. This would be the equivalent

of a lifting competition being judged on how fast an individual could squat 405# with time being the variable measured in both. If a competition were to transpire this way, someone with a faster bar speed would likely *perceive* the task as easier even if they were giving maximum effort.

Overall, this study demonstrates how *expectation* of benefit can improve performance in *some* athletes. With the plethora or treatments, ergogenic aids, training templates, recovery tools, passive modalities on the market, the degree to which an athlete *believes* they work influences *if* they work. It also raises an ethical dilemma for practitioners and coaches. If research has demonstrated that a performance aid does not work by a physiological mechanism beyond *belief*, is it okay to use? Also, is it ethical to knowingly misinform athletes that a device or treatment will help them recover faster or perform better using a physiological explanation that is unsubstantiated. The subjects in this study were all debriefed to the fact they were receiving a placebo injection. That does not invalidate the results the athletes achieved regarding their performance. We can continue to apply explanations to treatments such as *neurophysiological changes, breaking up adhesions, diffuse noxious inhibitory control,* or any other manner of polysyllabic explanation, or we can be honest with athletes that it is ultimately up to them to believe in what they can do and train accordingly. We are also *all* exposed to the effect our beliefs have on performance. The athletes in this study who believed they would experience a bigger effect did. Those who did not, or experienced anxiety regarding adverse effects of the drug did not.

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