The placebo effect in nutritional supplementation and improvement in performance outcomes: a meta-analysis

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The placebo effect in nutritional supplementation and improvement in performance outcomes: a meta-analysis

by

Tarra Linn Rawdon

A thesis submitted to the graduate faculty in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

Major: Exercise and Sport Science

Program of Study Committee:
Rick Sharp, Major Professor
Jerry Thomas
Kevin Schalinske

Iowa State University
Ames, Iowa
2006

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This is to certify that the master's thesis of

Tarra Linn Rawdon

has met the thesis requirements of Iowa State University
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INTRODUCTION

In many clinical trials and research studies on the effects of a treatment, pharmacological drug, or nutritional supplement a placebo is used as a control. In Latin the word placebo means 'I shall please'. Today the word placebo refers to any treatment or substance given to a patient or subject that is thought to be ineffective and should not produce any physiological benefits. However, an increase or improvement in the placebo group is often observed as well as the experimental group and is known as the placebo effect. This is defined as “the measurable, observable, or felt improvement in health not attributable to the treatment” (16).

Evidence of the placebo effect can be seen in clinical trials such as a study by Kirsch and Sapirstein that studied the effectiveness of antidepressants. They found that 75% of the effectiveness of the drug was due to the subjects’ expectations of getting better and not the drug itself (27). The power of a placebo and subject expectation in respect to supplements as well is frequently observed. For example, Ariel and Saville found a 10% increase in strength when their subjects, weight lifters, were told they were taking a steroid, but were actually taking a placebo, compared to the 2.3% increase in strength with training alone (2). This large increase in percent strength gained was attributed to their belief that they should get stronger and not to the placebo.

The purpose of this study is to determine if there is a significant placebo effect with nutritional supplements and performance measures of muscle strength, endurance, and power. A meta-analysis is used to quantify the size of the placebo effect and to compare a wide variety of supplements and different outcome measures.
LITERATURE REVIEW

Placebo Effect Theories

Different theories exist as to the cause of the placebo effect. The first and most common theory is the psychological or mentalistic theory. According to this theory the placebo effect results from the subject’s expectations for the benefits of the placebo and its positive effects. This is reflected by the previously cited study by Kirsch and Sapirstein on the effectiveness of antidepressants in clinical trials where 75% of the improvement was due to the subjects expectations of getting better, not the effectiveness of the drug (27).

Another theory is that the effects from a placebo are a conditioned response. This means that the simple act of taking a pill, getting a shot, or even seeing a medicine bottle, may trigger a conditioned response similar to that of a drug. There is some debate about this theory however, because some individuals without any past experience with drugs still experience a placebo effect (41).

A third theory about the effect a placebo has on a subject is that nature is taking its course. Some speculate that when looking at the placebo effect of a drug on an injury or illness, the natural course of healing should be taken into account. Instead of attributing the improvements of an injury or disease to the placebo effect, they should be credited to nature running its course. This is not always the case, in some instances the subjects that receive a placebo or experimental treatment do better than those who were not given anything (20).
A final theory is that simply receiving treatment or being part of a study leads to improvements. The placebo effect is not a result of the placebo substance, but instead a result of the process of receiving the placebo treatment. The attention, care, affection, and encouraging attitude of the experimenter or doctor may affect the mood of the subject or patient (9). This change in mood is thought to cause physical changes, like releasing endorphins. Being part of a study has also been shown to cause improvements by increasing the subject’s knowledge and interest in their health, which often leads to changes in risky behavior. An example of how simply receiving treatment can lead to improvements can be seen with the internal mammary ligation surgery that used to be done to decrease chest pain and increase blood flow to the heart. The operation consisted of small incisions in the chest and tying knots in two arteries of the heart. Ninety percent of the patients said the procedure helped, but when compared to a fake operation where only incisions were made in the chest, the results were the same and the procedure is no longer performed (27).

Clinical Trials and the Placebo Effect

In the mid-1900s the double-blind, randomized control trial was first developed. At that time the placebo began to be used as a control in clinical trials, for researchers to compare their drugs and treatments against (23). Presently, the placebo effect is greatest in clinical trials on treatment of Parkinson’s disease, pain, and depression. Clinical trials on drugs used to treat Parkinson’s disease have shown a reasonable placebo effect. The drug pergolide resulted in improvements of Parkinson’s symptoms of 17% in 4 weeks and 30% in 24 weeks; however, these were not significantly different than the 16% and 23% improvement seen with a placebo. A review of 36 Parkinson’s studies showed that 12 of the articles resulted in
improvements with the placebo ranging from 9-59% compared to the experimental drug. Even fake operations used to treat the symptoms of Parkinson’s have resulted in mild to equal improvements in the placebo surgery compared to the actual surgery (16).

The placebo effect in Parkinson’s patients is believed to be a result of the reward theory. The brain releases dopamine in response to either a reward or the expectation of a reward. A PET scan was used to show that an injection of saline (placebo) causes a release of a considerable amount of dopamine in the brain which is related to an improvement in motor function. Since the placebo could not cause the dopamine release it must be the expectation of the reward, improved function, and not the reward itself, that causes the release (16).

Other diseases or disabilities also produce the placebo effect in clinical trials. A placebo-controlled trial on the effectiveness of secretin, which was being heralded as the cure for autism, resulted in a 30% improvement in symptoms and behavior with both secretin and the placebo (42). This large placebo effect could have been due to the normal variation of autistic symptoms from day-to-day and the high expectancy the parents had for the benefits of the drug. Thus any decrease in symptoms after starting the treatment would have been attributed to the placebo. Similar results have been seen in clinical trials of treatment for cerebral palsy and ADHD (42).

The placebo effect can be found in analgesic research as well. A trial where subjects received a placebo, but were told it was a painkiller showed a decrease in pain due to both the opioid and non-opioid mechanisms. This means that the pain was decreased because of a
physical change caused by the placebo that inhibited the pain pathway and also because of a psychosocial component being the expectancy of a decrease in pain. The main problem with placebo analgesia is that it’s hard to determine if a drug effects the pain pathway and is a true painkiller, or if it acts on the expectancy pathway along with the placebo. Thus the only way to determine a drugs true effectiveness on pain is to administer it to the patient without them knowing. It was found that a saline injection in plain sight of the patient was just as successful at relieving pain as 6-8 mg of morphine given to them without knowing (13).

This is where the ethical debate of using a placebo becomes an issue. Is it ethical to give a subject or patient a drug without them knowing? Is it ethical to give them a placebo, but tell them it is a drug? In clinical trials a placebo group is used as a control to compare the experimental group against. If subjects are made aware which group they are in the trial becomes unblinded and the results are no longer valid. However, using placebos is thought to be ethical when there is a strong scientific reason, informed consent is used, risks are decreased, and the trial is approved by the Institutional Review Board (37).

Nutritional Supplements and the Placebo Effect

Clinical trials on drugs for Parkinson’s disease, pain, and other disabilities are not the only studies where a measurable placebo effect can be found. Studies on nutritional supplements and physical performance improvements often seem to have at least a mild if not larger placebo effect. The use of dietary supplements to augment or improve one’s health, memory, activity performance, strength, power, or body composition have become common place in today’s society. Some supplements are thought to be effective by simply ingesting them,
while others help to enhance the effects of additional activities, such as resistance or aerobic training. It is hard to know which supplements are actually beneficial and which are not, especially when “experts” and novices alike claim to have proof of the improvements caused by these supplements.

Using personal testimonies as “proof” that a supplement is beneficial along with not including a control or placebo group in the experimental design are two frequent errors in supplementation research. Without baseline or control data to compare the experimental findings with it is hard to determine if outcome improvements are due to the supplement or a placebo effect. Including a placebo group along with the control group in the experimental design, helps to reduce the chance of a placebo effect. It can also be used to rule out whether the increase is due to training (the experimental and placebo group’s improvements are similar) or to the supplement (the experimental group improved significantly more than the placebo).

A classic example of how powerful a placebo can be is illustrated in a study by Ariel and Saville, which resulted in significant strength gains in trained individuals when they were receiving what they believed, was an anabolic steroid, when in fact it was a placebo (2). Fifteen male, experienced weight lifters went through a 16-week pre-treatment training program. Six of the 15 participated in the treatment period, which consisted of four additional weeks of training, during which time they were told they were given 10 mg of Dianabol (an anabolic steroid) per day, but they were actually only receiving a placebo.
The authors collected data on four different lifts for a 7-week period during the pre-treatment and the 4-week treatment period. The data showed significant strength gains in the pre-treatment time (2.3% increase), but a substantial gain during the treatment time (10.0% increase). These improvements in strength were not due to a training effect because the participants were already trained and were not due to a supplement because it was merely a placebo. Thus strength gains were attributed to their belief that they should get stronger since they thought they were taking a strength enhancing supplement, clearly illustrating the placebo effect (2).

Chromium picolinate is a nutritional supplement that has recently gained exposure as possibly being beneficial in improving sport performance and body composition. A study by Walker et al. using both a placebo and a control group demonstrated the ineffectiveness of the supplement at causing significant upper and lower body strength gains in wrestlers. There was no significant improvements for the controls from pre to post treatment in 1RM for power cleans or bench press, or upper and lower body endurance (reps) or power measures (W·kg⁻¹). In the placebo group there were significant improvements in strength with upper body endurance (reps), pre 22.29 ± 1.71 and post 27.57 ± 2.88, and bench press power (W·kg⁻¹), pre 7.80 ± 0.60 and post 9.77 ± 0.92 (P< 0.05) (49).

A study by Bemben et al. examined the effects creatine supplementation had on muscle strength and anaerobic power improvements in college football players. The results indicated that the creatine supplemented group had larger improvements in strength (5.2%, 3.8%, and 8.7%) and anaerobic power (19.6% and 18.4%) compared to both placebo and
control groups. However, the placebo group had small strength gains (1.9% and 5.1%) compared to the control group which did not show any improvement. Neither the placebo nor control group improved in anaerobic power. Thus, a small placebo effect may be seen in the measures of muscle strength, but not power (4).

Clark et al. examined the effect of carbohydrate feedings on performance in a 40-km time trial. All subjects completed one time trial consuming water as a control trial. In the second trial subjects were given either carbohydrate or placebo, and either told they were getting carbohydrate, placebo, or not told at all. The percent change in power from the control time trial for subjects told they were getting carbohydrate was 4.3 ± 4.8%, the majority of that improvement was seen with the placebo group, told placebo 0.5 ± 5.8%, and not told -1.1 ± 8.5%. Subjects who were told they were receiving carbohydrate but it was really placebo had a positive change in power of about 7%, but subjects who were receiving the carbohydrate but were told it was placebo had no change in power. So, when the subjects believed they were taking a supplement that was supposed to be very beneficial for strength gains and body composition, they saw improvements even when taking a placebo, yet when they were told it was a placebo most subjects saw no performance improvements, even those taking the carbohydrate (12).

The main purpose of this meta-analysis was to determine whether there is a significant placebo effect found in studies on nutritional supplementation and increases in the performance outcomes of muscle strength, endurance, and power. If the research hypothesis is true and a placebo effect does exist, there will be a significant difference between the
placebo group and the control group. This study will focus on the effect of supplementation on gains in strength, endurance, and power rather than muscle substrate levels and other physiological markers due to the fact that a placebo effect or psychological influence will not impact any inherent changes seen in substrate levels. Additional hypotheses include the effect certain variables have on the presence of a placebo effect. The first is that studies that are double-blind will have a smaller chance of displaying a placebo effect. The second is that trained subjects may be more likely to display a placebo effect than untrained subjects, owing largely to the fact that trained individuals are more likely to have preconceived ideas of the benefits of dietary supplements.
METHODS

Data Selection

The initial literature search was performed using the PubMed and PsycINFO databases, with keywords; (nutritional) supplementation, placebo, training (or resistance/strength training), and muscle power, strength, and endurance. The online database for the Journal of Applied Physiology was also searched using the same keywords. All of the matching titles were then screened and those that did not include a dietary supplement, a placebo group, or used subjects that were not considered healthy were not considered.

From there, inclusion in the meta-analysis was based on the following criteria. Studies had to have been published in a peer-reviewed journal. The duration of the treatment time was not a factor; however, it needed to be long enough for improvements to develop. As far as the supplements used, the dose given had to be higher than the normal daily amount. The studies were not restricted by the method or how often they were given or even to those that used only one supplement. The studies included had to have measured changes in strength, muscle endurance, or muscle power.

Data Coding

All of the studies that were to be included in the meta-analysis were then placed on a coding sheet. The following information was placed on the code sheet for each study: age, gender of subjects, same or different groups, random, familiarization session, double blind, study length, outcome measure, training load, training frequency, and training status. These characteristics were chosen because of their possible impact on the placebo effect.
Effect Size Calculation

An effect size was calculated for each study so that the results could be put in a similar unit and compared. The effect size (ES), pooled standard deviation (Sp), standard error (SE), and inverse variance (w) of changes in muscle strength, endurance, and power were calculated using the following formulas from Lipsey and Wilson (31):

Within groups formulas were used for post-pre supplementation calculations:

\[
ES = \frac{X_{T2} - X_{T1}}{S_p} \quad S_p = \frac{(S_1 + S_2)}{2}
\]

\[
SE = \sqrt{\frac{2(S_p^2)(1-r)}{n}} \quad S_p^2 = \frac{(S_{T1}^2 + S_{T2}^2)}{2}
\]

\[
w = \frac{1}{SE^2}
\]

Having \(X_{T2} = \text{post}, X_{T1} = \text{pre}, S_1 = \text{standard deviation pre}, S_2 = \text{standard deviation post}, \) and \(r = 0.6\)

Between groups formulas were used for post-post supplementation calculations:

\[
ES = \left[ 1 - \frac{3}{(4N-9)} \right] (ES_{sm}) \quad ES_{sm} = \frac{X_1 - X_2}{S_p}
\]

\[
S_p = \sqrt{\frac{(n_1-1)S_{G1}^2 + (n_2-1)S_{G2}^2}{(n_1-1) + (n_2-1)}} \quad SE = \sqrt{\frac{n_1 + n_2 + (ES)^2}{(n_1)(n_2) + 2(n_1+n_2)}}
\]

\[
w = \frac{1}{SE^2}
\]

Having \(ES_{sm} = \text{unbiased effect size}, X_1 = \text{group 1}, X_2 = \text{group 2}, S_{G1} = \text{standard deviation group 1}, S_{G2} = \text{standard deviation group 2}\)

Effect sizes were calculated for the difference between post and pre supplement for each group included in the study; treatment, placebo, and control (if included). Effect sizes were
also calculated between groups (treatment-placebo, placebo-control, and treatment-control) to determine the difference in post supplementation measures. An ES of 0.0 would indicate that there was no difference between the values being compared; an ES of 0.2 was considered small, 0.5 was average or moderate, and 0.8 a large ES.

**Statistical Analysis**

The effect sizes for between groups comparisons and within groups comparisons were determined according to appropriate formulas in Lipsey and Wilson (31) and Thomas (46), and were analyzed using the SPSS statistical package. The original ES data were examined using exploratory statistical methods to determine whether their distribution was approximately normal. A backward elimination multiple regression was used to determine which independent variables were significant predictors of the effect size. To adjust for the lack of normality in the distribution of the original effect size results, additional backward elimination multiple regression analyses were conducted on the ranks of the effect size data for each group (treatment, placebo, and control) and for each coded variable.
RESULTS

Study Inclusion

Of the 649 studies that were found pertaining to nutritional supplements only 37 met all criteria and were included in the meta-analysis. The characteristics of each of the included studies are summarized in Table 1.

Post-treatment Group Comparisons

When analyzing the difference of the mean effect sizes calculated for the post-treatment groups, there was a significant difference between the treatment group and the control group (ES=0.98). Comparison between the placebo group and control group resulted in a large effect size (ES=0.67), indicating a difference between the two groups, but not as large as compared to treatment. The mean effect size between the treatment and placebo groups (ES=0.06) demonstrated the mean post-treatment results were not significantly different for the two groups (Figure 1).

![Graph showing effect sizes](image)

Figure 1. Mean effect sizes calculated for post-post supplementation for between the control, placebo, and experimental groups; * P<0.05; Mean ± SD.
Table 1. Summary of characteristics of all studies included in meta-analysis.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Journal</th>
<th>Treat. (n)</th>
<th>Pla. (n)</th>
<th>Con. (n)</th>
<th>Gender</th>
<th>Supplement</th>
<th>Dosage/day</th>
<th>Ave. Age</th>
<th>Train Status</th>
<th>Training session/wk</th>
<th>Duration (wks)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antonio et al.</td>
<td>2000</td>
<td>Nutrition</td>
<td>10</td>
<td>9</td>
<td>0</td>
<td>Female</td>
<td>Essential AA</td>
<td>18.3 g</td>
<td>27</td>
<td>U</td>
<td>3</td>
<td>6</td>
<td>Str, End</td>
</tr>
<tr>
<td>Ariel &amp; Saville</td>
<td>1972</td>
<td>Med &amp; Sci in Sports</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>Male</td>
<td>Placebo (&quot;Dianabol&quot;)</td>
<td>~10 mg*</td>
<td>18-22</td>
<td>T</td>
<td>5</td>
<td>4</td>
<td>Strength</td>
</tr>
<tr>
<td>Ayocama et al.</td>
<td>2003</td>
<td>J Sports Med Phys Fit</td>
<td>13</td>
<td>13</td>
<td>0</td>
<td>Female</td>
<td>Creatine Monohydrate</td>
<td>20g/20g + 20g/3g</td>
<td>19</td>
<td>T</td>
<td>5/1st wk</td>
<td>4</td>
<td>Str, Pow</td>
</tr>
<tr>
<td>Brilla &amp; Haley</td>
<td>1992</td>
<td>J Amer College Nutrition</td>
<td>12</td>
<td>14</td>
<td>0</td>
<td>Mixed</td>
<td>Magnesium</td>
<td>8mg/kg bw/day</td>
<td>18-30</td>
<td>U</td>
<td>3</td>
<td>7</td>
<td>Strength</td>
</tr>
<tr>
<td>Broder et al.</td>
<td>2000</td>
<td>Arch Intern Med.</td>
<td>32</td>
<td>18</td>
<td>0</td>
<td>Male</td>
<td>Androstenediol-diol</td>
<td>200 mg</td>
<td>35-65</td>
<td>U</td>
<td>3</td>
<td>12</td>
<td>Strength</td>
</tr>
<tr>
<td>Brose et al.</td>
<td>2003</td>
<td>The Journals of Ger</td>
<td>14</td>
<td>14</td>
<td>0</td>
<td>Mixed</td>
<td>Creatine Monohydrate</td>
<td>5g CrM + 2g dextrose</td>
<td>68</td>
<td>U</td>
<td>3</td>
<td>14</td>
<td>Str, Pow</td>
</tr>
<tr>
<td>Brown et al.</td>
<td>1999</td>
<td>J Appl Physiol</td>
<td>9</td>
<td>10</td>
<td>0</td>
<td>Male</td>
<td>DHEA</td>
<td>150 mg</td>
<td>23</td>
<td>U</td>
<td>3</td>
<td>8</td>
<td>Strength</td>
</tr>
<tr>
<td>Burke et al.</td>
<td>2003</td>
<td>Med Sci Sports Exer</td>
<td>12</td>
<td>12</td>
<td>0</td>
<td>Mixed</td>
<td>Creatine Monohydrate</td>
<td>16.8 g/d &amp; 4.2 g/d</td>
<td>32.5</td>
<td>U</td>
<td>3</td>
<td>8</td>
<td>Str, End</td>
</tr>
<tr>
<td>Campbell et al.</td>
<td>1999</td>
<td>J Appl Physiol</td>
<td>9</td>
<td>9</td>
<td>0</td>
<td>Male</td>
<td>Chromium Picolinate</td>
<td>924 μg</td>
<td>56-69</td>
<td>U</td>
<td>2</td>
<td>12</td>
<td>Power</td>
</tr>
<tr>
<td>Cooke et al.</td>
<td>1996</td>
<td>J Appl Physiol</td>
<td>9</td>
<td>8</td>
<td>0</td>
<td>Male</td>
<td>Creatine Monohydrate</td>
<td>20g CrM + 4g glc</td>
<td>24</td>
<td>U</td>
<td>0</td>
<td>5 days</td>
<td>Power</td>
</tr>
<tr>
<td>Crist et al.</td>
<td>1983</td>
<td>J Appl Physiol</td>
<td>9</td>
<td>9</td>
<td>0</td>
<td>Mixed</td>
<td>Testosterone cypionate, Nandrofone decanoate</td>
<td>100 mg/wk</td>
<td>10-31</td>
<td>T</td>
<td>norm activity 3 or/2 wks</td>
<td>3</td>
<td>Str, Pow</td>
</tr>
<tr>
<td>Eijnde et al.</td>
<td>2003</td>
<td>J Appl Physiol</td>
<td>23</td>
<td>23</td>
<td>0</td>
<td>Male</td>
<td>Creatine Monohydrate</td>
<td>5 g</td>
<td>63</td>
<td>U</td>
<td>2 or 3</td>
<td>6 mo</td>
<td>Str, End</td>
</tr>
<tr>
<td>Gallagher et al.</td>
<td>2000</td>
<td>Med Sci Sports Exerc</td>
<td>23</td>
<td>14</td>
<td>0</td>
<td>Male</td>
<td>HMB</td>
<td>3 g or 6 g</td>
<td>22</td>
<td>U</td>
<td>3</td>
<td>8</td>
<td>Str, End</td>
</tr>
<tr>
<td>Hellisten et al.</td>
<td>2004</td>
<td>Am J Phys Regul Integ</td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>Male</td>
<td>Ribose</td>
<td>200 mg/d x 3</td>
<td>25</td>
<td>U</td>
<td>14</td>
<td>2</td>
<td>Power</td>
</tr>
<tr>
<td>Authors</td>
<td>Year</td>
<td>Journal</td>
<td>Treat.</td>
<td>Pla.</td>
<td>Con.</td>
<td>Gender</td>
<td>Supplement</td>
<td>Dosage/ day</td>
<td>Ave</td>
<td>Train</td>
<td>Training session/wk</td>
<td>Duration</td>
<td>Outcome</td>
</tr>
<tr>
<td>-----------------</td>
<td>------</td>
<td>----------------------------------</td>
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<td>---------------------</td>
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<tr>
<td>Jowko et al.</td>
<td>2001</td>
<td>Nutrition</td>
<td>11, 11</td>
<td>11</td>
<td>0</td>
<td>Male</td>
<td>Creatine &amp; HMB</td>
<td>Cr (20,10g) HMB (3 g)</td>
<td>21</td>
<td>U</td>
<td>3</td>
<td>3</td>
<td>Strength</td>
</tr>
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<td>Kenny et al.</td>
<td>2003</td>
<td>J Am Geriatr Soc</td>
<td>33</td>
<td>32</td>
<td>0</td>
<td>Male</td>
<td>Cholecalciferol</td>
<td>1,000 IU/d</td>
<td>76</td>
<td>U</td>
<td>0</td>
<td>6 mo</td>
<td>Strength</td>
</tr>
<tr>
<td>Kilduff et al.</td>
<td>2003</td>
<td>Int J Sp Nutr Exer Meta</td>
<td>9</td>
<td>10</td>
<td>0</td>
<td>Male</td>
<td>Creatine Monohydrate</td>
<td>22.8g/d &amp; 5.7g/d</td>
<td>20</td>
<td>U</td>
<td>3</td>
<td>4</td>
<td>Strength</td>
</tr>
<tr>
<td>King et al.</td>
<td>1999</td>
<td>JAMA</td>
<td>10</td>
<td>10</td>
<td>0</td>
<td>Male</td>
<td>Androstenedione</td>
<td>300 mg</td>
<td>19-29</td>
<td>U</td>
<td>3</td>
<td>8</td>
<td>Strength</td>
</tr>
<tr>
<td>Kocak &amp; Karl</td>
<td>2003</td>
<td>J Sports Med Phys Fit</td>
<td>10</td>
<td>10</td>
<td>0</td>
<td>Male</td>
<td>Creatine Monohydrate</td>
<td>20 g/d</td>
<td>24</td>
<td>T</td>
<td>recreational</td>
<td>5 days</td>
<td>Power</td>
</tr>
<tr>
<td>Kreider et al.</td>
<td>1998</td>
<td>Med Sci Sports Exerc</td>
<td>11</td>
<td>14</td>
<td>0</td>
<td>Male</td>
<td>Creatine Monohydrate</td>
<td>15.75 g</td>
<td>20</td>
<td>T</td>
<td>5</td>
<td>4</td>
<td>Str, Pow</td>
</tr>
<tr>
<td>Madsen et al.</td>
<td>1996</td>
<td>J Appl Physiol</td>
<td>9</td>
<td>9</td>
<td>0</td>
<td>Male</td>
<td>Glucose &amp; BCAA</td>
<td>5% CHO, 18g BCAA</td>
<td>28.9</td>
<td>T</td>
<td>norm activity</td>
<td>3</td>
<td>Power</td>
</tr>
<tr>
<td>McKenna et al.</td>
<td>1999</td>
<td>J Appl Physiol</td>
<td>7</td>
<td>7</td>
<td>0</td>
<td>Mixed</td>
<td>Creatine Monohydrate</td>
<td>30 g</td>
<td>20</td>
<td>U</td>
<td>0</td>
<td>4</td>
<td>Power</td>
</tr>
<tr>
<td>Morrison et al.</td>
<td>2000</td>
<td>J Appl Physiol</td>
<td>7</td>
<td>7</td>
<td>0</td>
<td>Male</td>
<td>Pyruvate</td>
<td>7 g/day</td>
<td>31</td>
<td>T</td>
<td>norm activity</td>
<td>4</td>
<td>Endurance</td>
</tr>
<tr>
<td>Nissen et al.</td>
<td>1996</td>
<td>J Appl Physiol</td>
<td>35</td>
<td>6</td>
<td>0</td>
<td>Male</td>
<td>HMB</td>
<td>3.0 g/d</td>
<td>19-22</td>
<td>U</td>
<td>3</td>
<td>3</td>
<td>Strength</td>
</tr>
<tr>
<td>Nissen et al.</td>
<td>1996</td>
<td>J Appl Physiol</td>
<td>15</td>
<td>13</td>
<td>0</td>
<td>Male</td>
<td>HMB</td>
<td>3.0 g/d</td>
<td>19-29</td>
<td>T</td>
<td>6</td>
<td>7</td>
<td>Strength</td>
</tr>
<tr>
<td>Oostenbrug et al.</td>
<td>1997</td>
<td>J Appl Physiol</td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>Male</td>
<td>Fish oil &amp; Vitamin E</td>
<td>6 g fish oil, 300 IU/Vit E</td>
<td>19-42</td>
<td>T</td>
<td>norm activity</td>
<td>3</td>
<td>Endurance</td>
</tr>
<tr>
<td>Panton et al.</td>
<td>2000</td>
<td>Nutrition</td>
<td>21</td>
<td>18</td>
<td>0</td>
<td>Male</td>
<td>HMB</td>
<td>3.0 g/d</td>
<td>24</td>
<td>Both</td>
<td>3</td>
<td>4</td>
<td>Strength</td>
</tr>
<tr>
<td>Panton et al.</td>
<td>2000</td>
<td>Nutrition</td>
<td>18</td>
<td>18</td>
<td>0</td>
<td>Female</td>
<td>HMB</td>
<td>3.0 g/d</td>
<td>27</td>
<td>Both</td>
<td>3</td>
<td>4</td>
<td>Strength</td>
</tr>
<tr>
<td>Parcelli et al.</td>
<td>2004</td>
<td>Int J Sp Nutr Exerc Meta</td>
<td>10</td>
<td>12</td>
<td>0</td>
<td>Male</td>
<td>Cordyceps Sinensis</td>
<td>3 g/d</td>
<td>25</td>
<td>T</td>
<td>norm activity</td>
<td>5</td>
<td>Endurance</td>
</tr>
<tr>
<td>Slater et al.</td>
<td>2001</td>
<td>Int J Sp Nutr Exerc Meta</td>
<td>9, 9</td>
<td>9</td>
<td>0</td>
<td>Male</td>
<td>HMB (2 kinds)</td>
<td>3 g</td>
<td>24</td>
<td>T</td>
<td>2 or 3</td>
<td>6</td>
<td>Strength</td>
</tr>
<tr>
<td>Stone et al.</td>
<td>1999</td>
<td>Int J of Sport Nutrition</td>
<td>9, 11,11</td>
<td>11</td>
<td>0</td>
<td>Male</td>
<td>Creatine &amp; Ca Pyruvate</td>
<td>0.22g/kg/d</td>
<td>18.4</td>
<td>T</td>
<td>5 or 6</td>
<td>5</td>
<td>Str, Pow</td>
</tr>
<tr>
<td>Authors</td>
<td>Year</td>
<td>Journal</td>
<td>Treat.</td>
<td>Pla.</td>
<td>Con.</td>
<td>Gender</td>
<td>Supplement</td>
<td>Dosage/day</td>
<td>Ave Age</td>
<td>Train Status</td>
<td>Training session/wk</td>
<td>Duration (wks)</td>
<td>Outcome</td>
</tr>
<tr>
<td>-------------------------</td>
<td>------</td>
<td>----------------------------------</td>
<td>--------</td>
<td>------</td>
<td>------</td>
<td>--------</td>
<td>----------------------</td>
<td>------------</td>
<td>---------</td>
<td>--------------</td>
<td>---------------------</td>
<td>----------------</td>
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<tr>
<td>Vanderberghe et al.</td>
<td>1997</td>
<td>J Appl Physiol</td>
<td>10</td>
<td>9</td>
<td>0</td>
<td>Female</td>
<td>Creatine Monohydrate</td>
<td>20 g</td>
<td>19-22</td>
<td>U</td>
<td>3</td>
<td>10</td>
<td>Str, Pow</td>
</tr>
<tr>
<td>Volpe et al.</td>
<td>2001</td>
<td>J Amer College Nutrition</td>
<td>22</td>
<td>22</td>
<td>0</td>
<td>Female</td>
<td>Chromium Picolinate</td>
<td>400 µg</td>
<td>27-51</td>
<td>U</td>
<td>2</td>
<td>12</td>
<td>Strength</td>
</tr>
<tr>
<td>Yarasheski et al.</td>
<td>1992</td>
<td>Am J Physiol</td>
<td>7</td>
<td>9</td>
<td>0</td>
<td>Male</td>
<td>Growth Hormone</td>
<td>40 µg/kg</td>
<td>27</td>
<td>U</td>
<td>5</td>
<td>12</td>
<td>Strength</td>
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</tbody>
</table>

**Treatment, Placebo, and Control Groups**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Journal</th>
<th>Treat.</th>
<th>Pla.</th>
<th>Con.</th>
<th>Gender</th>
<th>Supplement</th>
<th>Dosage/day</th>
<th>Ave Age</th>
<th>Train Status</th>
<th>Training session/wk</th>
<th>Duration (wks)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bemben et al.</td>
<td>2001</td>
<td>Med Sci Sports Exerc</td>
<td>9</td>
<td>8</td>
<td>8</td>
<td>Male</td>
<td>Creatine</td>
<td>20g/d 5days, 5g/d</td>
<td>18-22</td>
<td>T</td>
<td>4</td>
<td>9</td>
<td>Strength</td>
</tr>
<tr>
<td>Clark et al.</td>
<td>2000</td>
<td>Med Sci Sports Exerc</td>
<td>21</td>
<td>22</td>
<td>43</td>
<td>Mixed</td>
<td>Carbohydrate</td>
<td>7.6 g/100 mL</td>
<td>23-37</td>
<td>T</td>
<td>3 or 4</td>
<td>1</td>
<td>Power</td>
</tr>
<tr>
<td>Kovacs et al.</td>
<td>1998</td>
<td>J Appl Physiol</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>Male</td>
<td>CHO &amp; caffeine</td>
<td>68.8g CHO</td>
<td>23.3</td>
<td>T</td>
<td>norm activity</td>
<td>5</td>
<td>Power</td>
</tr>
<tr>
<td>Willoughby &amp; Rosene et al</td>
<td>2001</td>
<td>Med Sci Sports Exerc</td>
<td>8</td>
<td>8</td>
<td>6</td>
<td>Male</td>
<td>Creatine</td>
<td>6g/d</td>
<td>20.41</td>
<td>U</td>
<td>3</td>
<td>12</td>
<td>Strength</td>
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</table>
Table 2. Mean effect size, standard deviation, and 95% confidence intervals for each coded variable.

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Mean ES</th>
<th>SD</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Post-Post</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Treatment-Placebo</td>
<td>123</td>
<td>0.0574</td>
<td>0.576</td>
<td>0.103</td>
</tr>
<tr>
<td>Treatment-Control</td>
<td>11</td>
<td>0.9763*</td>
<td>1.706</td>
<td>1.146</td>
</tr>
<tr>
<td>Placebo-Control</td>
<td>9</td>
<td>0.6721</td>
<td>0.992</td>
<td>0.763</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strength</td>
<td>193</td>
<td>0.7425*</td>
<td>1.180</td>
<td>0.168</td>
</tr>
<tr>
<td>Endurance</td>
<td>40</td>
<td>0.3169</td>
<td>0.459</td>
<td>0.147</td>
</tr>
<tr>
<td>Power</td>
<td>101</td>
<td>0.1498</td>
<td>0.550</td>
<td>0.109</td>
</tr>
<tr>
<td>Training Load</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>39</td>
<td>0.1862</td>
<td>0.200</td>
<td>0.065</td>
</tr>
<tr>
<td>Moderate</td>
<td>57</td>
<td>0.6277*</td>
<td>1.257</td>
<td>0.333</td>
</tr>
<tr>
<td>Heavy</td>
<td>238</td>
<td>0.5381</td>
<td>0.998</td>
<td>0.127</td>
</tr>
<tr>
<td>Training Frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>39</td>
<td>0.1862</td>
<td>0.200</td>
<td>0.065</td>
</tr>
<tr>
<td>1-2 hr/wk</td>
<td>24</td>
<td>0.4081</td>
<td>0.723</td>
<td>0.305</td>
</tr>
<tr>
<td>3-4 hr/wk</td>
<td>169</td>
<td>0.7115*</td>
<td>1.104</td>
<td>0.168</td>
</tr>
<tr>
<td>5-7 hr/wk</td>
<td>102</td>
<td>0.3315</td>
<td>0.987</td>
<td>0.194</td>
</tr>
<tr>
<td>Familiarization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>198</td>
<td>0.4035</td>
<td>1.001</td>
<td>0.140</td>
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<tr>
<td>Yes, not good</td>
<td>44</td>
<td>0.3093</td>
<td>0.717</td>
<td>0.218</td>
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<tr>
<td>Yes, good</td>
<td>92</td>
<td>0.8436*</td>
<td>1.033</td>
<td>0.214</td>
</tr>
<tr>
<td>Training Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Untrained</td>
<td>192</td>
<td>0.6969</td>
<td>1.046</td>
<td>0.149</td>
</tr>
<tr>
<td>Trained</td>
<td>142</td>
<td>0.2627</td>
<td>0.870</td>
<td>0.144</td>
</tr>
<tr>
<td>Double Blind</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>37</td>
<td>-0.058</td>
<td>0.707</td>
<td>0.236</td>
</tr>
<tr>
<td>Yes</td>
<td>297</td>
<td>0.5833</td>
<td>1.006</td>
<td>0.115</td>
</tr>
<tr>
<td>Study Length</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 week</td>
<td>18</td>
<td>0.1203</td>
<td>0.783</td>
<td>0.389</td>
</tr>
<tr>
<td>&gt; 1 week</td>
<td>316</td>
<td>0.5346</td>
<td>1.004</td>
<td>0.111</td>
</tr>
<tr>
<td>Randomization</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>330</td>
<td>0.5189</td>
<td>1.001</td>
<td>0.108</td>
</tr>
<tr>
<td>No</td>
<td>4</td>
<td>-0.031</td>
<td>0.060</td>
<td>0.096</td>
</tr>
<tr>
<td>Age</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>18-29</td>
<td>247</td>
<td>0.4956</td>
<td>1.067</td>
<td>0.134</td>
</tr>
<tr>
<td>30-49</td>
<td>33</td>
<td>0.3471</td>
<td>0.757</td>
<td>0.268</td>
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<tr>
<td>50+</td>
<td>54</td>
<td>0.6907</td>
<td>0.753</td>
<td>0.206</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>221</td>
<td>0.5696</td>
<td>1.078</td>
<td>0.143</td>
</tr>
<tr>
<td>Female</td>
<td>39</td>
<td>0.3236</td>
<td>0.881</td>
<td>0.286</td>
</tr>
<tr>
<td>Mixed</td>
<td>74</td>
<td>0.4406</td>
<td>0.772</td>
<td>0.179</td>
</tr>
<tr>
<td>Groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Same</td>
<td>36</td>
<td>0.3386</td>
<td>1.416</td>
<td>0.479</td>
</tr>
<tr>
<td>Different</td>
<td>298</td>
<td>0.5333</td>
<td>0.935</td>
<td>0.107</td>
</tr>
</tbody>
</table>

*The mean difference is significant at the .05 level.
Influence of Other Experimental Design Factors

Certain factors of a study have a significant impact on the mean post-pre effect size. There
was a larger effect size (decreased risk of a placebo effect) for studies that were double blind,
than for those that were not. Studies that included a well-done familiarization trial had a
significantly larger effect size than those that included a familiarization trial that was not well
done or did not include familiarization at all. There also tended to be a larger effect size for
the studies that used strength as the outcome measure, compared to endurance or power. A
moderate training program, including a moderate resistance load and 3-4 hr/wk of training,
resulted in the largest mean effect size (Table 2).

Table 3. Analysis of variance of backward elimination multiple regression

<table>
<thead>
<tr>
<th>Source</th>
<th>Type III Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>L</th>
<th>Partial Eta Sq.</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corrected Model</td>
<td>1057948.169</td>
<td>12</td>
<td>88162.347</td>
<td>113.45</td>
<td>.342</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Intercept</td>
<td>668152.402</td>
<td>1</td>
<td>668152.402</td>
<td>71.65</td>
<td>.336</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PlaceXcon</td>
<td>577298.851</td>
<td>5</td>
<td>115459.770</td>
<td>61.91</td>
<td>.235</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Groups</td>
<td>27994.781</td>
<td>1</td>
<td>27994.781</td>
<td>3.00</td>
<td>.035</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Familiar</td>
<td>50592.126</td>
<td>2</td>
<td>25296.063</td>
<td>5.43</td>
<td>.038</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Double-blind</td>
<td>119042.017</td>
<td>1</td>
<td>119042.017</td>
<td>12.77</td>
<td>.017</td>
<td>&lt;.001</td>
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<tr>
<td>Train Freq</td>
<td>106466.208</td>
<td>3</td>
<td>35488.736</td>
<td>11.42</td>
<td>.035</td>
<td>&lt;.01</td>
</tr>
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<td>Error</td>
<td>2056555.436</td>
<td>321</td>
<td>6406.715</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>12404730.000</td>
<td>334</td>
<td></td>
<td></td>
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<tr>
<td>Corrected Total</td>
<td>3114503.605</td>
<td>333</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Significant Determinants of Effect Size

The results of the elimination regression are found in Table 3. This analysis indicated which variables were significant determinants of the effect size. Significant variables included: group (control, placebo, or experimental), whether or not the study was double-blind, frequency of training, good/poor familiarization trial, and if the groups were the same or different. The following variables were not significant determinants: age, gender, study randomization, length of study, outcome measure, training load, and training status of subjects.

Control, Placebo, and Experimental Group Differences

The results of a univariate ANOVA of ranked effect sizes indicated there were no statistically significant differences between the mean overall effect sizes of the control, placebo, and experimental groups. The mean effect size was calculated for the change from pre to post-supplementation for each group. All three of the group’s effect sizes were considered between moderate and large, indicating a significant difference between pre and post measures. The mean effect size of the placebo and treatment groups tended to be larger than the control group, but the difference was not statistically significant.

Determining Non-normal Distribution

A Quantile-Quantile (Q-Q) plot was used to determine if the two data sets, expected effect size values and actual effect size values, have a common distribution. In this analysis, the actual effect size values were plotted against the expected values which have a normal distribution. Thus, if the original effect size data were normally distributed the data points
would fall generally along the 45-degree reference line. The original data do not fall along this line because they are not normally distributed (Figure 2). In addition the original effect sizes also had a skewness of $1.94 \pm 0.14$ and kurtosis of $7.20 \pm 0.27$. Thus ranked effect sizes were used in place of the original effect sizes for all additional analysis.

Figure 2. Original effect size values plotted against the expected normal values; if both data sets have similar distributions the data points should fall along the 45-degree reference line.
DISCUSSION

The major finding of the meta-analysis was that the mean effect sizes calculated for the difference between post-supplement measures of the three groups suggests a placebo effect. The effect sizes are: 0.06 for experimental-placebo, 0.98 experimental-control, and 0.67 placebo-control. Since the effect size comparing the experimental and placebo groups is positive the change in the experimental group was larger. However, this is a small effect size, implying the difference between the two groups was not meaningful. Thus, the experimental and placebo groups experienced an equivalent increase in the outcome measure.

In comparison, the effect sizes calculated for the differences between the placebo and control groups (0.67) and experimental and control groups (0.98) clearly shows a considerable difference between the groups. As could be expected if nutritional supplements were beneficial, the post-supplement measurements of the treatment group would be significantly larger than those of the control group, this is confirmed with the large effect size. The ratio of the post-supplement effect size between placebo and control groups with the effect size between the experimental and control groups suggests the placebo effect accounts for roughly 70% of the total effect. So any improvements seen with supplementation should not be solely attributed to the supplement itself.

Analysis of the post-pre supplementation data for all groups showed that certain variables may impact the effect size. One such variable was whether a familiarization trial was included in the study and if there was one, how well was it described and implemented in the study. The data show that if there was a well done familiarization trial in the study, there is a
significantly larger effect size. The study by Kilduff et al. included a detailed description of the familiarization process, which included two separate trials that were used to assign subjects to each group. The mean effect size for this study was 0.4 (25). The analysis also indicates that including a poor familiarization trial in a study is the same as not including one at all. Two studies included in this meta-analysis both had mean effect sizes of -0.05; one by Clark et al. had a poor familiarization trial, while the one by Crist et al. had none at all (12, 15). Thus, when a subject was familiar with the protocol of the study before any data was collected and knew what to expect there was a greater difference between the pre and post supplement measurements.

Another study characteristic that influenced the amount of change from pre to post is whether the study was double blind. The analysis shows that a study that is double blind has an effect size that tends to be higher than if the study was not blinded, however, the difference is not statistically significant. This makes sense in relationship to the placebo effect. A study by Clark et al. examined the effectiveness of carbohydrate supplementation and time to completion of a cycling time trial. The study was not double blind, in fact, subjects were further divided into subgroups based on what they were told they were being given; some were told they were receiving carbohydrate, some placebo, and some were not told either. The mean effect size calculated for the difference between the treatment group and placebo group in post-supplement measures in this study was -0.75 (12), indicating that the two groups were not significantly different after supplementation.
In comparison, a study on the effect of creatine supplementation and improved strength by Burke et al. resulted in a mean effect size of 0.63 for the difference between treatment and placebo groups on post-supplement strength increase (10). This study was completely double-blind, all supplements were prepared and coded by someone outside of the study and which group the subjects were in was not exposed until the end of the study. Thus, when the study was double blind and the subjects were unaware if they were receiving the supplement there was a larger difference in the groups; the treatment group improved more compared to the placebo group. However, when the study was not double blind the treatment and placebo groups were not different from each other and a negative effect size indicates the placebo group was actually greater than the treatment group, both indicating a probable placebo effect. It is important to note that only 5 of the studies included in the meta-analysis were not double blind. Thus, even though the majority of nutritional supplement studies are double blinded, those that are not may have a greater chance of displaying a placebo effect.

The type of outcome measure used to establish the effectiveness of the nutritional supplement may also be important in determining the effect size and the presence of a placebo effect. Analysis showed that when the measured outcome was improvement in strength the mean effect size was 0.74, for endurance it was 0.32, and for power it was 0.15. This indicates that the chances of a study having a placebo effect tend to be greatest when muscle power is the outcome measurement. However, the limited number of studies included in the meta-analysis that measured muscle power (n=11) and endurance (n=10) compared to muscle strength (n=25) must be considered when evaluating the results. Thus, since the effect sizes for power and endurance were considered small and the elimination
regression showed that outcome measure was not a significant variable in determining effect size, it can be implied that the specific outcome measure does not significantly contribute to a possible placebo effect.

Most of the studies included involved some type of training regimen that varied in resistance load and frequency of training. Analysis of the mean effect sizes for the different levels of these two variables showed that the studies which included a moderate resistance load and trained 3-4 hours per week had the greater effect sizes, 0.63 and 0.71 respectively. Therefore, using a moderate training protocol in respect to load and frequency is shown to be the most successful in displaying the effectiveness of the nutritional supplement. Only two of the eight studies that examined the acute effect of nutritional supplementation showed a positive result from the supplement (28, 29).

Other variables that were thought to possibly contribute to the magnitude of the effect size but were found to not have a significant influence included subject age, gender, and different groups/cross-over study. Each of the different subgroups of these 3 variables had similar effect sizes so it can be inferred that they have no influence on effect size. There are two variables that did not show a significant influence on the effect size, study length and subject training status. Analysis indicated that a study lasting longer than 1 week had a larger effect size, 0.53 compared to 0.12, so there was a greater difference between groups and more of a chance to observe possible improvements due to the supplement. Results also revealed that untrained subjects tended to have a larger effect size and thus show a superior enhancement with supplementation, 0.70 versus 0.26 for trained. This supports the hypothesis that trained
individuals may demonstrate an increased chance of a placebo effect, possibly due to their increased exposure and background knowledge of nutritional supplements and what benefits they are purported to offer.

Effect sizes calculated for the pre- to post- difference between experimental, placebo, and control indicated there was not a significant difference between any of the three groups. The effect sizes calculated for each of these groups fell between moderate and large, 0.73, 0.73, and 0.67. This finding suggests there was a large difference between pre and post measurements in each group. The experimental and placebo effect sizes tend to be slightly larger than the control group, but similar to each other. It could be speculated that even though some improvement results from using a nutritional supplement, the benefit is similar to that of a placebo treatment. Thus, when the effect sizes of all the studies included in this meta-analysis were analyzed together the results showed there is a considerable placebo effect when examining nutritional supplements and their effect on muscle strength, power, and endurance.

The intent of this meta-analysis, however, is not to contradict the effectiveness of some nutritional supplements. As the research indicates, some supplements have been shown to be beneficial. The results of a study by Bemben et al. indicated that muscle strength increased by as much as 8.7% with creatine supplementation, while the placebo group increased by 5.1% and the control group had no change (4). Creatine supplementation also increased anaerobic power by 19.6%, but there was no improvement seen in either placebo or control groups (4). HMB has also been shown to improve muscle strength as measured by change in
bench press. The placebo group increased by 5.2, while the group supplemented with HMB improved 7.5, which was significantly different from the placebo group (39).

Even though many of the studies included in this meta-analysis found improvements with supplementation, there were enough that did not, such as one study that examined the effect of adding HMB to a resistance training program. This study by Gallagher et al. resulted in a similar increase in strength (1-RM for 10 lifts) for the control group and groups with two different levels of HMB supplementation (19). Thus, even though some of the studies individually illustrated the benefits of some nutritional supplements, when all of the studies were analyzed together the studies that may have shown no improvement or an increase in the placebo group obscured any increases that may have otherwise been observed.

A possible limitation of the study is the number of studies that contained a control group. Very few of the studies that met the inclusion criteria contained an experimental, placebo, and control group. Most of the studies included either a placebo group or a control group. There were only 5 studies that included all three groups and only 11 effect sizes comparing treatment-control and 9 effect sizes comparing placebo-control. This is compared to the 123 effect sizes calculated for treatment-placebo differences. Thus, when analyzing the data with such a small number it is possible for one outlier to have a large effect on the results. Additional research on the presence of a placebo effect is also needed in respect to other outcome measures, more specific training regimens, and possibly with more recent nutritional supplements.
CONCLUSION

In conclusion, the results of the meta-analysis indicate the presence of a placebo effect in studies on nutritional supplementation and improvements in muscle strength, endurance, and power. This is obvious when examining the mean effect size between treatment, placebo, and control groups for post-supplementation measures. If a significant placebo effect does exist, we hypothesized there would be very little difference between the treatment and placebo group, while both group outcomes would exceed those in a control group. The observed effect sizes for the treatment-placebo (ES = 0.06), placebo-control (ES = 0.67), and treatment-control (ES = 0.98) support this hypothesis and indicates the placebo effect accounts for roughly 70% of the total effect of supplementation.

Thus, it is indicated that when setting up a research study on the effect nutritional supplementation has on improvements in strength, power, and endurance certain criteria must be met. These include using both a control and placebo group, a good familiarization trial, making sure the study is double blind, using a moderate training load and frequency. In respect to nutritional supplements it seems that using untrained individuals and measuring improvement in strength performance are also more effective.
REFERENCES


APPENDIX: ADDITIONAL LITERATURE REVIEW

Placebo Effect

However, there are also negatives to using a placebo group. Some studies inform their subjects that they may be receiving a placebo, while others do not. In either case, subjects may report or show improvements in strength or other measures because neither the subjects nor the experimenters know who is in which group. Since there is the possibility that they are receiving an advantageous supplement they think they should be improving and it is often this belief in the benefits of the treatment alone that causes the desired physical improvements. This is known as the placebo effect, which is an improvement or increase in a measurable outcome attributed to an ineffective treatment. The recipient of the treatment is unaware that they are receiving a “fake” supplement and because they expect to experience improvements or changes they often do.

Placebo & Experimental Groups with Specified Training

Many studies show the benefits of adding a supplement to a resistance training program. One such study showed the effect creatine had when combined with another supplement and resistance training. Twenty-five division I football players received 15.75 g/d of HPCE pure creatine added to Phosphagen HP for 28 days and participated in 5 hours/wk of resistance training and 3 hours/wk of agility/speed training. This resulted in a significant increase in total body weight in the creatine (Cr) group (2.42 +/- 1.4 kg) compared to the placebo (P) group (0.85 +/- 2.2 kg) (30). The creatine group also showed an increase in the volume of weight lifted during the bench press that was significantly higher than the placebo group (Cr: 225 +/- 246 and P: -5 +/- 134) as well as a larger change in the total volume lifted with all
three lifts combined (P: 1,105 +/- 429 and Cr: 1,558 +/- 645). Cycle ergometer sprint performance was also affected, the creatine supplemented group showed a significantly higher amount of work done in the first 5 sprints compared to the placebo group. These results support the thought that strength and power activities are improved with the supplementation of creatine for 9-56 days (30).

Other creatine studies have found similar improvements in maximum strength, muscle fiber area, maximum arm flexion torque, and functional task performance with considerably smaller doses (5g), less intense training, and in women and older individuals (7, 47). A study by Ayoama et al. examined the effects of creatine supplementation in women (collegiate softball players) and if previous anaerobic exercise would increase the effect (3). The results indicated that in trained women, the supplementation of creatine along with previous performance of anaerobic activity leads to an increase in mean strength and muscular endurance with repeated contractions. This was shown by the increase in mean torque for the final 20 contractions in the last three measurement groups compared with the initial measurement for the #2 creatine group which participated in anaerobic exercise and received both an initial dose of 20 g/d Cr and 3g/d Cr for the last 2 weeks (3).

The effects of other supplements such as β-hydroxy-β-methylbutyrate (HMB) have also been shown to improve strength, fat-free mass, and decrease muscle proteolysis. A study by Nissen et al. consisted of two experiments; one used a placebo (P) and two different levels of HMB and also examined the influence of normal protein intake and higher protein supplementation. The other used a placebo and only one HMB group and used a more
intense resistance training program. The first study showed that total strength increased over 3 weeks in all three groups, but was significantly higher in the two HMB groups (P: 8% increase, 1.5 HMB: 13%, and 3.0 HMB: 18.4%, P<0.02) (36). Also, the amount of essential amino acids in the plasma is an indicator of the amount of muscle break-down, and was 32% higher in the placebo group, 9% lower in the 1.5g, and 18% lower in the 3.0g (36).

The second study showed that fat-free mass was initially significantly impacted by HMB supplementation, as was strength, shown by the significantly higher change in bench press in the HMB group (15.0) compared to the placebo group (5.4) (36). Similar results for increases in upper body strength (P 5.2 +/- 0.6 kg HMB 7.5 +/- 0.6 kg P=0.008) and decreases in muscle break-down have been displayed in women and in both trained and untrained participants (39).

Since many supplements have been shown to help improve strength and performance it is thought that taking more than one supplement may be even more beneficial. This may be the case with creatine and HMB. The study by Jowko illustrated that lean body mass and strength did increase when subjects were given each supplement individually, but the increase is significantly higher when subjects receive both creatine and HMB. Lean body mass improved 0.92 kg with creatine, 0.39 kg with HMB, and 1.54 kg with Cr/HMB over the placebo, which was statistically significant (p=0.05). Strength also increased at a similar rate compared to the placebo, 39.1 kg with creatine, 37.5 kg with HMB, and 51.9 kg with Cr/HMB (p=0.001). This supports the notion that Cr and HMB are additive in their physiological effects and thus result in greater improvements (22).
Even when supplementation does not result in strength increases, it may improve other power outcomes. Supplementation of ~3.0 g/day of HMB was found to cause a significant improvement in peak isometric torque (p<0.05) and ~6 g/day of HMB increased peak isokinetic torque when combined with 3 days/wk for 8 weeks of resistance training on 10 exercises at 80% 1RM (p<0.05). However, no statistically significant difference in strength improvement was found between the placebo and the two levels of HMB (19).

Supplementation of essential amino acids has also been found to improve aerobic endurance without changes in strength. By using treadmill time to exhaustion the EAA supplemented group went from 13.15 +/- 3.67 min pre-treatment to 14.73 +/- 4.26 min post-treatment (p<0.05), while the placebo group did not improve significantly (1).

In contrast, other studies show no improvement in strength, body composition, or other measured outcomes with the addition of a supplement. Even though many studies show statistically significant changes associated with creatine supplementation, this is not always the case. In two studies using 5 g of creatine supplementation in older and college-aged men using moderate resistance training and interval sprint training neither body composition measurements nor power output measurements were significantly changed (p>0.05) (14, 17).

Yarasheski et al. showed that supplementation of growth hormone had no added benefit for younger or older men. After 12 weeks of resistance training and supplementation in young men a similar strength increase was seen in both the 40 µg GH supplemented group (54 +/- 5%) and the placebo group (50 +/- 5%); both were significantly (p<0.01) different from pre-training (51). Data collected on strength increases with GH supplementation in older men
supported the previous data, the supplemented group increased 57 +/- 7% and the placebo group increased 60 +/- 8% (51). Thus, even though strength gains were made with GH supplementation, they were not significantly higher than the placebo group. This indicated the GH supplementation is of no added benefit for increasing strength.

According to a study by Slater et al. HMB supplementation in well-trained athletes did not result in significant strength gains. The supplementation group did show improved strength, however, it was not significantly different from the placebo group. Thus the strength gains were due to the training and not the supplement (43).

A study on the effects of supplementation with chromium picolinate (CP) on body composition found that the CP supplemented group had a larger decrease in body fat compared to the placebo group; however the difference was not statistically significant. When the two groups were combined together the difference between pre and post-treatment body fat was significant at p<0.05, however, the authors attributed this to the resistance training like in the previous study by Slater et al. (49).

Supplementation of testosterone precursors has also proved fruitless. Even though taking DHEA, androstenediol, or androstenedione increases serum androstenedione levels, they do not affect the serum testosterone levels and so do not lead to strength increases (6, 8). The study by Brown et al. examined both the short and long-term effects of DHEA, but found that with both, serum androstenedione levels increase (by as much as 150% in 60 minutes) but serum testosterone was unchanged. Changes in strength for both groups resulted in
significant increases from pre-training levels; but the DHEA group was not significantly
different from the placebo group (8).

Hellsten et al. performed a study on the effects of ribose on resynthesis of adenine
nucleotides after intermittent exercise and if the exercise performance was affected by the
decrease in muscle ATP levels. The results indicated that supplementation of ribose did
increase the rate of recovery of pre-exercise levels of ATP compared to the placebo group
(p<0.05). However, even with the faster recovery of ATP with ribose supplementation there
was not a significant improvement in performance. Both mean and peak power output were
statistically similar for the two groups (p>0.05) and the total work performed both between
groups and between time was not different (21). Thus even though ATP recovery was
increased, there was no added benefit of ribose supplementation to any measurable
performance outcome.

*Placebo & Experimental Groups with Unsupervised Training*

Not all nutritional supplement studies use a specific training regimen. Some studies allow
the subjects to continue their normal training program or just require them to keep an
exercise log. Many of these studies have individuals that are all trained in the same thing so
that even though they are not all following the same protocol, the type and amount of training
is similar. The use of unsupervised training in supplementation studies has resulted in both
supporting and refuting the benefits of supplements.
One such study examined the effects of androgenic-anabolic steroids also shows the power of a placebo effect. Nine adults were each supplemented with a placebo, 100 mg of testosterone cypionate, and 100 mg of nandrolone decanoate for 3 weeks each and participated in resistance training (15). They were objectively tested after each of the 3 treatments and were then asked to subjectively rate, 1 to 10, each of the treatments as far as how much total strength they thought they gained. The results indicated that there were no significant differences in strength or power between the 3 treatments, but the subjective ratings show that the subjects felt they had more strength gains with testosterone (7.8 +/- 0.7), than nandrolone (6.0 +/- 0.8), and finally placebo (4.3 +/- 0.66). Even though the objective measurements did not show any increases in strength or power, the participants thought they felt stronger after taking all 3 treatments, especially testosterone (15). This increased feeling of strength could be partly responsible for why steroids have been so widely used and thought to improve strength.

Another study that used national wrestlers in their off-season as the subjects and creatine supplementation resulted in similar findings of a significant improvement in anaerobic activity. A statistically significant difference between average power, peak power, and body weight (p<0.01) was found between the creatine and placebo groups (28).

Two studies looking at the effects of caffeine and glucose plus branched-chain amino acids on cycling performance (muscle power) used trained cyclists as subjects and allowed them to continue their normal training protocol. The study by Kovacs et al. showed that cycling time trial performance improved with the addition of caffeine to a carbohydrate-electrolyte drink.
As the amount of caffeine increased, the amount of time to finish the set workload decreased; 62.5 ± 1.3, 61.5 ± 1.1, 60.4 ± 1.0, 58.9 ± 1.0, and 58.9 ± 1.2 minutes (29). In contrast, the study by Madsen et al. on the effect of glucose and glucose plus branched-chain amino acids on 100 km cycle performance showed that neither supplement had any effect on the performance outcome. Time to complete 100 km was 160.1 ± 4.1 min for the glucose supplement, 157.2 ± 4.5 min for the glucose plus branched-chain amino acids, and 159.8 ± 3.7 min for the placebo group (32).

Three studies on the effects of supplementation on endurance performance without a standard training program all showed no improvement in the experimental group over the placebo. One study examined the effect of pyruvate supplementation for 1 week in trained cyclists. The data indicated that the time until exhaustion did not significantly improve in the pyruvate group (88 ± 8 min) compared to the placebo (91 ± 9 min) (34).

The second study evaluated the effects of fish oil and vitamin E supplementation on cycling endurance. Unlike previous studies, this study did not result in any improvement with the supplementation. Endurance test times changed from the baseline measure by 0.11 ± 0.49 min with placebo, -0.23 ± 1.35 min with fish oil, and -0.07 ± 1.16 min with fish oil and vitamin E (38).

The use of herbal supplements is often thought to be beneficial. However, a study on the effects of Cordyceps Sinensis (CordyMax Cs-4) supplementation on aerobic capacity and endurance performance did not support this hypothesis. The 22 male trained cyclists...
completed a pre-time trial and VO₂ peak test, had 5 weeks of either CordyMax Cs-4 or placebo supplementation, then performed a post-VO₂ peak and post-time trial. The results indicated there was not a significant improvement seen in either the VO₂ peak or time trial performance with supplementation (40).

**Placebo & Experimental Groups with no Training**

Some nutritional supplements claim to be effective in improving outcome measures even without training of any kind. These supplements are supposed to have an acute physiological effect which leads to physical improvements in strength, power, endurance, or other measures of performance.

In a study by McKenna et al. on the effects of creatine a placebo effect was displayed. The subjects were informed that they would be in either the creatine supplemented or placebo group, that creatine has been shown to improve performance, and that how long those improvements last is unknown. The results showed similar statistically significant increases in maximal intermittent cycling, peak power, and work output for both creatine and placebo groups. The experimenters concluded that a placebo effect had taken place due to the information the subjects were given before the study, causing them to believe that their performance would increase with supplementation (33).

Similar results were found with a study on the effects of Vitamin D supplementation and physical performance in the older population. Even though there was a significant increase in 25-hydroxyvitamin D (25OHD) in the cholecalciferol supplemented group compared to
the placebo group (p<0.001), there was not a significant improvement in strength, performance, or perception of health in the participants (24). Hence, even though supplementation of some products may cause physiological or physiological changes, measurable outcomes are not always significantly improved.

When the results for the experimental and placebo groups show there is not a significant difference in the measured outcome it can easily be assumed that the supplement is of no additional benefit. However, when the placebo group shows significantly greater increases than the supplemented group, explanations are rather limited. One such explanation could be that the groups were not chosen at random and would not have similar results. Another more likely reason is the placebo effect. Since the subjects did not know which group they were in, but knew they could be receiving a supplement that had the potential to increase whatever outcomes were being measured, they may have been displaying improvements only because they thought that they should.

Campbell et al. studied supplementation of 17.8 μmol of chromium picolinate and resistance training for 12 weeks. The results indicated that there were no changes in body composition or muscle fiber area in the supplemented or placebo group and that muscle strength at 20, 40, 60, & 80% of 1RM improved in a similar fashion for both groups (p<0.0001). Except for knee extensions, where the placebo group increased strength significantly more than the supplemented group at 20% (p=0.005), 40% (p=0.024), & 60% (p=0.069) (11). Physiologically there is no explanation for why the placebo group would improve that much compared to the experimental group, thus their belief that they should be getting stronger
may have influenced how they felt and how much they lifted. Thus, many studies that include a placebo group often display at least a slight placebo effect; however, it is not known whether this effect is meaningful.