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Can some blueberries each day keep the doctor away?

Blueberries improve biomarkers of cardiometabolic function in participants with metabolic syndrome—results from a 6-month, double-blind, randomized controlled trial.



Introduction

Metabolic syndrome refers to a cluster of issues that arise from a disordered metabolism, including impaired glucose tolerance, elevated triglycerides and LDL-cholesterol. Metabolic syndrome increases the risk of several chronic diseases, specifically type 2 diabetes (T2DM) and cardiovascular disease (CVD). As of 2012, the prevalence of metabolic syndrome in the U.S. was about 35% in adults and about 5-7% in young adults. Accordingly, interventions that can address metabolic syndrome are warranted.

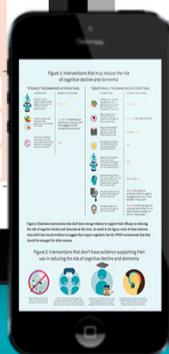
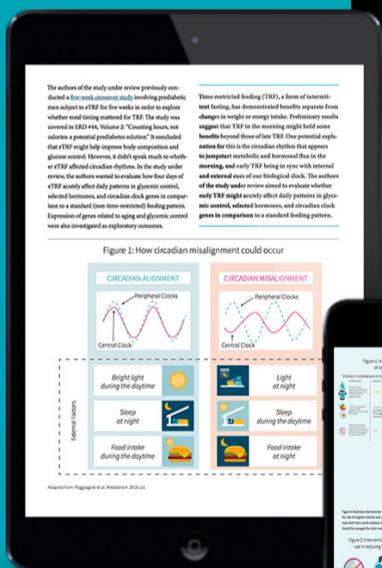
Metabolic syndrome can be addressed through pharmacological interventions and/or lifestyle modification. Pharmacological options often utilize glucose-lowering agents such as metformin or GLP-1 receptor agonists, and/or lipid lowering agents such as statins, fenofibrates, or thiazolidinediones. Lifestyle interventions, on the other hand, rely heavily on exercise and caloric restriction. They have been shown, time and again, to provide therapeutic benefits and improve many of the aspects of metabolic disease synergistically. In addition to pharmacological interventions and lifestyle modifications, specific nutritional interventions, such as nutraceuticals, may also be a useful tool in the management of metabolic syndrome. Blueberries are one such intervention that shows promise.

Blueberries contain many bioactive compounds. Specifically, they contain a group of compounds called flavonoids. Anthocyanins are a group of flavonoids that are found in high concentration in blueberries. In observational studies, higher intakes of anthocyanins are associated with a lower risk of diabetes and a previous randomized controlled trial found that 50 grams of blueberries per day reduced blood pressure and provided antioxidant benefits to people with metabolic syndrome. The present study is a randomized controlled trial examining the effect of six months of dietarily achievable blueberry intake on insulin resistance and cardiometabolic function in people with metabolic syndrome.

Metabolic syndrome occurs in roughly one-third of all adults in the U.S. Blueberries contain bioactive compounds, specifically a family of compounds called anthocyanins that may provide benefits for people with metabolic syndrome. The present study is a randomized controlled trial examining the effect of six months of dietary blueberry intake on insulin resistance and cardiometabolic function in metabolic syndrome.

Who and what was studied? The study under review was a pre-registered randomized, double-blind, placebo-controlled trial studying

“[...] specific nutritional interventions, such as nutraceuticals, may also be a useful tool in the management of metabolic syndrome. Blueberries are one such intervention that shows promise.”



YES! SIGN ME UP

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From the Editor

The ERD has just turned five! And while most five-year-olds are learning addition and subtraction, the ERD is distilling and critiquing clinical trials and meta-analyses. I don't wanna brag, but that's pretty precocious!

The ERD covers the more rigorous types of studies on a wide range of topics. To celebrate its fifth anniversary, I selected from past issues six articles covering two randomized trials, three meta-analyses of randomized trials, and one umbrella review, on topics ranging from muscle gains to creativity. Each article exemplifies the nutrition-nerdy, deep-dive analyses you've come to expect from the ERD.

The ERD is a critical, no-nonsense take on recent research. But while its nature hasn't changed over the past five years, its form has evolved. For instance, you'll notice a "Nitty-gritty" section in the article selected from our very first issue ("The best diet is the one you can stick to"). This section type doesn't exist anymore.

Not all changes are betrayed by the five articles gathered here, of course. Notably, while I was involved with the ERD from the start, I didn't become its editor in chief until 2017, when I succeeded Kamal.

We've also rotated through different formats. In the early days, we had op-eds and "ask the researcher" segments. Last year, we've introduced an "ERD Mini"

segment to give you quick takes on interesting research not quite appropriate for a deep dive. And, speaking of quick takes, we've recently added a "Quick Takes" section to our deep-dive articles, so you'll get some key takeaways right up front.

The next few months will bring several more changes, each thought-out to make our articles even more relevant, readable, and digestible (pun intended). Also, ERD will undergo a slight rebranding; its new name will be the *Nutritional Examine.com Research Digest*, or NERD, to better reflect what we're all about: getting nerdy about nutrition research!

While the ERD has evolved over the past five years, and will continue to change in the future, we've always kept our two commitments: to independent, unbiased, and thoughtful takes on recent nutritional research; and to you, our reader. **Our aim is to make nutritional research clear and useful to you.** If we miss the mark, please let us know; [the door's always open!](#)

Aside from our two commitments, the other constant is a sentiment expressed by Kamal in his introduction to the very first ERD: our gratitude for your support, your thoughtfulness, and your intellectual curiosity about nutritional science.

Thank you.



Gregory Lopez, *Editor-in-Chief*

The best diet is the one
you can stick to

[Comparison of Weight Loss Among Named
Diet Programs in Overweight and Obese
Adults: A meta-analysis](#) 



Introduction

People have been trying to figure out the most effective weight loss diet for as long as diets have existed. When researched in clinical trials, diet questions are often addressed through head-to-head comparisons, like an endless nutritional tournament dedicated to finding the ultimate diet. Unfortunately, it's only feasible to compare two or three diets at a time. Since new diets appear often, it's often hard to draw conclusions about a single diet in comparison to the entire landscape of options.

To address this problem, the authors collected the results of many studies and analyzed them together, in order to simultaneously compare the effectiveness of many diet styles.

The nitty-gritty

This study was a meta-analysis of name-brand diet interventions on weight loss.

Initially, the researchers cast a broad net to identify potential studies to include in the analysis. They tried to identify any study of overweight or obese adults who were treated with a specifically named diet or a diet that was equivalent to a named diet, even if that name was not explicitly mentioned. For example, a study diet could be not explicitly called "Atkins," but would be grouped under "Atkins-like diets" if they were funded by Atkins or fit the general guidelines of the Atkins diet.

These criteria were used to search the largest databases of published research, like PubMed. The authors confirmed assigned each study as either being at low or high risk of bias using the Cochrane risk of bias tool. This tool evaluates the quality of a study's methodology and reporting, such as sufficient reporting of all main outcomes and adequate description of blinding procedure.

Studies that included exercise or behavioral interventions were included, and those factors were later

assessed to determine if they contributed to overall weight lost. Similarly, the researchers allowed studies that included some meal replacements, but the intervention could not involve any drugs or drug-like supplements, like ephedra or similar "fat burners." The studies also had to have lasted at least six months. Many of the studies lasted longer than that. The longest study the researchers analyzed lasted 12 months.

There were 59 articles identified in total, which were based on 48 randomized controlled trials enrolling a total of 7286 individuals. These reports included 11 diets, which were roughly categorized as moderate macronutrient, low-carb, or low-fat. Control groups included participants who followed no diet and who received "usual care," which included adaptive or variable weight management strategies, such as LEARN (Lifestyle, Exercise, Attitudes, Relationships, Nutrition: a behavior-based approach to weight loss), which can be modified based on an individual's needs.

This study compared various diets intended for weight loss in an attempt to find the most effective one.

Named diets evaluated

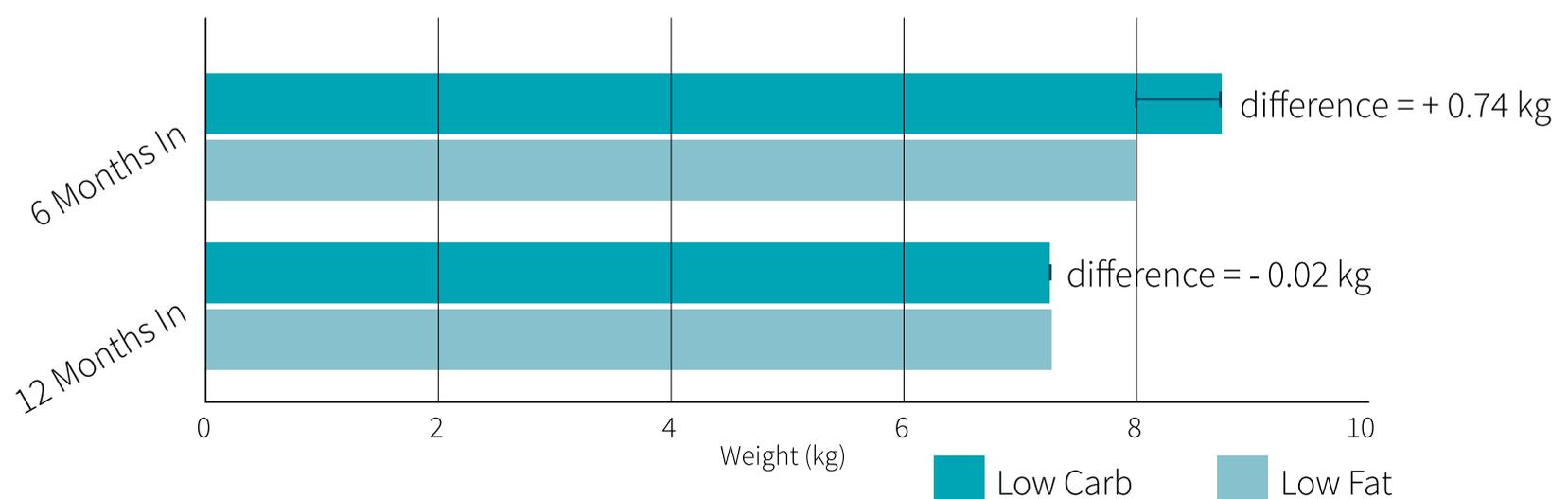
To analyze the effects of each diet, the authors used a Bayesian network approach. This is a statistical method that assesses the likelihood of various outcomes based on multiple associated factors, including variables like which diet was used, whether exercise was done, and whether any behavioral modification was used. For instance, a Bayesian network can be used to answer questions like, "How much weight is a person likely to lose on the Atkins diet, and how is that potential weight loss affected by exercise?"

When the researchers performed these analyses on all the relevant studies for both six and 12 month intervals, the authors found several interesting results:

Diet	Characteristics	Classification
Atkins	Induction phase with 4-5% kcal from carbs	Low carb
Biggest Loser	Individualized calories; <30% kcal from fat	Moderate
Jenny Craig	Personalized meals	Moderate
LEARN	Variable	Low fat or moderate
Nutrisystem	Nutrisystem foods	Moderate
Ornish	<10% kcal from fat	Low fat
Rosemary Conley	Selection of foods with <4% kcal from fat	Low fat
South Beach	Induction phase with low carbs, high protein	Low carb
Volumetrics	Consumption of foods with low energy density	Moderate
Weight Watchers	Points-based system	Moderate
Zone	Weight loss phase followed by weight maintenance; 40% kcal from carbs, 30% from fats	Low carb

- Any diet was superior to no diet at all.
- Six months in, low-carb diets (with 8.73 kg lost on average) led to the most weight loss on average, but weight loss was not significantly greater than low-fat diets (with 7.99 kg lost).
- After 12 months, low-carb (7.27 kg lost) and low-fat (7.25 kg lost) diets were superior to all other diets, and both had nearly equal effects on weight loss (see Graph 1).
- When comparing individual diets, the Atkins (10.14 kg lost) and Ornish (9.03 kg lost) diets were some of the most effective, both six and 12 months in.
- In the short term, behavioral support resulted in

Graph 1: Average Weight Loss of Low-Carb and Low-Fat Diets



greater additional weight loss (3.23 kg lost), and in the long term, the effect of behavioral support waned and the effect of exercise (with 2.13 kg lost) increased. This effect occurred regardless of what diet the participant used.

It is important to note that in a study like this, “superior” is a relative term. Because there are so many factors involved, and the difference in weight lost was generally small (one to two kg) when comparing most individual diets against one another, it is hard to make conclusive statements. The authors recognize this in the discussion of the results, and they are careful to emphasize that despite statistical significance, most of the nuanced differences they noticed are likely irrelevant when applied to a single individual.

The researchers emphasize that their analyses are based on the intended treatment of the selected studies, rather than actual adherence to a given diet. This applies when interpreting any dietary trial — the results do not exactly reflect the diet as designed, rather they reflect the diets as followed by trial participants.

The researchers also performed a sensitivity analysis on the data. Sensitivity analysis is a way of evaluating the strength of the conclusions of a meta-analysis by considering the quality of the studies it’s based on. They performed the sensitivity analysis as follows.

First, the authors determined that 60% of the studies they analyzed were high quality with a low risk of bias. To make sure that their findings still held true even when only the highest quality studies were included, this group of studies was tested separately. The results were similar to the results generated during the entire meta-analysis. They also tested for studies based on their loss to follow-up, percentage of female participants, and baseline participant bodyweight. None of these factors substantially affected results.

In short, this was a very rigorous analysis with some interesting findings that confirm much of the anecdotal evidence in the nutrition and dietetics community. The small effect sizes imply that the existence of a “universally optimal” diet is unlikely. The authors said it best in their discussion when they stated, “because different diets are variably tolerated by individuals, the ideal diet is one that is best adhered to by individuals so they can stay on the diet as long as possible.” In other words, sustainable eating habits are more successful than a typical “diet.”

What does this study tell us?

For overweight and obese adults, any diet is better than no diet at all. Low-carb and low-fat diets are likely most effective for long term weight loss in this population, when looking at named diets. There are two major caveats though. One is that the diets within each group often varied quite a bit. For example, the Ornish diet is not just a macronutrient-guideline diet, but a variety of different approaches to health such as emphasizing plant foods and reducing stress.

A second point is very important to interpreting this study. This meta-analysis didn’t include all diets, it only included named diets or studies that approximated named diets. So if a previous study had tested a low-carb diet against a Mediterranean diet and a low-fat diet without a brand name, only the low-carb arm would be included in this meta-analysis.

Thus, this meta-analysis should not be used to bolster arguments for the superiority of low-carb and low-fat diets. Rather, it is specifically aimed at named diets, or diets that the authors deem to be similar enough to named diets.

The authors also found that exercise and behavioral modification were important aspects of weight loss. Behavioral modification and counseling was associat-

Efficacy versus effectiveness

Sometimes results are reported according to what treatment was initially assigned, which is called “intention-to-treat analysis.” Sometimes results are reported according to the treatment that was actually used at the final measurement (per-protocol analysis). Ideally, both results are provided, so that the reader can compare results using those who followed through with treatment to those that didn’t for whatever reason.

This issue equates to efficacy versus effectiveness, which is a [major research issue](#). Efficacy refers to how the effect of the treatment under ideal conditions, such as with 100% adherence. Effectiveness is the real-world effect, which incorporates factors like how difficult the treatment is to follow. How results are reported can substantially change how the study is interpreted. If a trial tests a diet entirely devoid of sweets on those with massive sweet teeth, compared to a moderate-sweet diet, then what results would you expect? Let’s say half the “no-sweets” participants drop out because the intervention is just too difficult, and some switch to a moderate-sweet diet. If the results are reported only per-protocol, according to the treatment assigned, the no-sweets diet may be deemed successful. But intention-to-treat analysis would likely show a much smaller effect.

ed with more weight lost six months in, while exercise showed a much stronger effect 12 months into the study. The authors caution that those findings may be influenced by their definition of “behavioral modification,” which is usually some sort of counseling at the outset of a study, and hence a greater effect at 6 months than at 12 months. But the finding is still in line with the general wisdom that the effects of most types of counseling or education wane over time.

It should also be noted that most large-scale network analyses like this have relatively large “credible intervals” (a Bayesian term that indicates a high degree of uncertainty). This study is no different. Although many of the findings were statistically significant, most of the 95% credible intervals were relatively large. This makes it difficult to say how important the small differences (two to three kg) are between the various diets.

The meta-analysis suggests low-carb and low-fat diets are the most effective diets for overweight and obese adults. Ultimately, however, the most effective diet is the one that you stick to the longest.

The big picture

This study provides very strong confirmation of what is anecdotally known among most professionals in the field: whatever diet a person can stick with is the best diet for them, if their goal is weight loss. The difference is that this study was a rigorously conducted analysis of clinical trials. It provides scientific evidence instead of anecdotes.

Although these findings seem to oppose the recent media buzz surrounding a long term low-carb trial, the

actual results of this analysis and that trial [are in relative agreement](#): weight loss is similar between groups, behavioral interventions (counseling) may help, and compliance is relatively poor for dietary interventions.

At its core, this research exemplifies the difference between “exciting” and “excellent” science. The authors of this study were careful to use rigorous statistical methods in an effort to answer an age-old question. Their findings didn’t smash any myths and likely won’t change many practices, but it’s still important to have objective data to support commonly held beliefs, and this study provides those data.

There are many effective diets. Sustainability is more important than macro preference.

Frequently asked questions

What is the best diet?

The best diet is the one that is supported by scientific evidence, healthy, and sustainable for a given individual. This study provides some evidence that low-carb and low-fat diets may be most effective in the long term, but not by much, and it only included named or branded diets.

Diets that focus on macronutrients have different pros and cons than those involving more factors. Low-carb and low-fat diets may act as only a temporary solution for some, unless additional emphasis is placed on food quality. Many different aspects of diet, lifestyle, and the food environment have been shown to impact energy intake and fat mass. That may have impacted this study, since the low-carb diets were mostly single-factor interventions yet they were compared with multi-factor low-fat diets like the Ornish diet.

In terms of specific diets, this study suggests that a wide variety of diets lead to weight loss. It’s important to

keep in mind that many diets have overlapping features, and it is difficult to know which of those features are most important for a given person. Two diets can have the exact same effects in one person and radically different effects in another.

If every diet works, why diet at all? Why not just eat healthy foods?

This is a valid question without an easy answer. Diets provide a framework in which to think about the foods one eats. Many people grow up with complex relationships to food, such as eating certain foods for comfort or avoiding certain foods for religious reasons.

Many authors and diet creators claim to have a diet guideline that can help everyone. While that may be true to an extent, refer to the above section on efficacy versus effectiveness -- the best diet is the one that can be sustained long enough to provide health benefits. For some people, avoiding diets altogether and choosing foods one-by-one based on the preponderance of research is simply not a realistic strategy.

What should I know?

There are a lot of diets available to help overweight and obese individuals lose weight. The best diet for weight loss is the one a person can stick to the longest. After a year of dieting, low-carb or low-fat diets appeared superior to other types, but that only applies to diets that are named or branded.

This meta-analysis is also a perfect example of why headlines can be so misleading when covering diet studies. Trials comparing specific named diets against control diets may appear to show substantial benefit, but effects are quite similar when named diets are compared against each other in a statistically rigorous and systematic manner. ◆

Does marijuana actually boost creativity?

Cannabis and creativity: highly potent cannabis impairs divergent thinking in regular cannabis users. 📌



Introduction

Steve Jobs once said that “marijuana and hashish ... make me relaxed and creative.” And many people agree with his assessment. [One study](#) found that over 50% of users report enhanced creativity when using marijuana. But, Steve Jobs was wrong about things before (the [Apple Lisa](#), anybody?). Could he have been wrong about marijuana enhancing creativity as well?

Researchers know enough about the brain to take a decent stab at predicting how marijuana may affect creativity. The story starts with the neurotransmitter dopamine and its influence on two cognitive processes first fleshed out in the 1960s, a decade of great creativity!

While creativity is a hard thing to measure objectively, some components of it are being teased out. Specifically, two cognitive processes are thought to play a strong role in creativity. They are called convergent and divergent thinking. Divergent thinking is best described as the skill behind brainstorming. It's being able to explore options through loose associations to generate novel ideas. Convergent thinking works in the opposite direction: it takes a bunch of loosely-organized ideas and finds a common thread between them.

There is a common thread winding its way through these thought processes and dopamine. Dopamine is often thought of as the “reward neurotransmitter” (although this is a major overgeneralization because dopamine has [multiple functions](#)). However, it also seems to have a role in the neuroscience of creativity. Specifically, [one study](#) found that dopamine has a negative linear correlation with convergent thinking, whereas it shows an “inverted U” shape correlation with at least one aspect of divergent thinking, where too much or too little harms it, but a middle amount is just right.

The main psychoactive ingredient of marijuana, delta-9-tetrahydrocannabinol (THC), is known to stimulate release of the neurotransmitter dopamine in a part of the brain called the [striatum](#), a part of the brain that has been seen to be involved in creative activities [like writing](#) (and also [addiction](#)). Chronic marijuana use, however, may lead to [depressed dopamine activity](#).

The authors of the current study put together the facts about dopamine, marijuana's effects on it, and creativity to suggest a hypothesis about how marijuana may affect divergent and convergent thinking. Since long-term cannabis users would have depressed dopamine activity, their divergent thinking before marijuana use would be

Dopamine: a double-edged molecule

The trope of the mad artist is worn out enough to have its own [TV Tropes](#) page. While this is clearly an oversimplified stereotype, there is an interesting connection to be found here.

Dopamine activity seems to correlate with creativity, as mentioned in the introduction. However, it is also related to schizophrenia. [One study](#) found that creative people without schizophrenia had low dopamine receptor levels in their thalamus (but not the striatum; the science is still young on this), which is also found in some people with schizophrenia. The authors of this study suggest that low dopamine receptor levels lead to less filtering of information. In people without schizophrenia, this can lead to creative, divergent thinking. In people with schizophrenia, it can lead to troubling symptoms.

on the left hand side of the inverted “U” shaped curve. For them, acute use of marijuana may push them to the right on that curve, improving divergent thinking. Convergent thinking, however, is negatively correlated with dopamine activity, so marijuana use should hamper this aspect of creative thinking in any marijuana users, regardless of how long they’ve used it. These relationships are summarized in Figure 1.

The goal of the current study was to put this hypothesis to the test.

Two aspects of creativity are related to dopamine activity in the brain. Divergent thinking, the skill behind brainstorming new ideas, may get worse with very low or very high dopamine activity, and is best in the middle range. Convergent thinking, the skill behind unifying ideas into a coherent whole, worsens as dopamine activity increases. Since long-term marijuana users have depressed dopamine function, use of marijuana in this population could improve divergent thinking while worsening convergent thinking. This hypothesis was put to the test in the current study.

Who and what was studied?

A total of 54 healthy Dutch people (six women and 48 men) in their early 20s who regularly used marijuana were included in this study. “Regular use” was defined as consuming marijuana at least four times per week for the past two years. “Healthy” here meant that the participants did not have significant mental or physical disorders, did not abuse alcohol, were not on any psychotropic medications, and did not use any other drugs recreationally. People who smoked cigarettes were included in the study.

After recruitment, the participants were then randomized to inhale vaporized marijuana that contained one of three levels of THC. The vaporizer they used (a Volcano-brand vaporizer, depicted in Figure 2) had a large balloon attached to it which filled with the vapor, and the participants were asked to inhale the contents of the balloon deeply and hold their breath for ten seconds before exhaling. It’s a pretty big balloon, so it took several inhalations to completely consume the balloon’s contents.

The total amount of THC delivered to each participant in the three groups was 22 milligrams (high dose), 5.5

Figure 1: Theoretical predictions of how dopamine activity is related to creativity

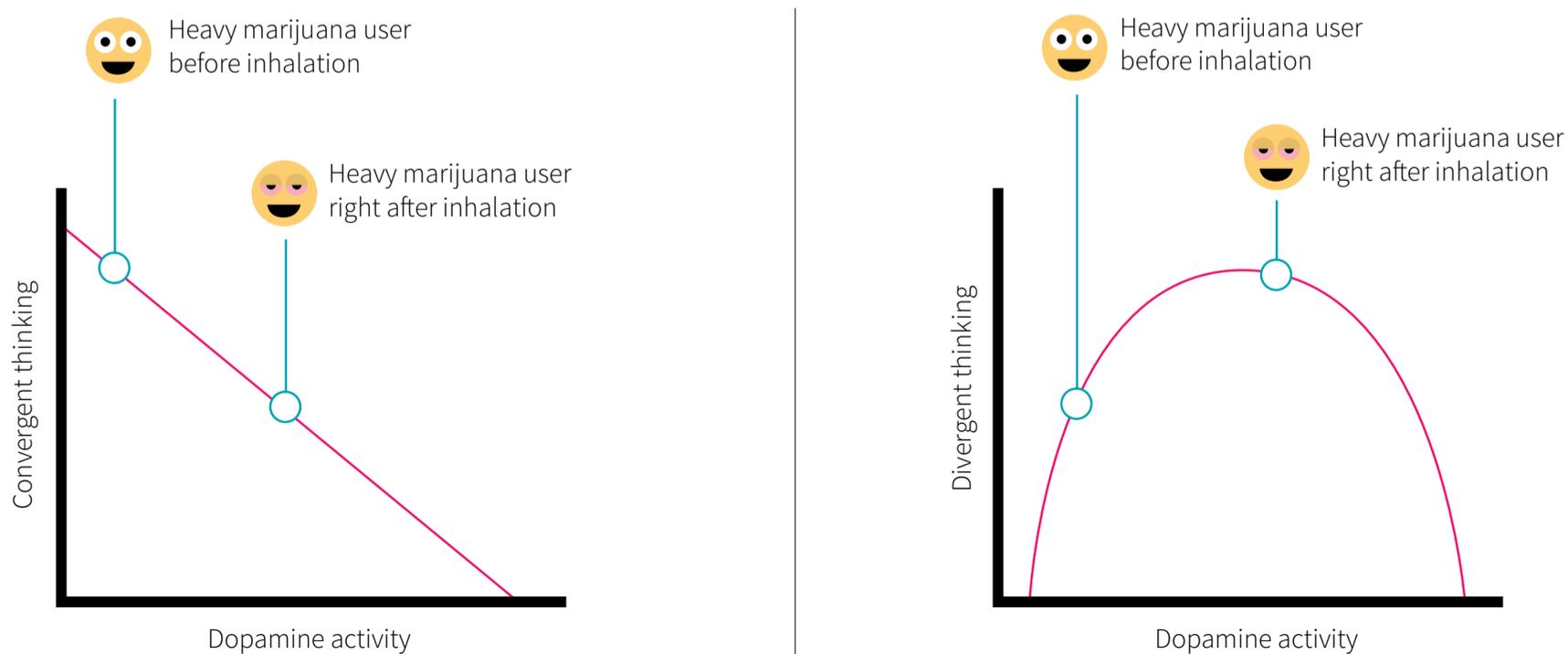
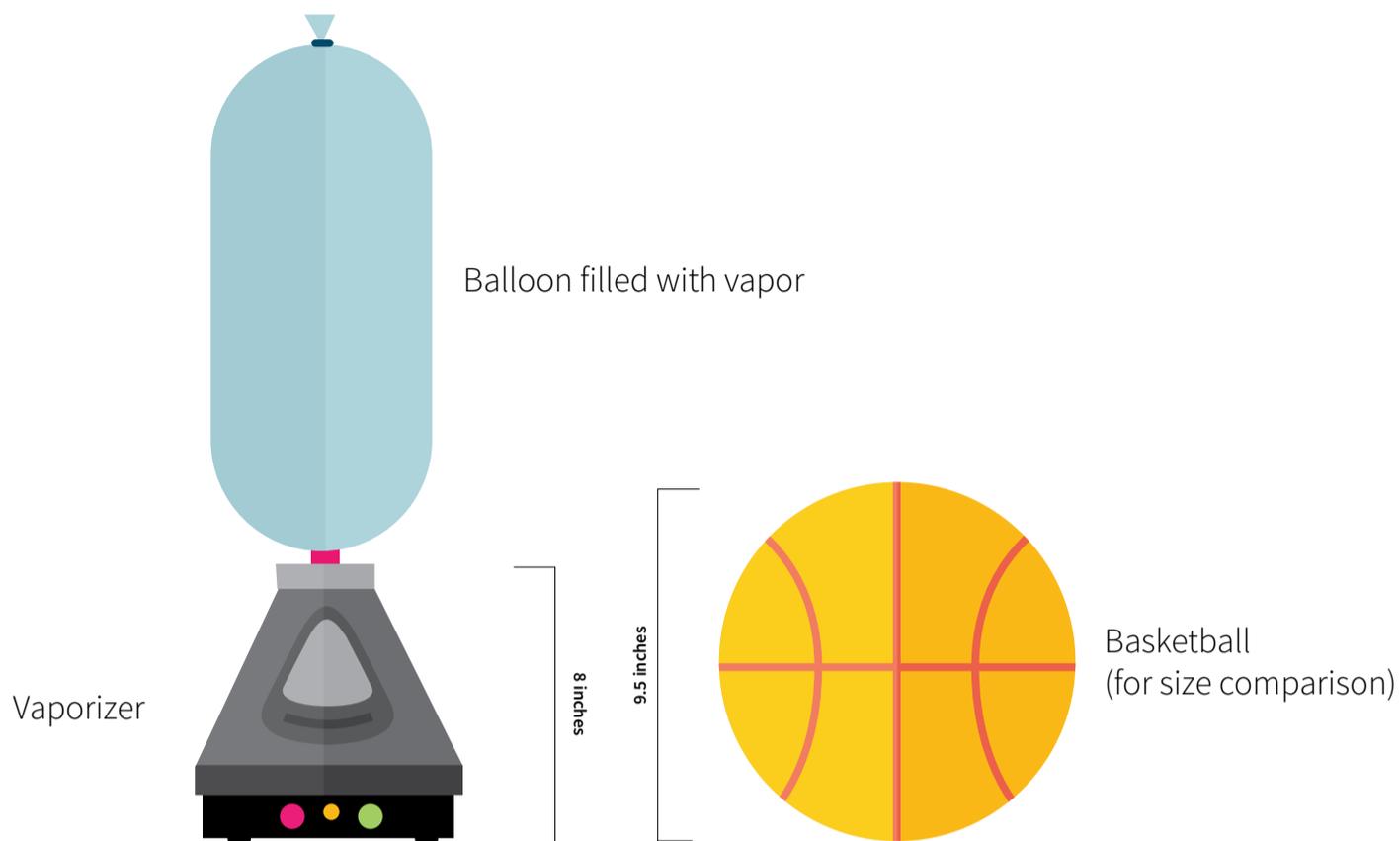


Figure 2: The Volcano vaporizer



milligrams (medium dose), or almost 0 milligrams (placebo). Acknowledging that not all the THC in the plant is vaporized, and not all of the inhaled THC is absorbed through the lungs, the researchers estimated that the actual doses absorbed were eight milligrams, two milligrams, and zero milligrams, respectively. The participants and experimenters were blinded to what dose of THC was being delivered.

The study participants were then asked to report their subjective feelings six minutes after completely consuming the marijuana. They then completed two tasks to measure their creative thinking 35 minutes and then 60 minutes after consuming the marijuana, and given 10 minutes to complete each task. But ... how can you measure creativity? Well, psychologists, being a somewhat creative bunch themselves, have come up with a few tests to do so.

One of the tests was the Alternate Uses Test (AUT), which measures divergent thinking, an aspect of creativity. The AUT asks people to generate as many as possible uses for a common household items as they

can think of in a given span of time. For instance, a pen can write, hold a door open, be used as a bookmark, be melted and molded into a shape, etc. The answers were then rated by two independent reviewers blinded to treatment condition according to four different criteria: fluency, flexibility, originality, and elaboration. The scores highly correlated with each other, which suggests that the tests were rated reliably.

The other test was the [Remote Associates Task](#) (RAT), which is considered a measure of convergent thinking. This task involves giving a group three words and encouraging them to try to find a fourth word that links them. One example is “back, go, light.” The fourth word for this set is “stop.” Since the RAT has “objective” answers, it is easier to come up with a final score for it than the AUT. You just count the number of right answers.

The tests were administered in a random order to each participant to make sure the order of administration didn't affect the results. Also, after each creativity test, the experimenters again asked the participants to rate their subjective feelings.

This study recruited 59 people who were young, healthy, and frequently used cannabis. Researchers intended to test the effect of cannabis on creativity. Participants were randomized to inhale marijuana which had either high, medium, or almost no THC. After consuming the marijuana, they were administered two tests of creativity: the Remote Associates Task (RAT), which measures convergent thinking, and the Alternate Uses Test (AUT), which measures divergent thinking. Their subjective feelings were also measured throughout the experiment.

What were the findings?

The study's findings are summarized in Figure 3. The three treatment groups did not differ in convergent thinking as measured by the RAT, indicating that the THC content of marijuana did not affect remote associations in this population.

Also, there was no difference between the placebo and medium-dose group's performance on any of the four

subscores of the AUT, indicating no effect on divergent thinking at this dose of THC. However, the high-dose group performed significantly worse on three of the four AUT subscores, with no difference between the three doses for the elaboration subcategory.

Before they used marijuana, the participants in this study performed [similarly](#) to people not under the influence of any substances on the AUT and RAT.

In terms of subjective feelings, people felt higher when they inhaled vaporized marijuana with THC in it (surprise, surprise), and also said they had higher "good drug effect" scores. A little more surprisingly, there was no difference in either of these scores between the medium- and high-dose THC groups. Also, people in the high-dose THC group reported experiencing significantly worse drug effects compared to the medium-dose and placebo groups. The latter two groups didn't differ statistically from each other in terms of bad drug effects. Finally, THC level did not affect measures of mood, and mood did not change significantly over time.

Figure 3: Summary of results

		AUT (Divergent Thinking)			
RAT (Convergent Thinking)		Fluency	Flexibility	Originality	Elaboration
Medium THC vs Placebo	—	—	—	—	—
High THC vs Placebo	—	↓	↓	↓	—

Convergent thinking as measured by the RAT was not affected by THC at any dose. Divergent creative thinking was unaffected at medium doses of THC, and made worse in three of four subcategories of the AUT at high doses, with no effect on the fourth category of elaboration.

What does the study really tell us?

The study provides some evidence against the view that marijuana enhances creativity. Instead, it either seemed to have no effect or a negative effect. But, as usual, there are a lot of caveats to this statement.

First, the measures of creativity used in this test were all based on word association on the written page. It is not immediately clear if this relates to creativity in other domains, such as the visual arts, dance, music, or the spoken word. There is some [evidence](#) along with varying [hypotheses](#) that address how related different types of creativity are, but results are quite mixed, and studies use varying methodologies.

Second, recall that the population being studied were people who used marijuana fairly heavily for at least two years. Thus, even if the results of this study are true (a great rule of thumb is that one study alone never proves anything), the results would only strictly apply to people whose marijuana use is similar to those of this study. Not to mention that different marijuana strains can have wildly different effects, with different effects possible in different people.

Perhaps the theory laid out in the introduction (that predicts how the creativity of less heavy users of marijuana would change with marijuana use) could shed some light here, but this study also showed that the theory didn't quite pan out as anticipated. This is not terribly surprising, since the authors seemed to base

their hypothesis on [one study](#) alone (or at least their text justifying their hypothesis relies heavily on this one study). The referenced study used eye blinking rates as a proxy for dopamine activity, which may not be entirely reliable.

The authors of the study offer a few other possibilities for why their hypothesis didn't seem to hold in the study, beyond the possible unreliability of eye blink rates as a measure of dopamine activity. One possibility is that the high-dose group received too high of a dose, pushing them to the far right of the inverted U-shaped curve. A more fine-grained dosing study in the future could shed some light on this possibility. Alternatively, the authors noted that the high dose group experienced more negative effects than the other two groups. This led them to suggest that maybe the participants had to spend their cognitive resources dealing with the bad feelings rather than the task at hand, which fits with the [“ego depletion”](#) model of cognitive control.

As for why the placebo and low-dose groups performed equally in the AUT, the authors suggest several possibilities. One is that the dose was too low, since the participants were tolerant to THC and [some studies](#) have shown that higher doses are needed for the same effect in this population. Alternatively, the placebo may have contained other active ingredients or a minimal dose of THC that was necessary to induce an effect. Finally, perhaps the placebo effect was strong in the placebo group, since it was identical in smell and taste to marijuana with a higher THC level. This may have led to increased dopamine output simply based on expectation, which is an effect that has been noted in [other research](#).

The authors were less prolific in providing possible explanations as to why convergent thinking didn't differ between any of the treatment groups. The main hypothesis they put forward is that they used a truncated, 14-question version of the RAT, which may not have been sensitive enough to measure differences accurately.

ly. Many possible factors weren't discussed, such as the impacts of cannabinoids from marijuana on non-dopamine aspects of brain function, some of which may theoretically impact creativity.

The generalizability of this study is limited, both because it was done exclusively in people who used marijuana heavily, and because it only measured two aspects of creativity, both related to words on a written page. In addition, this study also generated a lot of possible hypotheses as to why the predictions of the authors didn't pan out, many of which could be tested through further research.

The big picture

The current study somewhat clashes with a larger body of research on marijuana's and THC's effects on convergent and divergent thinking. The effects on divergent thinking tends to have more evidence surrounding it.

[Early research](#) examining the effects of THC on divergent thinking found that low dose marijuana cigarettes (three milligrams of total THC) improved divergent thinking compared to higher doses (6 milligrams of THC). [Later research](#) using oral THC noted increased verbal fluency in doses up to 15 milligrams. Long-term users of cannabis were tested in [another study](#) which found that smoking marijuana improved divergent thinking, but only in those who assessed themselves to be not very creative in the first place. [Another study](#) found smoking marijuana improved aspects of divergent thinking only in long-term users, but not in people without a long history of exposure to cannabis. While all the previous studies found an improvement in divergent thinking, at least in some populations, [one](#) study came up empty-handed.

Studies of marijuana's effect on convergent thinking are fewer and far between, and both were mentioned above.

One of the [same studies](#) mentioned above found convergent thinking to be impaired by joints containing three or six milligrams of THC, compared to a control. Another [later study](#) used the RAT and found that marijuana containing 10% THC may harm convergent thinking in people who rated themselves to be fairly creative.

While the conclusions that can be drawn from the body of research are not crystal-clear, it seems that the current study goes against what little evidence there is concerning marijuana's effects on creativity, at least to some degree. Fortunately, contradictory and confusing research can serve as grist for the mill of scientists' creativity in the future as they search for solutions.

Previous research done on marijuana's and THC's effects on convergent and divergent thinking tend to indicate that acute marijuana use can improve divergent thinking and harm convergent thinking. However, the evidence to date is limited and mixed.

Frequently asked questions

How potent was the marijuana used in this study compared to that of average marijuana?

The THC content of most marijuana is [between 5-10% THC](#), although THC content has been rising sharply in recent years, sometimes [hitting the 30% mark](#). For comparison, the highest THC dose in this study was the equivalent of around 9% THC. However, the participants in this group had to inhale a large balloon full of the vapor, which required several hits.

This study was done in long-term users of marijuana.

What would the hypothesis be for how marijuana affects the creativity of people who don't use it frequently?

By the reasoning laid out in the Introduction, marijuana use should make both divergent and convergent thinking worse. Recall that convergent thinking is inversely correlated with dopamine activity and

divergent thinking has an upside-down “U” shaped correlation with respect to dopamine activity. This implies that any increase in dopamine activity will worsen convergent thinking, just like in people who use marijuana heavily over the long-term. However, since people who don’t use marijuana frequently will lie in the middle of the inverted “U” curve for divergent thinking, marijuana use on one occasion would push them to the far right of the curve, worsening their divergent thinking as well. This is different from the prediction the authors made for chronic cannabis users.

That’s the theory, anyway. As the study reveals, it didn’t quite pan out as expected.

So the authors’ hypothesis was that marijuana’s effect on creativity is mediated by dopamine. Does this mean that other drugs that affect dopamine would in theory affect creative thinking?

Assuming the authors’ hypothesis is correct (which isn’t a great assumption, given the results of this study), this would indeed be the case. In fact, it’s somewhat odd that the authors of the current study didn’t take their hypothesis to its logical conclusion and mention other drugs in their discussion section.

There aren’t a whole lot of solid studies on other drugs’ effects on creativity. [One study](#) on Adderall, which affects dopamine levels, found no effect on divergent

thinking, and a positive effect on convergent thinking, but only in those who scored lower in convergent thinking to begin with; those with higher convergent thinking ability to start out with were either unaffected or impaired.

Do other supplements affect creative thinking?

Remember that dopamine activity is related to creative thinking. Dopamine is synthesized from the amino acid [tyrosine](#). So, in theory, it’s possible that tyrosine supplementation could affect creativity. One group recently put this hypothesis [to the test](#) and indeed found that tyrosine improved convergent, but not divergent, thinking. While one study doesn’t prove anything, this is an interesting result. Hopefully, more research will be done in this area.

What should I know?

This study found that acute marijuana use in heavy users has no effect on one aspect of creativity called convergent thinking, which is the ability to unify disparate themes into a common thread. It also found that marijuana that contains high doses of THC may impair divergent thinking, which is the ability to brainstorm and come up with unique, loosely connected ideas. Marijuana containing lower doses of THC had no effect on divergent thinking. These results were somewhat unexpected based on past research. ♦

Work, tower, wise. What is the fourth word that links them? Find out on the private [ERD Facebook forum](#)! You can also discuss this article and others, too, while you’re there...

Want to hear commentary on this issue?

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Quoth the insulin hypothesis, “Nevermore”

Energy expenditure and body composition changes after an isocaloric ketogenic diet in overweight and obese men 



Introduction

Adversarial collaboration is when researchers who hold conflicting opinions gather to conduct experiments that will help to resolve or reduce their differences. The present study was a product of this process. The Nutrition Science Initiative (NuSI), co-founded by Gary Taubes (champion of the carbohydrate-insulin hypothesis of obesity), assembled [a team of experts](#) to run a clinical trial designed to answer the question: Will very-low-carbohydrate ketogenic diets lead to greater energy expenditure, and thus fat loss, when compared to a high carbohydrate diet?

Ketogenic diets usually take the form of severely restricted carbohydrate intakes, usually down to around 5% of total calories. Taubes has hypothesized that whenever someone goes on a diet, they “will remove the most fattening carbohydrates from the diet and some portion of total carbohydrates as well. And if we lose fat, this will almost assuredly be the reason why” ([Why We Get Fat](#), p. 144-47). Prior research [conducted by Dr. Kevin Hall](#), lead researcher of the study under review, has not supported this hypothesis. When investigating mechanisms of fat loss, Dr. Hall’s pilot study showed that a reduction in carbohydrate was not necessary for fat loss nor was any metabolic advantage (i.e. increased metabolism) for fat loss seen when insulin secretion was reduced by 22% while on a low-carb diet. That trial (covered in [our blog post](#) and in ERD #11, Volume 2) had some limitations, though, such as its short 6-day duration. The present study aims to expand on this research, by conducting a two-month trial that compares a high-carbohydrate to a ketogenic diet.

As there are different versions of the carbohydrate-insulin hypothesis of obesity, it’s important to clarify which one is being tested. The hypothesis being examined here proposes the following: carbohydrate in the diet elevates insulin secretion, which suppresses the release of stored body fat and drives circulating fat to be stored. A decrease of circulating fatty acids leaves

less total energy available for use by organs like the heart, liver, and muscles, which can lead to a decline in energy expenditure and promote hormonal signaling, resulting in [increased food intake](#). Thus, it is posited that the development of obesity is a consequence of carbohydrate-induced insulin production driving fat into storage, preventing it from being oxidized for energy.

It would then stand to reason that reducing the amount of carbohydrate consumed, while keeping variables such as total calories and protein intakes constant, should result in a drop of insulin secretion, causing a cascade reaction that would allow for increased energy expenditure and increased fat loss. The competing calories in, calories out (CICO) hypothesis maintains that exchanging carbohydrate for fat will not notably affect body fat levels nor energy expenditure. This study was designed to test which of these hypotheses might be true.

A team of researchers, recruited by the Nutrition Science Initiative (NuSI), conducted a study to test the carbohydrate-insulin hypothesis of obesity. This hypothesis states that the development of obesity is brought about through elevated insulin, caused by too much carbohydrate in the diet, driving fat into storage and preventing it from being oxidized for energy.

Who and what was studied?

Seventeen men between the ages of 18-50 (average age: 33) who were overweight or obese were admitted to a metabolic ward for this cross-over study. In a metabolic ward, participants are confined to a building where all food intake is strictly measured and controlled, so as to be certain of how many calories are consumed. This offers a major advantage over free-living studies that can be fraught with [inaccurate self-reported food intake](#).

To give you an idea of how stringently food is monitored, here are some of the policies participants had to

comply with: All meals were consumed under observation of the research staff. While visitors were permitted, they could only meet with participants in a common area under supervision to ensure no exchanges of food were made. Additionally, one of the study sites did not have the metabolic chambers (where energy expenditure, as broken down in Figure 1, is measured) and the metabolic ward (where participants live) in the same location. In this case, all participants were transported to and from these sites under supervision to make sure they didn't sneak any food.

While participants were overweight or obese (BMI between 25-35), they were otherwise healthy and had been weight-stable in the six months prior to the trial. People on a reduced (less than 30%) or high-carbohydrate (greater than 65%) diet were excluded from the trial.

Two diets were employed during this eight-week study and were designed in partnership with Jeff and Brittanie Volk, two advocates for low-carb diets. The macronutrient profiles of each are shown in Figure 2. For the first four weeks, all participants consumed a

Figure 1: Components of energy expenditure

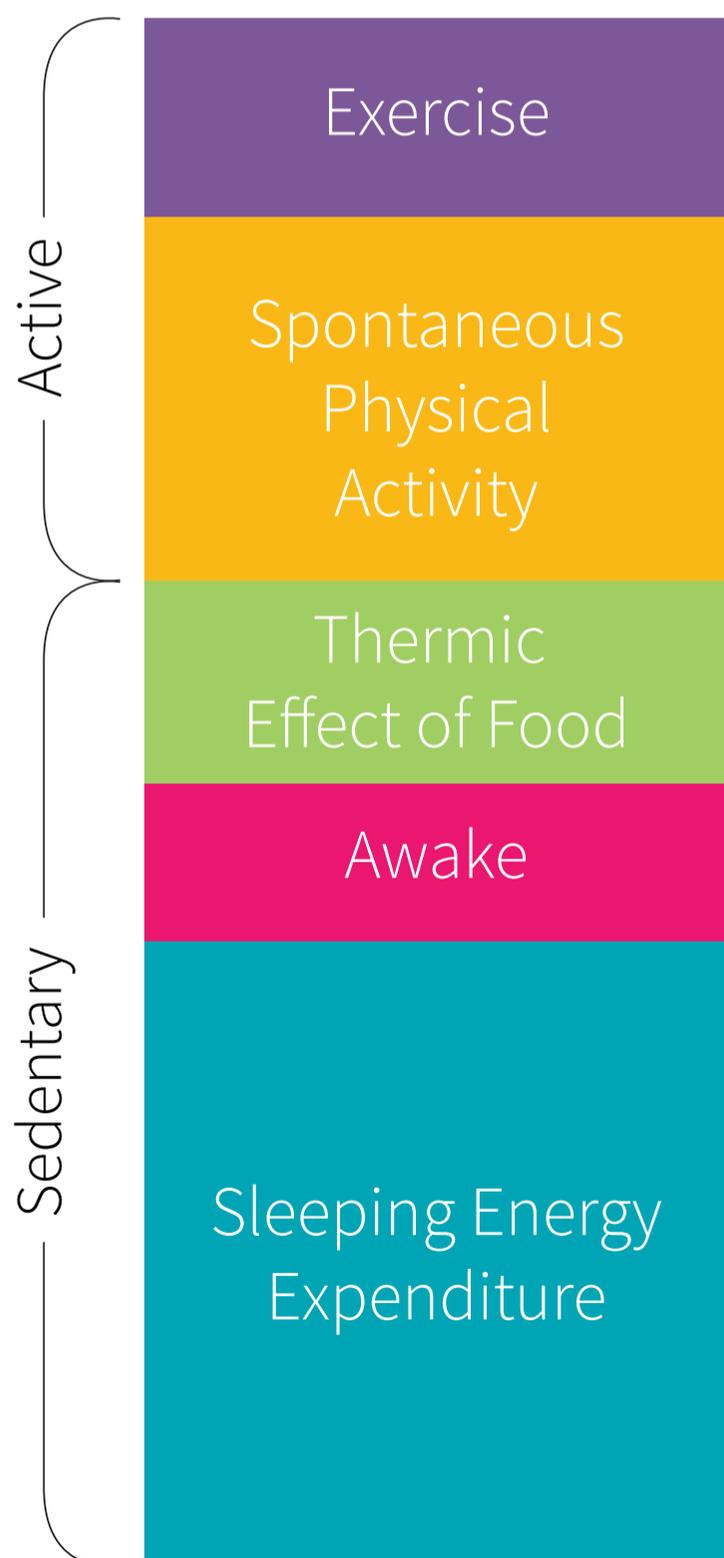
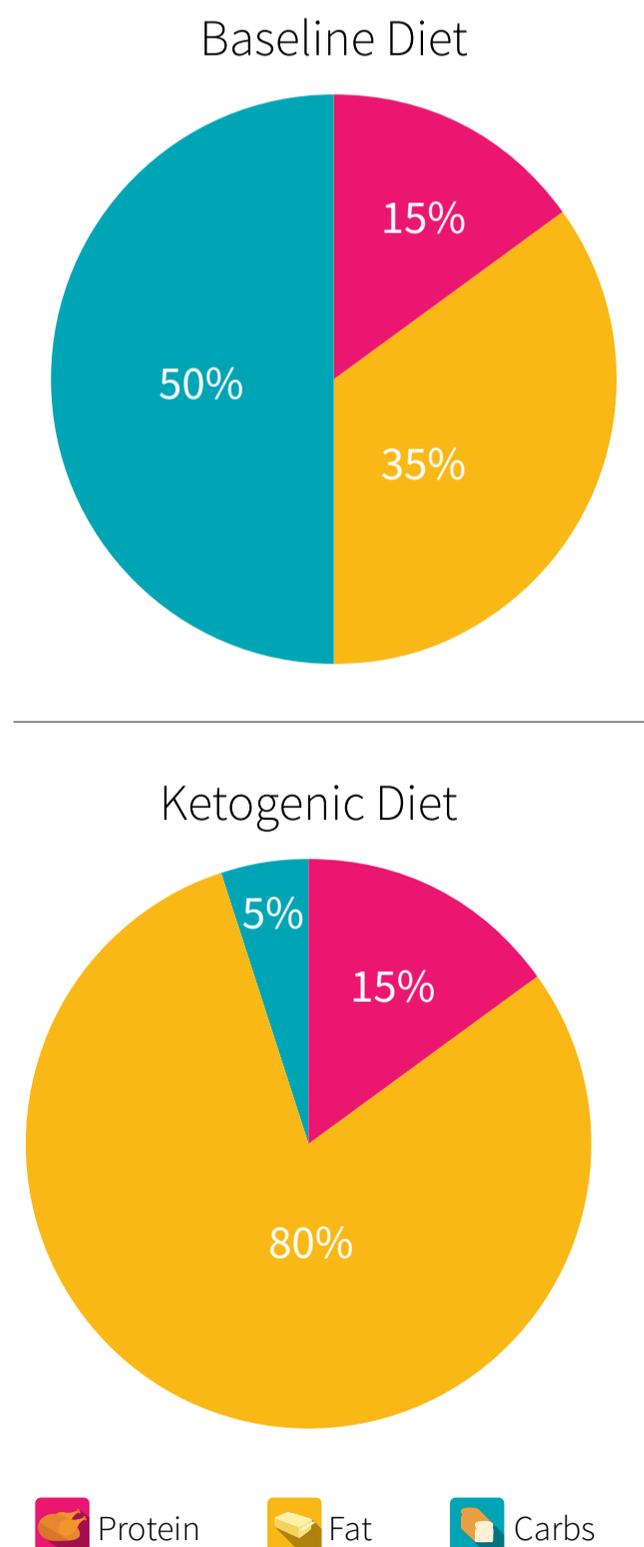


Figure 2: Macronutrient contents of the diets



2,398 kcal high-carbohydrate baseline phase (BP) that was 15% (91 grams) protein, 50% (300 grams) carbohydrate, and 35% (91 grams) fat. Of the carbohydrate content, 49% (147 grams) was sugar, but much of this was from naturally occurring sugars, as large amounts of added or liquid sugars were not used in the baseline phase. For reference, the [average American adult consumes](#) about 71 grams of **added** sugar per day. Aside from the higher sugar intake, this macronutrient composition is believed to represent a typical American diet.

In the second four-week period, participants ate a 2,394 kcal ketogenic diet (KD) that was protein matched to the BP diet at 15% (91 grams), 5% (31 grams) carbohydrate, and 80% (212 grams) fat. During the KD period, there was nearly a 10-fold decrease in carbohydrate intake and sugar consumption dropped by 93%, from 147 grams to 10 grams. Sample menus can be seen in Table 1.

It's important to note that energy intakes were altered weekly for the first two weeks of the BP. This was done to try and ensure everyone remained weight-stable. Fifteen days into the baseline phase, no more adjustments were made and daily caloric intake remained the same for the rest of the study. The compositions mentioned above represent the seven-day average BP and KD diets during the isocaloric periods.

There were two primary endpoints of this study: changes in energy expenditure and 24-hour respiratory quotient. This last measure is designed to see which substrate the body is primarily drawing energy from: fat or carbohydrate. Energy expenditure was measured every week by placing the participants in the metabolic chambers for two days. Results were corroborated by having participants drink doubly labeled water twice during the trial, once during each diet. Secondary endpoints looked at changes in body composition as

Table 1: Sample menus used in the trial

Baseline Phase	Ketogenic Diet
Breakfast	
Egg and potato hash with berries	Ham & Swiss omelet over spinach
Morning Snack	
Peanuts, oil-roasted, salted	Cheddar cheese
Chewy granola bar, chocolate chunk, low fat	Almonds, oil-roasted, salted
Lemonade, from concentrate	Bouillon cube, beef + Olive oil
Lunch	
Turkey burger with hot potato salad	Kielbasa with chilled mustard sauce & sautéed cabbage
Afternoon Snack	
Pretzel sticks	Celery with buffalo chicken dip
Wheat crackers & American cheese spread	
Dinner	
Cheese steak sandwich and pineapple	Spicy hamburger, sautéed squash, & mushrooms

measured by dual-energy X-ray absorptiometry (DXA), which were taken four times during the study. Various blood and urine measurements were also taken as exploratory measures.

Finally, as if being confined to a ward for two months wasn't hard enough, everyone had to exercise daily by cycling for 90 minutes. If you were wondering: Yes, these participants were financially compensated for their time.

Seventeen male participants (BMI 25-35) were confined to a metabolic ward for two months. Everyone consumed a high-carbohydrate baseline phase diet for four weeks prior to being switched to a ketogenic diet for the second four weeks. The primary endpoints were differences in energy expenditure and respiratory quotient. A major secondary endpoint was change in body composition. Exploratory blood and urine tests were also conducted.

What were the findings?

All 17 participants completed the study. While the researchers had aimed to keep participant weight stable

over the trial, a loss of fat mass was recorded during the last six weeks of the study. The study is focused on the last six weeks, not the entire eight, because calories were still being adjusted in the first two-week period of the trial in an attempt to find the caloric intake that would keep participant weight stable. The last six weeks are when calories were set for good, thus providing the most reliable time period for analysis.

Much has been made of the fat loss numbers in this study, which have been broken down into four parts: Total Fat Loss, BP-2 (weeks 3-4), KD-1 (week 5-6), KD-2 (weeks 7-8).

Total Fat Loss - Participants lost 2.2 pounds (one kilogram) over the last six weeks of the study. Participants lost as much fat in the last two weeks of the BP (rate of 0.55 pounds/week) as they did over the four weeks KD (rate of 0.27 pounds/week).

BP-2 (weeks 3-4) - Although researchers noted a significant 1.1 pound (0.5 kilograms) loss of fat during this two-week period, no adjustments to food intake could be made at this point to try and prevent further loss as the caloric intake of every participant had been locked

How does a DXA scan work?

DXA scans (dual x-ray absorptiometry) is one of the most accurate ways to measure changes in lean mass, body fat, and bone density. Two methods with greater accuracy are computerized tomography (CT) scan or undergoing an autopsy, where the different components are cut out and weighed (we do not recommend this latter method, as you have to be dead as a prerequisite).

When you get a DXA scan, you lay down on a bed while a robotic arm moves up and down the length of your body, emitting very low-level X-rays and measuring how many get absorbed. The whole process is fairly quick, usually taking 3-10 minutes, and it typically delivers measurements that are within 3% accuracy. Traditionally, DXA scans were employed to measure bone density to help detect or track development of osteoporosis. Modern machines can use equations to help calculate body fat and lean mass.

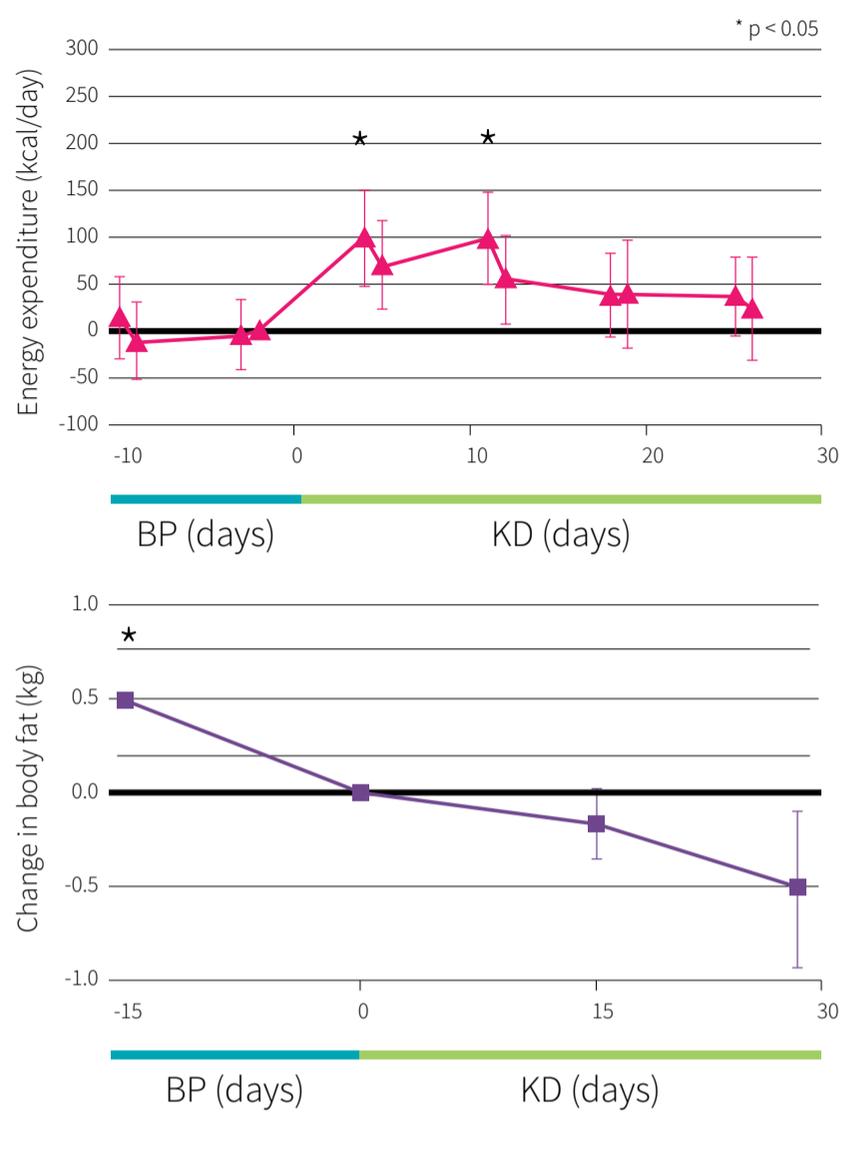
in. Adjusting them at this point would have confounded the results of the study.

KD-1 (week 5-6) - For the first two weeks of the KD phase, energy expenditure increased significantly. Participants were burning about 100 kcals more per day for 10 days. But (as shown in Figure 3) while energy expenditure increased, participants curiously experienced a slowdown in the rate of fat mass lost, losing only 0.44 pounds (0.2 kilograms) during KD-1. This indicates that, even though they were using more energy, stored fat mass was not utilized as much during this increase. However, protein loss significantly increased over this same period. It is possible that the increased utilization of protein (likely for gluconeogenesis, during which protein can be used to create glucose) accounted for some of the energy expenditure. This effect would diminish after the body becomes better adapted to running on ketones. Utilizing protein is an energy-intensive process compared to fat or carbohydrate. This increased protein use on low-carbohydrate diets has also been seen in Dr. Hall's [previous metabolic ward study](#). The utilization of stored glucose (glycogen) may have also displaced fat as an energy source during KD-1 as well.

KD-2 (weeks 7-8) - The spike in energy expenditure seen in KD-1 was not sustained in KD-2, where expenditure levels almost returned to baseline levels. The rate of fat loss picked up a bit here, as participants lost 0.66 pounds (0.3 kilograms) of fat, but this rate still remained lower compared to BP-2. It's possible that the participants' metabolisms had become well-adjusted to the ketogenic diet and were not relying so heavily on protein and glycogen oxidation anymore, allowing it to burn dietary fat more efficiently.

Comparing energy deficits over the last two weeks of both diet phases (BP-2 vs. KD-2, when participant's bodies had "settled in" to their diets), no significant differences were observed in either the DXA scans or the

Figure 3: Results of fat loss and energy expenditure



doubly labeled water. These data, when added together with the lower rate of fat loss seen during the KD indicates that a ketogenic diet does not confer an advantage to fat loss over a high-carb diet when matched for calories and protein.

After transitioning to the KD, insulin secretion decreased by 47% and participants shifted to predominantly burning dietary fat as fuel by day five. Despite the sharp drop in carbohydrate consumption and insulin secretion, no significant increases in fat loss were observed in the KD phase compared to the BP phase. This finding indicates that a large decrease in insulin secretion does not provide a fat loss advantage over diets that produce higher total daily insulin secretion when matched for calories and protein.

All participants completed the study. While energy expenditure increased (for ~10 days) and daily insulin secretions fell by 47% on the KD diet, no significant increases in fat mass loss were observed compared to the BP. The rate of fat loss slowed in the KD phase while energy expenditure increased. This fat loss rate picked up in the last two weeks of the KD but never surpassed that of the BP. These findings indicate no metabolic advantage to a ketogenic diet over a high-carbohydrate diet when calories and protein intake are matched.

What does the study really tell us?

This study provides more evidence supporting the calories in, calories out model of obesity. The carbohydrate-insulin hypothesis predicts that diets high in carbohydrate will drive up insulin and therefore increase fat mass accumulation while decreasing fat loss. However, the BP was high in carbohydrate, in particular, refined carbohydrate (147 grams of sugar per day!) and the rate of fat loss was slightly faster than the KD phase.

Proponents of the insulin model have indicated that a ketogenic diet should provide a [metabolic advantage](#) to the tune of 300-600 more kcals burned per day due to [increased energy expenditure](#). And yet, while the KD reduced carbohydrate intake by 89.7% and insulin secretion decreased by nearly 50%, no sustained energy expenditure increases were seen beyond the first 10 days and fat mass loss did not accelerate. In fact, loss of fat actually decreased during the period in which participant energy expenditure increased. If the keto diet period had continued long enough, energy expenditure and fat loss rate [would probably have converged](#) with the baseline diet.

This study was initially designed to keep people weight stable throughout the trial. That clearly did not happen,

as average fat mass loss was 2.2 pounds (one kilogram) over the course of six weeks. While not a substantial rate of fat loss (0.33 pounds per week), it still may be a marginal confounder for this study. On the other hand, if the KD condition were to provide a large metabolic advantage, as predicted by the carbohydrate-insulin hypothesis, there should have been a substantial increase in fat loss while participants were on the ketogenic diet, despite earlier fat loss. That effect was not borne out.

No study is without limitations. The authors did not measure energy lost in fecal content and did not have a control group that didn't receive the KD over the second half of the study. Nor did they have a group that received the diets in reverse order. The trial also used a protein intake level that may be lower than what some real-life ketogenic dieters employ. And the results cannot necessarily be extrapolated wholesale to women or men who have a BMI lower than 25, higher than 35, or who have various health conditions.

The hypothesis that low-carbohydrate diets provide a metabolic advantage of up to 300-600 additional calories burned per day was not seen in this well-controlled metabolic ward study.

The big picture

“Our data do not support the carbohydrate-insulin model predictions of physiologically relevant increases in (energy expenditure) or greater body fat loss in response to an isocaloric (ketogenic diet).”

This study shows that a ketogenic diet may not be a weight loss magic bullet, and it also gives us data indicating that a CICO model may start to reach its limits at macronutrient extremes, at least over periods of weeks. Energy expenditure and fat loss were different on two diets supplying the same calorie intake. These were due to different macronutrient compositions.

The findings of this study are a bit anticlimactic. Imagine if the results had come back that a ketogenic diet could blast your metabolism into the stratosphere. It would have been incredible. The public health approach to treating obesity would (in an ideal world) have experienced a cosmic shift. Alas, no such paradigm-altering results were observed. These findings build on [prior research](#) showing that [insulin is not the primary regulator](#) of body fat.

But do not despair, there is a bright side to this all. People who dread the thought of a keto diet or don't particularly care for the low-carb approach can be sure that it is not the only route to sustainable fat loss.

It's possible to go on a well-planned, whole-foods based, ketogenic diet. Some people find that a very-low-carb or reduced carbohydrate approach work best for them. Many people report feeling less hungry on a low-carb or ketogenic diet in a real world setting. Often, these increased feelings of satiety brought about through higher protein intakes that often occur on low-carb diets. If this is you, then keep at it, because in the end [adherence is king](#). If you force yourself into a pattern of eating you can't reliably sustain, your chances of failure are high.

Keto diets have not been shown to significantly increase your metabolism. Want to go low-carb? Do it. Want to go high-carb? Do it. Want to become a Breatharian, eat no food ever again, and only subsist on the air you breathe? Please don't do that. Both high-carb, low-carb, and somewhere-in-the-middle-carb approaches can work for weight loss, so choose the one that fits your lifestyle best.

Frequently asked questions: XXL Edition

Studies like this one tend to generate a lot of press, so many misconceptions and questions abound. To cut through some of the hype, we're bringing you another round of the F.A.Q: XXL Edition, to shed some light onto these queries.

Won't the diet order mess up the rate of fat loss for the second four-week period of the study?

The diet order would likely have little effect on the results of the study. It could in theory, but only slightly and not nearly enough to explain the slowdown in fat

“ Many people report feeling less hungry on a low-carb or ketogenic diet in a real world setting. Often, these increased feelings of satiety brought about through higher protein intakes that often occur on low-carb diets.”

loss observed in the first two weeks of the KD phase. The researchers even adjusted the calculations for energy expenditure to take into account the weight loss and this did not shift the results in any meaningful way.

Lead author Dr. Hall [explains](#): “The study was designed such that the baseline run-in diet was intended to match the typical composition of the subjects' habitual diet. We screened out people whose habitual diet was too different in composition. Therefore, randomizing the diet order would introduce a significant order effect that could confound the interpretation of the data given that the ketogenic diet would represent an extreme change from their habitual diet upon entry to the study.”

There were missing data for some of the metabolic chamber measurements. Won't this affect the final analysis?

The researchers collected a total of 272 days' worth of metabolic chamber data. Six data points had to be excluded due to chamber malfunctions: two from the BP phase and four from the KD phase. This accounts for 2.2% of all chamber data collected, so it is possible but unlikely that these exclude data points would significantly alter the analysis.

What effect does the small sample size have on the study results?

Good research practices dictate that you perform a

power calculation before you begin an intervention trial. This calculation will give you the number of people you will need to recruit into your study to ensure that you can detect significant differences between groups. The researchers of this study did perform this calculation and found that 16 subjects were needed to reliably detect a change of ~150 kcal/day in energy expenditure measured in the chamber between BP and KD. In their actual study, they recruited 17 subjects, all of whom completed the trial.

What should I know?

The big takeaway is that a ketogenic diet does not appear to confer a fat loss advantage over high-carbohydrate diets when calories and protein are strictly matched (at least in this population and in the context of the limitations of this study). How should you apply this knowledge to your everyday life? Easy, pick the eating style that you can stick with over the long term. This study is not bashing ketogenic or low-carb diets, but merely pointing out that they probably don't confer fat-burning super-powers. ♦

While this study won't end the Carb Wars, it provides some useful fuel for discussion. Not ketogenic fuel though. Discuss it at the [ERD Facebook forum](#).

Want to hear commentary on this issue?

Listen to our editor in chief Gregory Lopez facilitate a roundtable discussion about these six studies with our reviewers Dr. Adel Moussa and Dr. Stephan Guyenet, and Examine.com researcher and writer Michael Hull.

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The effect of protein supplementation on muscle mass and strength

A systematic review, meta-analysis and meta-regression of the effect of protein supplementation on resistance training-induced gains in muscle mass and strength in healthy adults 



Introduction

Resistance training is a type of exercise characterized by skeletal muscles (the muscles responsible for voluntary movement) being forced to contract against some form of external load. This unique type of exercise has important health benefits that are mediated, in part, through its ability to increase [muscle mass and strength](#). Not only does skeletal muscle help you look good naked, but it [plays an important role](#) in the prevention of many diseases such as obesity, type 2 diabetes, and osteoporosis.

Protein supplementation is a widespread practice among people who partake in resistance training, be they athletes or average. The idea is that protein supplementation will enhance training-induced gains in muscle mass and strength. Although a [single exercise session](#) increases muscle protein synthesis for up to 48 hours, overall muscle protein balance is negative without nutritional intervention. Consuming protein after training has [been shown](#) to shift muscle protein balance from a negative to a positive state.

Several [meta-analyses](#) and [systematic reviews](#) have [reported](#) that protein supplementation leads to increased muscle mass and strength. The [largest meta-analysis](#) to date was conducted in 2012 and included 22 randomized controlled trials. It reported that protein supplementation significantly enhanced muscle mass and strength in both young and older adults. However, a recent [systematic review](#) has challenged this conclusion, arguing that the effect of protein supplementation on muscle mass and strength is inconsistent and any benefit is minor, at best. This review was not a meta-analysis though, meaning that there are about five years of data that have not been evaluated quantitatively.

The study under review is a meta-analysis investigating the impact of protein supplementation on several important resistance training outcomes, including muscle mass and strength. It contains more than double the number of studies included in the previous meta-anal-

ysis from 2012, including studies published in the last five years that the other meta-analysis did not include.

Skeletal muscle plays an important role in health and resistance training, the go-to method for increased muscle mass and strength. The benefit of protein supplementation for enhancing resistance training-induced adaptations, while supported previously, has recently been questioned. The study under review is an updated meta-analysis investigating the effect of protein supplementation on muscle mass and strength.

Who and what was studied?

This meta-analysis included randomized controlled trials up to January 2017 comparing resistance training plus protein supplementation to resistance training without protein supplementation. Studies had to involve healthy adults that were not on an energy-restricted diet, supply the protein alone and not in combination other supplements that could influence muscle mass or strength (e.g., creatine), include resistance training at least twice per week, and have a duration of at least six weeks.

The primary outcomes were grouped into two different categories: performance improvements and changes in body composition. There were two different performance measurements explored: differences between groups in one-repetition-maximum strength (1RM) on any strength test, or maximum voluntary contraction (MVC) for any muscle group. Four body composition measurements were also examined: bodyweight as fat-free mass (FFM) and fat mass measured by DXA, underwater weighing or BodPod, muscle fiber cross-sectional area (CSA) obtained from the vastus lateralis or latissimus dorsi, and mid-femur whole muscle CSA measured by MRI or CT scan. Sub-group analysis was performed for training status (trained versus untrained) and age (younger than 45 years versus older than 45 years).

A meta-regression was used to investigate the influence of potential confounding variables that would lead to heterogeneity in the primary meta-analysis. These variables were determined in advance and included baseline protein intake (grams per kilogram of body-weight per day), post-exercise protein dose (grams), participant age, and training status. Many variables were also identified after the initial analysis and explored as other potential sources of variance.

A break-point analysis was performed on the change in FFM plotted against total daily and baseline protein intake from all comparisons that had available data. The goal was to answer the question: is there a protein intake beyond which protein supplementation no longer provides additional benefit for increasing muscle mass?

Ultimately, 49 studies from 17 countries were included in this meta-analysis and provided 58 comparisons for the body composition outcomes (bodyweight, FFM, fat mass, CSA, and mid-femur CSA) and 66 comparisons for the performance outcomes (1RM and MVC). When studies had more than one protein-supplemented group (e.g., whey and soy) or more than one measure of an outcome (e.g., squat and bench press 1RM), the average change was combined for the primary analysis.

Due to the expected variation in participant characteristics and supplement intervention, a random effects analysis was used. Each study was evaluated for risk of bias using the Cochrane Collaboration's domain-based criteria. The primary meta-analysis was restricted to studies with less than three (out of six) high or unclear risk domains. Nine studies were excluded, primarily due to a failure to blind the participants and study investigators, a failure to blind participants from the outcome of interest, and reported conflicts of interest.

The 49 studies contributed a total of 1,863 participants. There were 10 studies in resistance-trained participants

and 14 studies using exclusively females. The interventions lasted six to 52 weeks (average of 13), involved training two to five days per week (average of three), used one to 14 exercises per session (average of seven), used one to 12 sets per exercise (average of four) and used three to 25 repetitions per set (average of nine).

The protein supplement dose ranged from four to 106 grams per day (average of 36 grams), with 40 studies having participants consume five to 44 grams (average of 24 grams) immediately after training sessions. Whey protein was used in 23 studies, a protein blend in 13 studies, milk or milk protein in 10 studies, a whole-food protein in seven studies, soy protein in six studies, casein in three studies, and pea protein in one study.

Total daily protein intake increased by an average of 23 grams per day (range: -25 to 158 grams) in the protein supplemented group and did not change in the control group. Consequently, the protein group increased their relative protein intake from 1.4 to 1.8 grams per kilogram of bodyweight per day (g/kg/day), while the control group remained at 1.4 g/kg/day. Despite this difference in protein intake, there was no significant difference between the groups for total daily energy intake.

This meta-analysis included 49 studies and 1,863 participants comparing a protein supplemented group to a control group for changes in body composition outcomes (bodyweight, FFM, fat mass, muscle fiber CSA, and mid-femur CSA) and performance outcomes (1RM and MVC). None of the participants were on energy-restricted diets. Most studies were in untrained men supplementing with an average of 36 grams of protein per day, resulting in an increase in average daily protein intake from 1.4 g/kg at baseline to 1.8 g/kg during the intervention.

What were the findings?

The major findings from the meta-analysis are summarized in Figure 1. Protein supplementation led to significant increases in 1RM strength (+2.49 kg; 9%), FFM (+0.3 kg; 27%), muscle fiber CSA (+310 μm^2 ; 38%), and mid-femur CSA (+7.2 mm^2 ; 14%), and a significant decrease in fat mass (-0.4 kg), compared to the control group. There was no difference between the protein supplemented and control groups for changes in MVC or bodyweight. A sensitivity analysis including the nine studies at high risk of bias mentioned in the previous section found equivalent results, except that the inclusion of one study for muscle fiber CSA resulted in a non-significant increase (+153 μm^2).

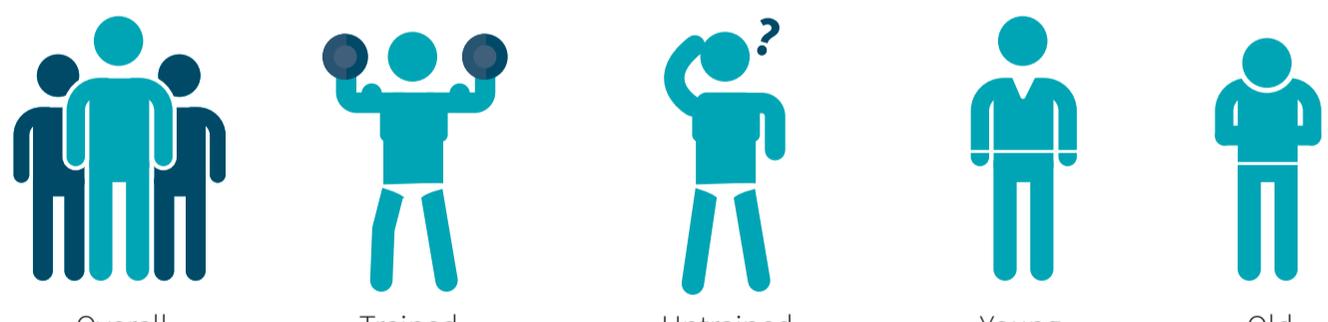
There was no significant relationship between changes in 1RM strength and baseline protein intake, post-exercise protein dose, age, or training status found by meta-regression. There were no statistically significant differences between improvements in trained versus untrained participants. However, looking at both groups individually compared to placebo, trained participants had a significant improvement in 1RM (+4.27

kg) while untrained participants didn't. Whole-body training sessions and unsupervised (versus supervised) sessions also correlated significantly with a greater increase in 1RM strength.

Increases in FFM were found to be significantly correlated with a higher baseline protein intake, a younger age, and more training experience in the meta-regression, but not with the post-exercise protein dose. Subgroup analyses suggested that the increase in FFM with protein supplementation was significantly greater in younger (+0.55 kg) and trained (+1.05 kg) participants compared to older (+0.06 kg) and untrained participants (+0.15 kg), respectively. Additionally, only younger and trained participants experienced a statistically significant benefit from protein supplementation, compared to the control group.

The breakpoint analysis for changes in FFM and total daily protein intake suggested that no further increase in FFM occurs when protein intake rises above 1.6 grams per kilogram of bodyweight per day. However, the 95% confidence interval ranged from 1.03 to 2.2 g/kg/day, suggesting a pretty wide margin of error for this estimate.

Figure 1: Effect of protein supplementation on strength and body composition



	Overall	Trained	Untrained	Young	Old
1RM Strength	+2.5 kg	+4.3 kg	+1.0 kg		
FFM	+0.3 kg	+1.05 kg	+0.15 kg	+0.55 kg	+0.06 kg
Fat Mass	-0.4 kg				
Muscle fiber CSA	+38%				

Significant and not significant vs control

When combined with resistance training, protein supplementation led to significantly greater increases in 1RM strength, fat-free mass, muscle fiber cross-sectional area, and mid-femur cross-sectional area without affecting MVC or bodyweight. Trained and younger populations experienced greater increases in FFM than untrained and older populations, respectively. There appeared to be no additional benefit towards increasing FFM when total daily protein intake was increased above approximately 1.6 g/kg/day, although this estimate had a lot of error, lying anywhere between 1.03 to 2.2 g/kg/day.

What does the study really tell us?

Performance outcomes

Protein supplementation led to a significant 2.49 kilogram (9%) increase in 1RM strength and had no significant effect on MVC strength compared to placebo, suggesting a small benefit from this widespread practice. The discrepancy between 1RM and MVC could be due to the type of measurement involved in each, with the former relying on dynamic contractions and the latter using primarily isometric contractions. Pragmatically, 1RM strength is a more useful metric because it is easily obtained by any individual performing resistance training.

Although there was no significant correlation between changes in 1RM and training status, this may be due to the sparse number of studies (four) that used trained participants. Considering that fat-free mass and muscle fiber CSA significantly increased with protein supplementation, and that there is a significant correlation between muscle mass and strength in [trained](#) but not [untrained](#) individuals, it is possible that a greater increase in strength would be seen in trained populations. However, more research is needed to verify this hypothesis.

Studies using whole-body training routines were associated with larger increases in strength than studies not employing this training method, and studies in which the training was supervised were associated with reduced strength than those without supervision. An explanation for these findings is not clear and warrants further investigation.

Finally, there is the question of whether a 9% increase in strength is worth supplementing protein. Considering how little effort consuming a protein shake after training is, the answer for many people may be “yes,” especially those involved in sports that require a strength component (e.g., powerlifting). Realistically, however, this meta-analysis suggests that performing a proper strength-oriented resistance training routine is far more influential since most covariates failed to explain the changes in 1RM strength in the meta-regression.

Body composition outcomes

Protein supplementation significantly increased FFM (+0.3 kg; 27%), muscle fiber CSA (+310 μm^2 ; 38%), and mid-femur CSA (+7.2 mm^2 ; 14%), and significantly decreased fat mass (-0.4 kg), compared to the control group, suggesting that protein supplementation is useful for maximizing muscle growth and facilitating optimal changes in body composition. Although FFM is not synonymous with muscle mass, the increase in muscle fiber CSA strongly supports the notion that protein supplementation promoted muscle growth, rather than simply affecting organ mass or water balance.

The increase in FFM was greater in trained (+1.05 kg) participants compared to untrained participants (+0.15 kg), which matches up nicely with the finding that changes in FFM were correlated with training status. Chronic resistance training appears to [dampen](#) growth-promoting signaling pathways in muscle tissue and [reduce levels](#) of muscle protein synthesis. As such, it is reasonable to speculate that protein supplementation may be more important in trained individuals to

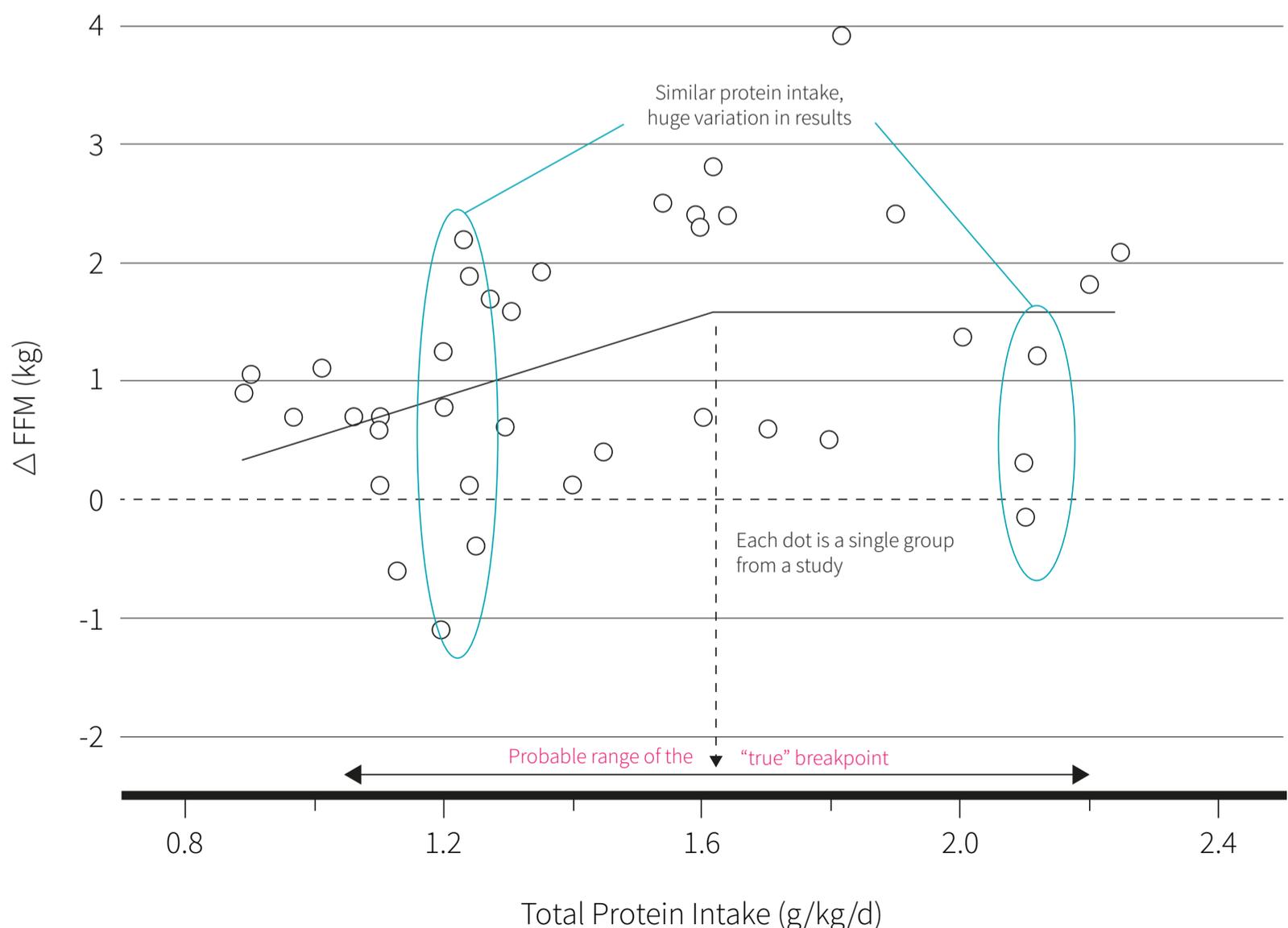
overcome this exercise-induced anabolic resistance to muscle protein synthesis.

The increase in FFM was also greater in younger (+0.55 kg) participants compared to older (+0.06 kg) participants. Older people suffer from “[anabolic resistance](#),” meaning that they [require more protein](#) to elicit the same growth-promoting response as younger people. The average daily protein dose in the older adult studies was about 20 grams per day, and only four of the 13 studies involving older adults had a baseline protein intake above 1.2 grams per kilogram of bodyweight, which is [considered a minimum](#) requirement when sedentary (see ERD #19, Volume 1, *How much protein does grandpa really need?* for a discussion of this research). The lack of a benefit of protein supplementation on FFM in older adults compared to placebo may be due to the overall low protein intake used in these studies. Future resistance-training and protein supple-

mentation research should use higher doses of protein to ensure that growth potential is maximized.

A novel finding of this meta-analysis is that people are likely to require anywhere between 1.0 to 2.2 grams of protein per kilogram of bodyweight per day to maximize changes in FFM with resistance training. This result was based on 42 data points from 723 young and old participants eating between 0.9 to 2.4 g/kg/day, and is depicted in Figure 2. This finding squares up nicely with the recommendations from several organizations, such as the [American College of Sports Medicine](#) and the [International Society of Sports Nutrition](#), who have recommended that physically active adults consume between 1.2-1.4 and 2.0 g/kg/day. It also supports the recent observation that [bodybuilders require](#) between 1.2 and 2.2 g/kg/day, which was discussed in ERD #29, Volume 1, *Should one gram per pound be the new RDA for bodybuilders?* Collectively, it seems prudent to

Figure 2: Breakpoint analysis for the optimal protein intake



recommend that resistance-training individuals aim to consume close to their bodyweight (in pounds) in grams of protein each day, at least in people who are relatively lean. So, someone who weighs 160 pounds should aim for 160 grams of protein.

Another notable finding is that the average baseline protein intake of the studies included in this meta-analysis was 1.4 g/kg/day, which is significantly higher than the [0.8 g/kg RDA](#) recommended by the U.S. and Canadian governments. Supplementing with an average of 35 grams of protein per day on top of this amount still resulted in further increases in FFM. It is becoming increasingly clear that the RDA is not sufficient for active individuals looking to maximize increases in muscle mass.

Limitations

Most of the studies included in the meta-analyses involved young participants with no resistance training experience. Although subgroup analyses did reveal some differences between these individuals and older and trained adults, the meta-regression grouped all of the studies together, which may have masked any notable relationships that exist in one population, compared to another. Additionally, this meta-analysis included only studies in which participants were at or above energy requirements, preventing conclusions from being drawn about the impact of protein supplementation on strength and body composition during periods of restricted dieting. Finally, the authors tested multiple

outcomes without correcting for multiple comparisons in their statistics, which increases the likelihood of finding a significant outcome by random chance. However, even after correcting for this ourselves, the key findings retained their statistical significance.

Protein supplementation significantly benefits resistance-training induced changes in 1RM strength and muscle mass. These effects are more pronounced in younger and trained individuals. People who are looking to maximize increases in muscle mass with training are likely to require an average of 1.6 g/kg of protein. More research is necessary to determine how protein supplementation influences these outcomes during times of energy restriction (i.e., dieting).

The big picture

The meta-analysis under review had broad inclusion criteria that allows for its results to be generalized to a large portion of the population. Although the increases in strength and muscle mass were modest, drinking a protein shake after training is low-hanging fruit. Pragmatically, it makes sense to do it if maximizing training adaptations is the goal, especially among people who are not otherwise tracking their food intake and macros.

This meta-analysis also sets the stage for many future studies. The meta-regression correlations are obser-

“ It is becoming increasingly clear that the RDA is not sufficient for active individuals looking to maximize increases in muscle mass. ”

vational and can be considered hypothesis-generating. Although few significant correlations were observed, they serve to be the basis of questions that future research can study directly. For example, why did so few variables correlate with strength and FFM? Are there situations in which these variables do have a noteworthy influence?

Another question that remains is why these findings contrast with a [recent systematic review](#) suggesting that protein supplementation is unnecessary. The discrepancy may be explained by the fact that the systematic review was not quantitative and relied on the two authors' qualitative evaluation of the studies they referenced.

The current meta-analysis is the largest to date with broader inclusion criteria that suggests multiple populations would benefit from protein supplementation. This meta-analysis also found several correlations that can be investigated directly with future controlled trials.

Frequently asked questions

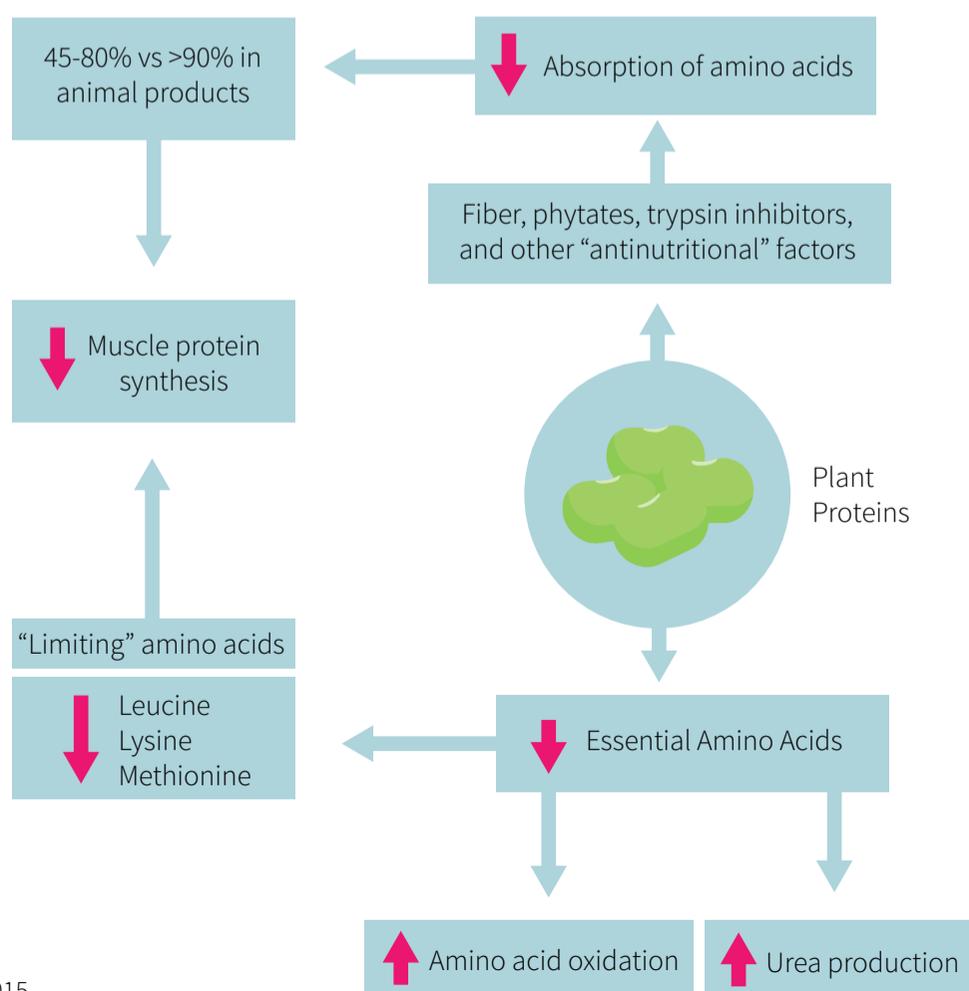
Does it matter what type of protein is used?

Probably not. One of the correlational analyses used in this meta-analysis looked at the impact of whey versus soy protein on changes in 1RM strength and FFM and found no significant difference between the two. Unfortunately, other sources of protein such as whole foods, blends, and milk protein were not investigated. Still, in the grand scheme of things, ensuring adequate protein consumption is [probably more important](#) than where the protein comes from, as least when discussing relatively high-quality sources and not whole-food proteins from plants, which have a notably [lower anabolic potential](#) for reasons depicted in Figure 3.

How much protein should be eaten per meal?

A recent [breakpoint analysis](#) suggested that maximal stimulation of muscle protein synthesis requires about 0.24 grams per kilogram of bodyweight (0.25 g/kg FFM) in young adults and 0.4 g/kg (0.6 g/kg FFM) in older adults (averaging 71 years). This amount per meal

Figure 3: Some problems with whole-food plant proteins



Reference: van Vilet et al. J Nutr. 2015

should be considered a minimum, especially considering that there are only so many meals in a day and our total daily protein intake is likely to be higher than the sum of these values. For example, a 165 pound (75 kilogram) athlete aiming to consume 165 grams of protein per day would only need to eat a minimum of about 20 grams of protein per meal to maximize muscle protein synthesis. Eating eight times per day to hit a protein quota is going to be rather inconvenient for most people. Plus, there is no convincing evidence that it would be superior for building muscle mass or strength compared to eating less frequently.

What should I know?

The study under review is the largest meta-analysis to date investigating the effect of protein supplementation on muscle mass and strength. This meta-analysis included 49 studies and 1,863 participants comparing a protein supplemented group to a control group for changes in body composition outcomes (bodyweight, FFM, fat mass, muscle fiber CSA, and mid-femur CSA) and performance

outcomes (1RM and MVC). None of the participants were energy restricted. Most studies were in untrained men supplementing with an average of 36 grams of protein per day, resulting in an increase in average daily protein intake from 1.4 grams per kilogram at baseline to 1.8 grams per kilogram during the intervention.

Protein supplementation led to significantly greater increases in 1RM strength, fat-free mass, muscle fiber cross-sectional area, and mid-femur cross-sectional area without affecting MVC or bodyweight. Trained populations experienced greater increases in FFM than untrained populations and younger people experienced greater increases in FFM than older people. People who are looking to maximize increases in muscle mass with training are likely to require between 1.0 and 2.2 grams of protein per kilogram of bodyweight per day. Other research is necessary to determine how protein supplementation influences these outcomes during times of energy restriction (i.e., dieting). ♦

Supplement your knowledge of protein supplementation in the [ERD Facebook forum!](#)

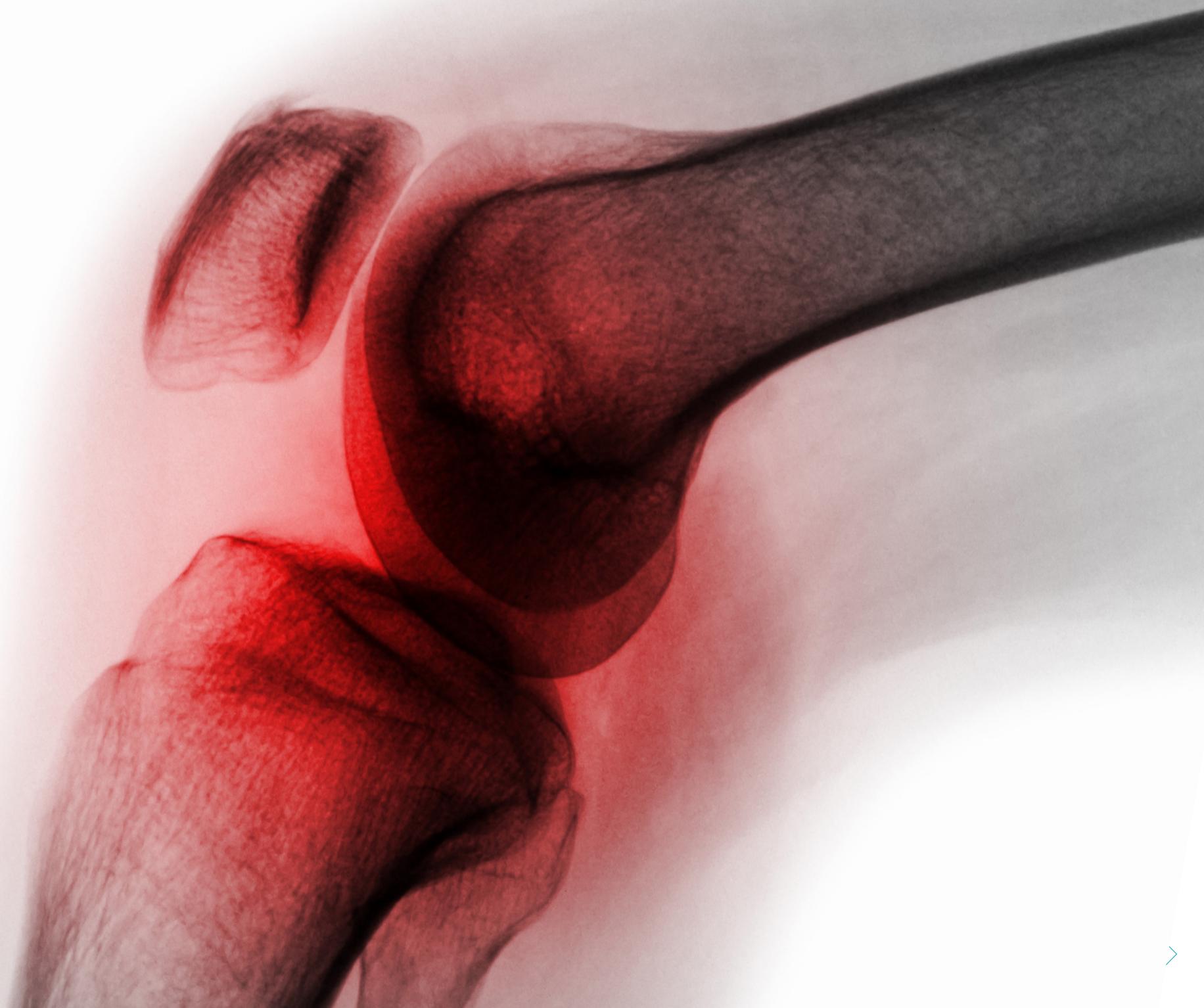
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A progress report on supplements for osteoarthritis

*Dietary supplements for treating
osteoarthritis: a systematic review and
meta-analysis* 



Introduction

Osteoarthritis is a [degenerative joint disease](#) resulting in pain, stiffness, and swelling. It most commonly affects the knees, hips, and hands, and is frequently characterized by damage to cartilage. An [estimated](#) 12% of the U.S. population, particularly the elderly, have osteoarthritis, and hip and knee osteoarthritis are the [11th](#) leading cause of disability worldwide. In addition, the [economic burden](#) of osteoarthritis is estimated to be 0.25% to 0.50% of a country's GDP (the annual market value of all goods and services within the country). Osteoarthritis is a disease that needs attention and researchers should be encouraged to investigate options for its prevention and treatment.

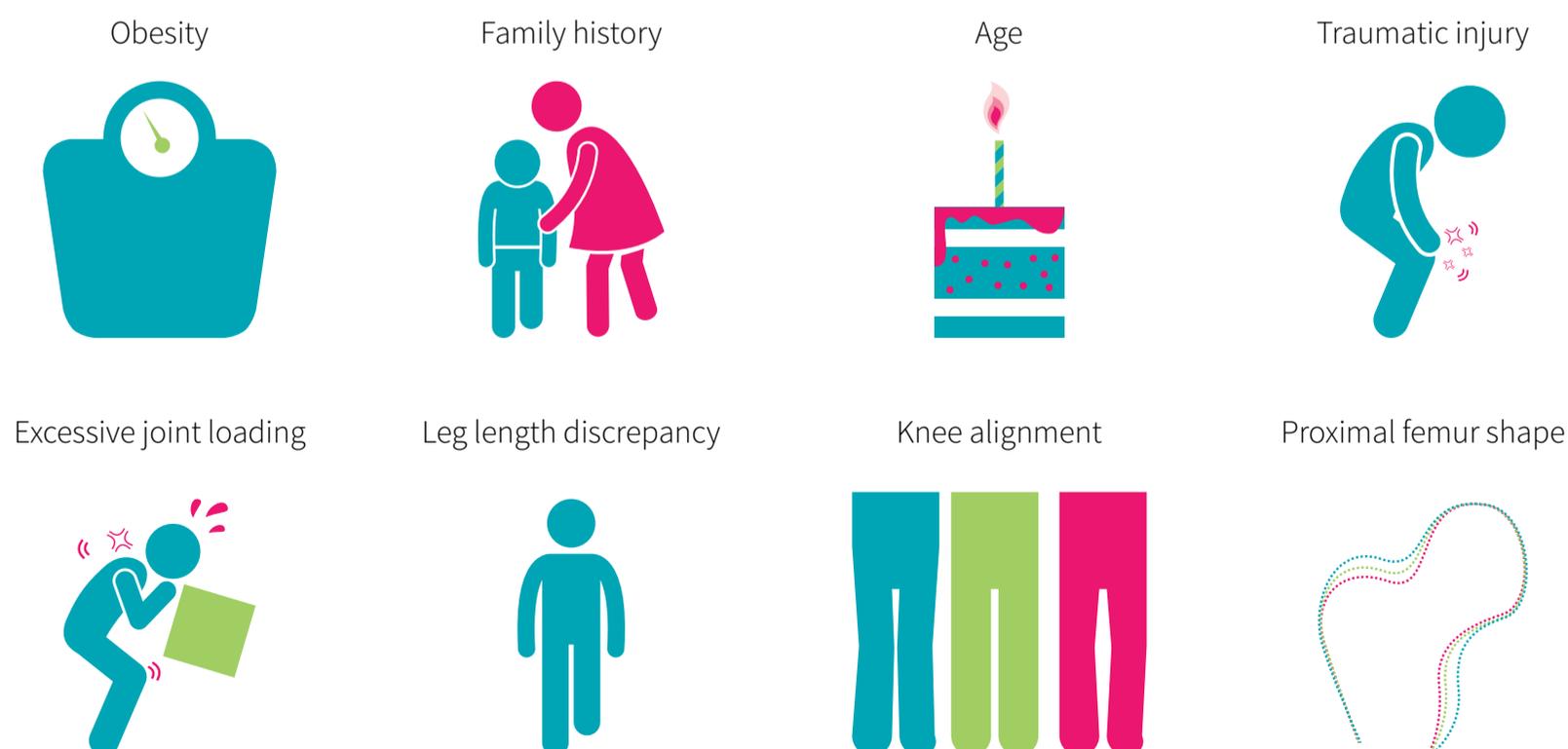
Distinct [risk factors](#) for osteoarthritis, summarized in Figure 1, include genetic susceptibility, morphological variations in bones and joints, traumatic joint injury, excessive joint stress, aging, and obesity. [Obesity](#) is a major risk factor for osteoarthritis of the knee, and [weight loss](#) can lead to improvements in the condition, though more long-term studies are warranted. [Exercise](#) can be [useful](#) for reducing pain and improving joint

function, though exercising with sore joints can be difficult, and not all forms of exercise are suitable for every [patient](#). Pharmaceutically, treatment mostly revolves around the use of non-steroidal anti-inflammatories ([NSAIDs](#)). While effective in reducing pain, these [drugs](#) aren't without their [risks](#), which include stroke and heart attacks.

Supplements are a popular drug alternative among people with osteoarthritis. Supplements for joint health can be loosely placed in two overlapping categories: structural and repair, which are intended to provide building blocks of joint tissue and facilitate its reconstruction, and anti-inflammatory agents, which reduce pain and may help prevent the [deterioration](#) of cartilage.

Glucosamine and chondroitin are the best known and most used supplements for osteoarthritis. They are currently the only supplement [endorsed](#) by the Osteoarthritis Research International group, and are used by 54-59% of people with osteoarthritis who decide to take supplements. However, a quick walk into any supplement store will reveal many other products marketed under the guise of joint health. The study

Figure 1: Osteoarthritis risk factors



Reference: Allen, K, Golightly, Y. Curr Opin Rheumatol. 2015 May

under review is a systematic review and meta-analysis of randomized controlled trials involving several joint supplements, so as to provide a broad and updated picture of which compounds may benefit joint health.

Osteoarthritis is a common degenerative disease of the joints. Many people with osteoarthritis resort to using supplements to help alleviate joint pain and stiffness, but both the efficacy and safety of popular supplements remains controversial. The study under review is a systematic review and meta-analysis aimed at clarifying the present state of the evidence for various joint supplements.

Who and what was studied?

The study was a systematic review and meta-analysis of randomized, placebo-controlled trials involving participants with hand, hip, or knee osteoarthritis. The studies could report on any supplemental intervention, but those using combination products or herbal supplements were excluded. Additionally, all studies needed to last at least two weeks.

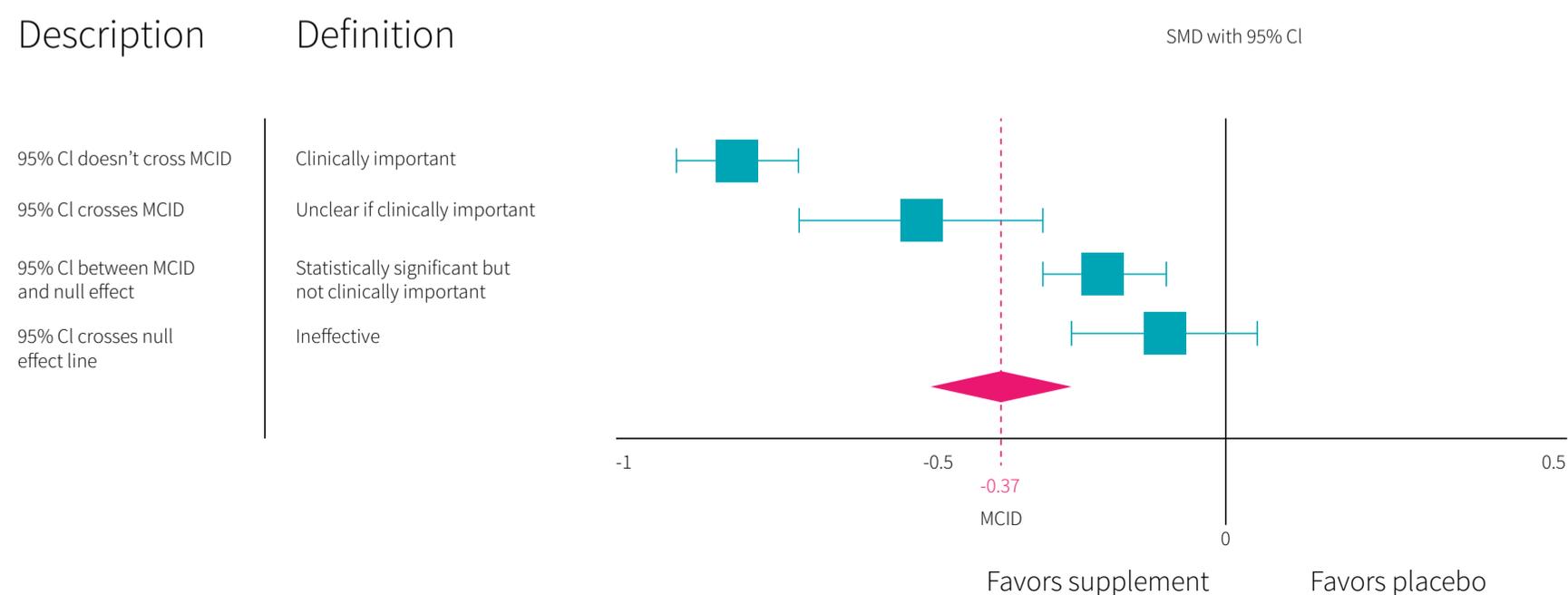
The study protocol was [preregistered](#) with four primary outcomes: pain, physical function, use of analgesics, and

quality of life. Secondary outcomes included changes to joint space width and adverse events. However, the authors reclassified the use of analgesics and quality of life outcomes as secondary during study publication. They also added joint stiffness as a secondary outcome. There were no corrections for multiple comparisons.

Outcomes were assessed with a random-effects model. A clinically meaningful difference between the supplement and placebo groups was predefined as an effect size greater than 0.37 standardized units. The idea of a minimal clinically meaningful difference is illustrated in Figure 2. This is an important concept, because a supplement can have a statistically significant effect that is meaningless in real life.

Ultimately, 63 studies involving 10,265 participants were included for analysis. A total of 19 different supplements were investigated, with eight having only one study each and nine having a mere two to six studies apiece. The remaining two supplements were glucosamine with 18 studies and chondroitin with 14 studies. Most studies (86%) involved participants with knee osteoarthritis and an average age of 48-69 years. Study length ranged from two weeks to three years, with 64% of studies reporting on short-term effects (shorter than or equal to three months), 25% on medium-term

Figure 2: Minimal clinically important difference and other definitions



effects (four to six months), and 25% on long-term effects (longer than six months).

Study risk of bias was assessed via the Cochrane Collaboration's tool. Only seven of the 63 included trials (10%) were judged at low risk of bias, whereas 29 (46%) were judged at high risk and 28 (44%) at an unclear risk. The most common source of bias was in the "other" domain, as 40 of the 63 included trials (63.5%) were funded by industry. Moreover, 25 of the 40 manufacturer-funded trials (62.5%) were judged at high risk of bias due to conflicts of interest (e.g., employees were authors or companies played an important role in conducting the trial).

This was a systematic review and meta-analysis of 63 randomized controlled trials investigating the effects of 19 different supplements on joint pain and physical function in people with osteoarthritis. Joint stiffness, quality of life, adverse events, changes to joint space width, and use of analgesics were evaluated as secondary outcomes. Most supplements had only one to six studies investigating their use and reported on short-term effects (shorter than six months).

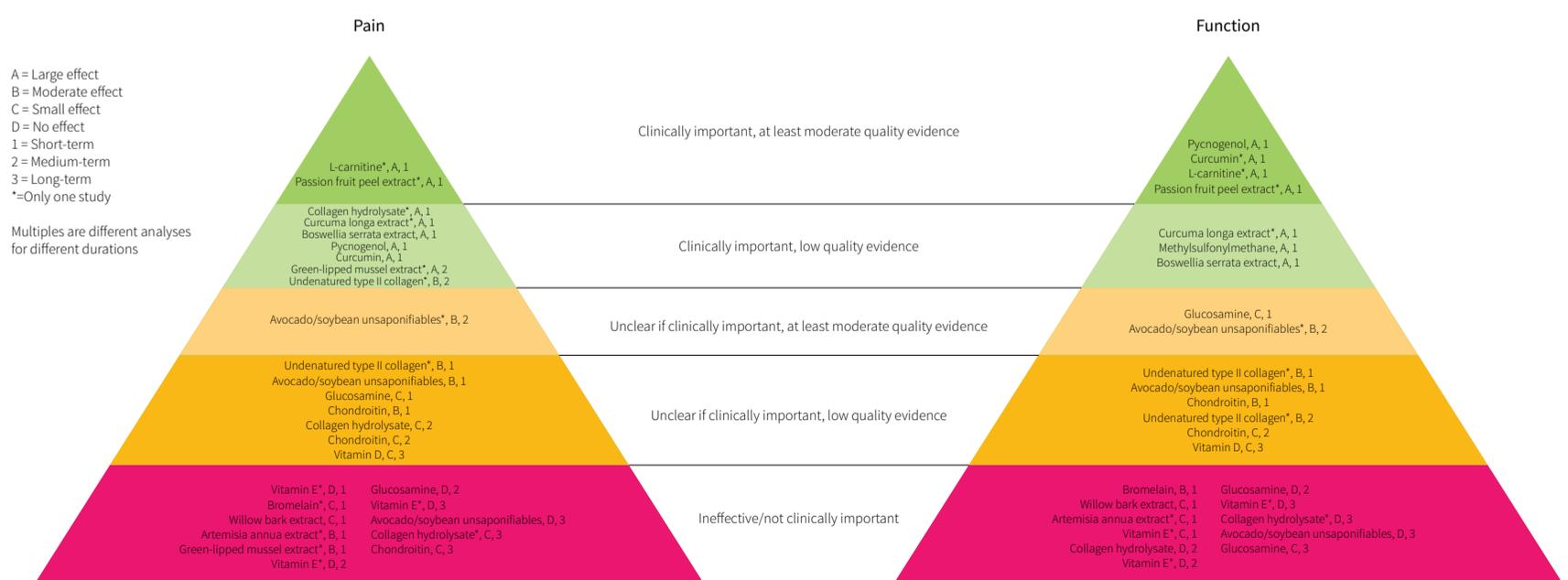
What were the findings?

The effect size classifications and quality of evidence from GRADE for pain and physical function in the short, medium, and long-term are shown in Figure 3. Nine supplements for pain and seven for function were found to be clinically meaningful, largely from short-term studies and based on very few studies. *Boswellia serrata* was the most extensively studied clinically meaningful supplement, with three trials and a total of 186 participants for both pain and function.

Subgroup analyses were performed only for short-term glucosamine and chondroitin trials due to the large number of studies for each. For glucosamine, improvements in pain were significantly greater in trials that were judged to be at a higher risk of bias for selective and incomplete outcome reporting, as well as among industry-funded studies and studies with smaller sample sizes (less than 50 vs. more than 50 people). Similar observations were made for chondroitin.

Only 29 studies involving 11 supplements reported on adverse events, including bromelain, artemisia annua extract, chondroitin, methylsulfonylmethane, avocado/soybean unsaponifiables, vitamin D, collagen hydrolysate, *Curcuma longa* (aka turmeric) extract, glucosamine,

Figure 3: Results for pain and function



Boswellia serrata extract and willow bark extract. None reported significant differences from placebo.

Only *Boswellia serrata* had a clinically meaningful effect on joint stiffness in the short-term, with no supplements having an effect over a longer time frame. Only *Curcuma longa* had a clinically meaningful impact on analgesic use. No supplements had a clinically meaningful effect on structural changes within the afflicted joints or quality of life.

There were nine supplements that were regarded as clinically meaningful for pain and seven for function, mostly in the short term. Quality of evidence and risk of bias were common issues that limit confidence in these findings. *Boswellia serrata* was the only supplement that had a clinically meaningful effect on stiffness, and only *Curcuma longa* extract was clinically meaningful for analgesic use. No supplements had a clinically meaningful effect on structural changes or quality of life. Of the supplements evaluated for adverse effects, all had good safety profiles.

What does this study really tell us?

The results of the meta-analysis suggest that most supplements for osteoarthritis, as single treatments, have insufficient evidence to tell if they're useful or not, especially over periods spanning more than several months. Not only are there few randomized controlled trials for most of the supplements, but the studies tend to carry a considerable risk for bias, most notably through conflicts of interest and study funding.

Glucosamine and chondroitin, the only supplements that have been studied in large numbers of trials for pain and physical function, exhibit small effect sizes and the quality of evidence is low. Some supplements, such as *Boswellia serrata* extract, curcumin, and pyc-

nogenol, look promising due to the large effect sizes for reducing pain and improving physical function. However, they were predominantly funded by industry interests and are therefore at a potentially higher risk for [bias](#). The subgroup analyses for both glucosamine and chondroitin showed significantly greater effect sizes among studies with conflicts on interest compared to those without, and there is no reason to think this would not also apply to the other supplements tested.

It's worth addressing the threshold for "clinically important" effects, which was derived from the average difference at which participants believed that their condition had improved at least slightly in previous [studies](#) evaluating pain, physical function, and overall well-being. From this, it's apparent that the threshold pertains more to the primary outcomes, pain and physical function, rather than the secondary outcomes.

The importance of this seemingly minor detail is apparent when looking at the effects of supplements on joint structure. For instance, structural deterioration may not [correlate](#) well enough with pain severity to be a good surrogate. This may be relevant for the long-term effects of chondroitin on structure, which didn't reach "clinically important" status, but might still be clinically meaningful. Future research specific to structure is needed to discern the effect size that can be rightfully regarded as being clinically important.

At the time of [registration](#), there were four primary outcomes declared: pain, function, use of analgesics, and quality of life. In the paper, this was reduced to pain and function. This isn't standard procedure and may be a cause for concern, but practically, it would be more concerning if primary outcomes were added instead of taken away, since that may be a stronger indication of crafting the analysis to look more positive. Furthermore, the outcomes that remained primary are of clinical significance. So, while changing the primary outcomes is of concern, in this specific case the concern is milder than it could have been.

Most of the supplements included in the meta-analysis had too few studies to perform meaningful subgroup analyses on many of the usual areas of interest, such as disease severity, dose, and demographics. In the case of [glucosamine](#), data from trials isn't frequently available. Accordingly, it's not possible to rule out potential benefits of supplements for different doses and for certain types of people. Also, the meta-analysis largely applies to knee osteoarthritis and hip osteoarthritis; there was very little research on hand arthritis, so extrapolation should be done cautiously. Some research suggests differences between knee and hip osteoarthritis in the capacity for [repair](#), which may mean that the efficacy of supplements for osteoarthritis could vary by which joint is affected, and research looking only at the efficacy of supplementation at one joint may not be safely extrapolated to other joints.

Another limitation was the duration of many of the studies that looked at adverse effects. Many supplements, while showing no signs of an increased risk, only had evidence in the short term. These were: curcumin, *Artemisia annua* extract, *Boswellia serrata* extract, *Curcuma longa* extract, willow bark extract, bromelain, MSM, and pycnogenol. It's possible that it could take longer than four months to observe the side effects from some supplements, and longer studies would allow for greater confidence in their safety.

Often overlooked, and with the potential to confound the findings, is the reduction of painkiller use in active treatment groups. While the effect of supplements on habitual painkiller use is valuable information to have, if one group uses fewer painkillers than the other, this may skew the comparison to the placebo group, who will be managing their pain more with painkillers. Glucosamine, avocado/soybean unsaponifiables, pycnogenol, and *Curcuma longa* extract had some evidence for reductions in painkiller use, and many of the studies on these and other supplements didn't take this confounding into account. Future studies which account for this could improve their accuracy.

A strength of this study, the exclusion of studies that used multiple-nutrient combinations, is also a limitation when it comes to judging the ultimate usefulness of supplements. The study didn't comment on possible synergies between supplements or rule out the possibility of multiple supplements with small effects adding up to a large effect that would be clinically important.

Conclusions derived from the present study were limited by the number and quality of the studies that were reviewed, which didn't provide strong evidence for any supplement for osteoarthritis. Considering the paucity of trials and high risks of bias for many of the supplements that were investigated, further research is necessary, especially studies that would allow for more detailed subgroup analyses on different variables and account for use of analgesics. We can conclude that there isn't solid evidence for meaningful benefits from any studied supplement for osteoarthritis, but not that there aren't effective supplements or combinations in various contexts.

The big picture

Chondroitin and glucosamine are by far the most studied and most popular supplements for osteoarthritis, and they're often thought of together. [In vitro and animal research](#) suggests that glucosamine and chondroitin do have a positive influence on the processes underlying osteoarthritis. They stimulate the production of the extracellular matrix of cartilage, counteract inflammatory activity, and inhibit degeneration of cartilage. The question is: how relevant is this to people with osteoarthritis, and are there cases where they will experience clinically important benefits? The results of the present study aren't encouraging, and neither is a recent [review](#), which came to a similar conclusion to the present study about glucosamine and chondroitin individually, though they could still be valuable for osteoarthritis sufferers when used in tandem or in addition to other supplements.

For the combination of glucosamine and chondroitin, a network meta-analysis that compared combination [trials](#) to either supplement individually or to placebo found greater reductions in pain and improvements in physical function for the combination. However, the difference compared with the supplements individually wasn't statistically significant, and there's good reason to be skeptical of the evidence quality. The combination did demonstrate a statistically significant improvement compared with placebo, which may be clinically important, though a more recent [study](#) failed to find superior efficacy of the combination, compared to placebo.

There's [some evidence](#) from trials that when methylsulfonylmethane is taken with glucosamine or the combination of glucosamine and chondroitin, the effects on pain and physical function are greater than for the other supplements alone, though this is also very preliminary and requires more study. More research on combinations that uses methodologically sound trial design is warranted.

At this point, given the lack of strong evidence found in the present study, it's important to acknowledge that supplements aren't the only nutritional factor that could be relevant in osteoarthritis. Changes in diet have the poten-

tial to reduce [inflammation](#) and [oxidative stress](#), and this may be relevant to osteoarthritis. One [study](#) observed a significant reduction in pain and improvement in well-being in a group randomized to follow a whole food diet compared to a group that continued eating normally, but this may be due to concurrent weight loss. Another [study](#) found that adherence to a Mediterranean diet was associated with an improvement in symptoms and quality of life in people with osteoarthritis.

One potentially important diet-related factor in osteoarthritis is fiber. [Lipopolysaccharides](#) are components of the outer membranes of Gram-negative bacteria and provoke an inflammatory response once translocated from the intestines into the bloodstream, which may have implications for osteoarthritis. [Fiber](#) can prevent the absorption of lipopolysaccharides through its fermentation to [short-chain fatty acids](#) which regulate intestinal tight junctions that act as a barrier between the GI tract and the rest of the body, and regulate the immune response. An inverse association between [fiber intake](#) and osteoarthritis risk has also been found in observational studies. The impact of a high intake of dietary fiber and the use of fiber supplements may be a new and fruitful area of inquiry.

“[...] supplements aren't the only nutritional factor that could be relevant in osteoarthritis. Changes in diet have the potential to reduce inflammation and oxidative stress, and this may be relevant to osteoarthritis.”

The same goes for other agents that lower systemic inflammation. The [microbiome](#) and its impact on inflammation may be a notable factor in osteoarthritis, and an [RCT](#) published just days later than the present meta-analysis found that the group taking the probiotic strain *Lactobacillus casei* Shirota experienced a significant improvement in pain, function and inflammation compared with the placebo group. Another supplement which may provide some benefit is [calcium fructoborate](#), a form of boron which has shown potent reductions in circulating inflammatory cytokines associated with osteoarthritis in a handful of small trials, and in [osteoarthritis](#) patients. Although its impact on osteoarthritis-specific endpoints has yet to be studied in humans, at least one study in [dogs](#) suggests an improvement in physical function. The future of supplements for osteoarthritis may be bright after all, but how bright it will be is yet to be seen.

While the present meta-analysis didn't find strong evidence for any of the tested supplements, combinations of supplements could theoretically add up to larger effects than the supplements individually, but more research is needed. Other reviews and meta-analyses come to similar conclusions about the present study for glucosamine and chondroitin individually. While evidence suggests that they probably do have some effect, they may not be very meaningful by themselves for the average person suffering from osteoarthritis. New research into plausible supplements for osteoarthritis and beneficial dietary changes beyond weight loss may add to the arsenal for tackling the disease.

Frequently asked questions

What about essential nutrients? Barely any of the supplements in this meta-analysis were essential.

It's plausible that some of the essential nutrients would be relevant to osteoarthritis, but evidence is sparse.

As already mentioned, boron may be overlooked and potent, though osteoarthritis-specific evidence is needed. [Vitamin K](#) is also plausible, but not well-studied. It would be beneficial to see studies of common nutrient deficiencies in osteoarthritis and more trials on plausible supplements in the future, though there isn't very much information at present.

I peeked at the study, and your reporting of the number of participants and studies included in this meta-analysis doesn't match what's in the paper. What's up with that?

That's because we excluded mentions of diacerein, which is a drug, but was included in the meta-analysis. Instead, we focused only on clear nutritional supplements in our review. Don't sweat it, though; diacerein didn't perform particularly well in terms of efficacy. More importantly, it was the only compound included in the meta-analysis that had clear safety concerns. This jibes with the European Medicines Agency's [view on the matter](#); they hold that the risks of diacerein outweigh its benefits for treating osteoarthritis.

What should I know?

Osteoarthritis affects a large number of people worldwide and supplementation is prevalent among osteoarthritis sufferers. Supplementation with various components of cartilage and anti-inflammatory nutrients and phytochemicals seems like a plausible way to reduce pain, improve function, and prevent deterioration, but evidence has been equivocal on the most well-researched supplements, glucosamine and chondroitin.

The study under review is a meta-analysis and systematic review of 19 different supplements for treating osteoarthritis. Pain and physical function were the primary outcomes, and quality of life, joint space width and narrowing, use of analgesics, adverse effects, and stiffness were the secondary outcomes. Some supplements, such as curcumin, *Boswellia serrata* extract and pycnogenol exhibited large effect sizes for pain and physical function but with poor quality evidence

and a significant risk of bias in research. Some supplements had many trials, but effect sizes were small and evidence quality was poor and with a considerable risk for bias. The meta-analysis doesn't rule out a role

of supplements in osteoarthritis, but does suggest that researchers have their work cut out for them in the future. ♦

How do you interpret this evidence? And what are your views on possibly effective supplement combinations, which this study didn't cover? Have your say over at the private [ERD Facebook forum](#).

**Want to hear
commentary
on this issue?**

Listen to our editor in chief Gregory Lopez facilitate a roundtable discussion about these six studies with our reviewers Dr. Adel Moussa and Dr. Stephan Guyenet, and Examine.com researcher and writer Michael Hull.

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Will eating breakfast keep you lean?

*Effect of breakfast on weight and energy
intake: systematic review and meta-analysis
of randomised controlled trials* 📌



Background

Breakfast, defined as the first meal in the morning after an overnight fast, has a healthy reputation in the popular opinion. Claims about its importance for a healthy lifestyle, ranging from weight control to chronic disease risk reduction, are widespread and come from several sources, including official authorities from different countries, including the [U.K.](#), the [U.S.](#) and [Australia](#). Recommendations from the aforementioned organizations highlight the importance of breakfast consumption for weight loss. Conversely, in some, skipping breakfast is [explicitly discouraged](#). Breakfast skipping has also been proposed to be a risk factor for developing [heart disease](#), [type 2 diabetes](#), and even increasing [all-cause mortality](#).

However, most claims about the positive effects of breakfast consumption on weight loss have been derived from [observational evidence](#) that has found a correlation between breakfast eating and lower weight gain or risk of obesity. Conversely, recent randomized controlled trials (RCTs) [have found no effect](#) of consuming breakfast on weight loss, arguing against an effect of this meal on weight control.

Because of the discordance between individual RCTs and observational evidence, the current systematic review and meta-analysis sought to examine data from available RCTs that evaluated the impact of breakfast eating on bodyweight and daily energy intake.

Breakfast consumption has been advocated as an important strategy for weight loss. However, this idea has been supported primarily by observational evidence, with discordant findings among RCTs. The current meta-analysis examined results from RCTs that tested the effects of breakfast consumption on bodyweight and energy intake.

Who and what was studied?

The current systematic review and meta-analysis was conducted according to the [PRISMA](#) statement and registered with [PROSPERO](#).

The authors searched for RCTs comparing the effects of consuming breakfast with that of skipping breakfast on energy intake (measured or self-reported) and/or bodyweight. These were the two primary outcomes. Studies involving children or adolescents, populations with conditions other than obesity (e.g., type 2 diabetes), or populations in low-income countries were excluded.

Ultimately, 13 RCTs were included in the systematic review, of which seven examined the relationship between breakfast and bodyweight (n = 486), and 10 analyzed the effect of breakfast consumption on 24-hour energy intake (n = 930). Six studies each were conducted in the U.S. and U.K., with the remaining study contributed by Japanese researchers. Five trials involved only overweight and obese participants, while the remainder included people with any BMI.

Studies evaluating bodyweight lasted two to 16 weeks (average of seven weeks), and those reporting on energy intake ranged from eight hours to six weeks (average of two weeks). Weight and energy intake were measured objectively in most studies (n=11), but only six studies directly monitored breakfast consumption in a research lab—the remainder used food logs and recall methods with participants eating at home.

Every study was deemed at high risk of bias, with the main issues being a lack of participant, researcher, and outcome assessor blinding, as well as unclear risks for random sequence generation and allocation concealment.

This meta-analysis investigated how breakfast consumption affected bodyweight (seven studies) and daily energy intake (10 studies) when compared to breakfast skipping (13 studies total). Studies involved mostly overweight and obese participants living in high-income countries.

What were the findings?

Overall, breakfast skipping resulted in a significantly lower bodyweight (-0.44 kilograms, or -0.97 pounds) compared to breakfast eating over an average of about seven weeks. These results weren't affected by the duration of trials or BMI.

Consistent with the results on weight loss, breakfast consumption resulted in a statistically significant increase in total daily energy intake (+260 kcal) compared to skipping breakfast. Excluding the single study with only obese participants did not meaningfully affect the outcome.

The main results are depicted in Figure 1.

Breakfast skipping led to lower daily energy intake and lower bodyweight compared to eating breakfast.

What does the study really tell us?

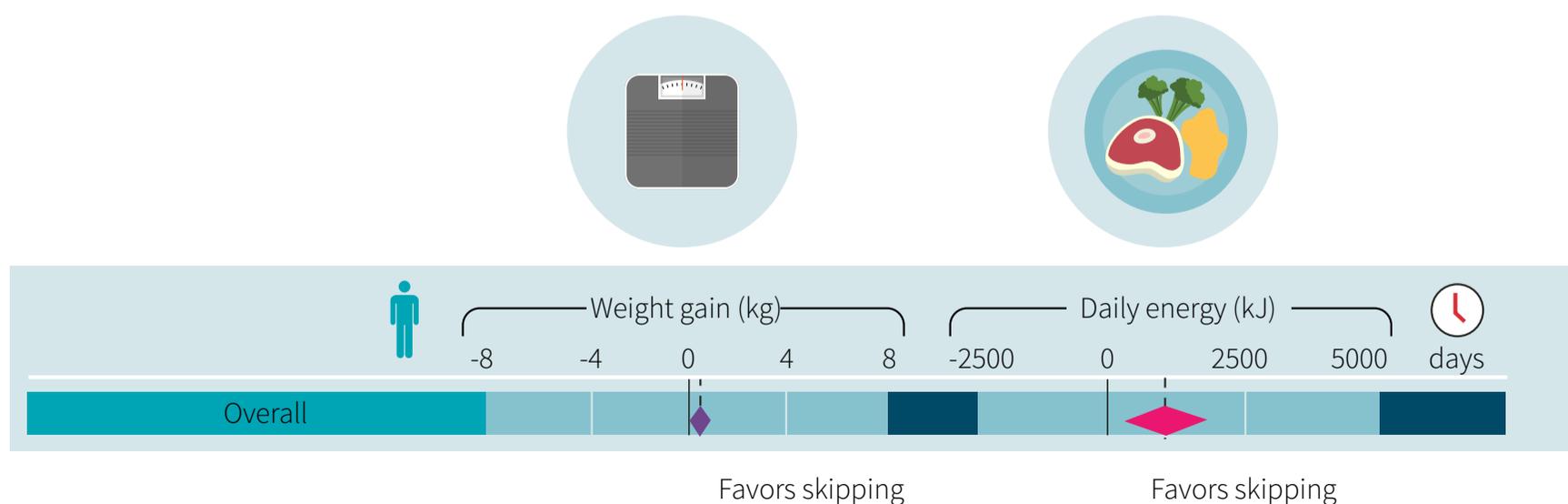
The current meta-analysis suggests that breakfast consumption increases total daily energy intake and bodyweight compared with breakfast omission. The extra calories consumed at breakfast do not appear to be fully compensated for later in the day.

These results go against what has been regularly promoted by many official nutritional guidelines, which encourage eating breakfast as one of the key strategies to maintaining a healthy weight. This recommendation is based primarily on observational data showing an association between breakfast consumption and lower weight and fat mass.

However, [this association is confounded](#) greatly by other habits of people who regularly eat breakfast, such as being more physically active, drinking less alcohol, and not smoking as much. Data from successful long-term weight loss maintainers, depicted in Figure 2, [has shown](#) that 78% eat breakfast daily, and that 90% eat breakfast at least four times per week. Yet, there were no differences between breakfast eaters and skippers for the degree of weight loss or duration of weight loss maintenance.

Overall, it is likely that breakfast is commonly part of a healthy lifestyle that promotes weight loss or the main-

Figure 1: Main results from the meta-analysis



tenance of a normal BMI, but it isn't the cause of either. When the effect of breakfast is directly tested (as in this meta-analysis), no positive effect on weight loss is seen.

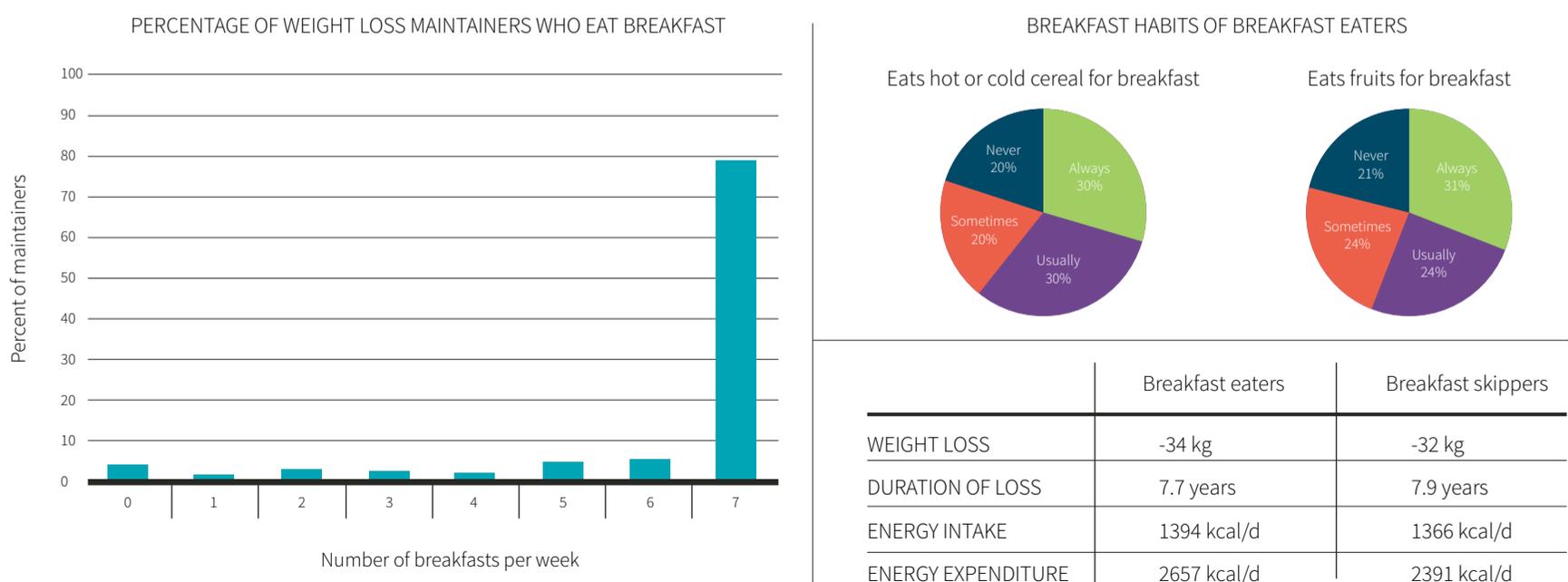
One of the main arguments in favor of consuming breakfast for maintaining a healthy body weight has been the suggestion that it would reduce subsequent food intake during the day, and therefore prevent the consumption of excessive calories later in the day. As this meta-analysis shows, breakfast consumption does not lead to lower food intake later in the day and hence adds more energy to the daily diet. This effect seems to be consistent, as it was observed in six of the nine trials included that assessed this metric. Accordingly, other authors have observed that the absolute amount of calories consumed for breakfast are strongly and positively correlated with total daily calorie intake. Because of this, eating breakfast *per se* does not constitute a necessary intervention for promoting a caloric deficit conducive to weight loss.

On the contrary, it could even promote weight gain, given that it adds more energy to the daily diet, compared to skipping breakfast. This has important implications for obesity recommendations, as people associate eating breakfast with healthy eating patterns and start eating breakfast in attempts to adopt a healthy lifestyle.

In some cases, this strategy could backfire and promote weight gain. This has been shown in an RCT included in the meta-analysis, which found that breakfast consumption in women who regularly skipped breakfast led to an increase in daily energy intake (+266 kcal) and gained 0.7 kilograms (1.5 pounds) over four weeks, compared to the group who kept skipping breakfast.

A major strength of this meta-analysis is that it included only trials from high income countries, which reduces heterogeneity due to food availability under different economic or geographic situations. On the other hand, the analyzed RCTs only included adults without any disease besides being overweight or obese (such as diabetes, metabolic syndrome, etc.), so extrapolation to other populations such as children, adolescents, older people, those with chronic diseases or highly active people is not possible. In addition, the effects of different breakfast compositions were not assessed. Finally, the included studies only followed participants for a very short time (less than four months) and overall were of low quality. Also, it is conceivable that adaptations to breakfast in the long term include a reduction on calorie intake later in the day, and therefore, the weight-promoting effect is only observed in the short term.

Figure 2: The breakfast habits of people who maintain weight loss



Reference: Wyatt et al. Obes Res. 2002 Feb.

In view of the overall high risk of bias, mediocre quality of the available research as a whole, and lack of assessment of breakfast composition or habits, higher quality evidence and adjustment for breakfast habits in future research could overturn these results in either direction down the road. So, while the evidence points toward breakfast helping with weight loss, it does so quite weakly. Higher quality evidence is needed to come to firm conclusions.

In contrast to what observational studies have suggested, this meta-analysis found that skipping breakfast does not increase bodyweight nor total daily energy intake. On the contrary, breakfast skipping reduces daily energy intake and bodyweight. This discrepancy might be explained by the fact that breakfast eaters also have other healthy habits that promote weight maintenance. However, the data that went into this meta-analysis is generally short-term and of low quality — longer and higher quality studies are needed.

The big picture

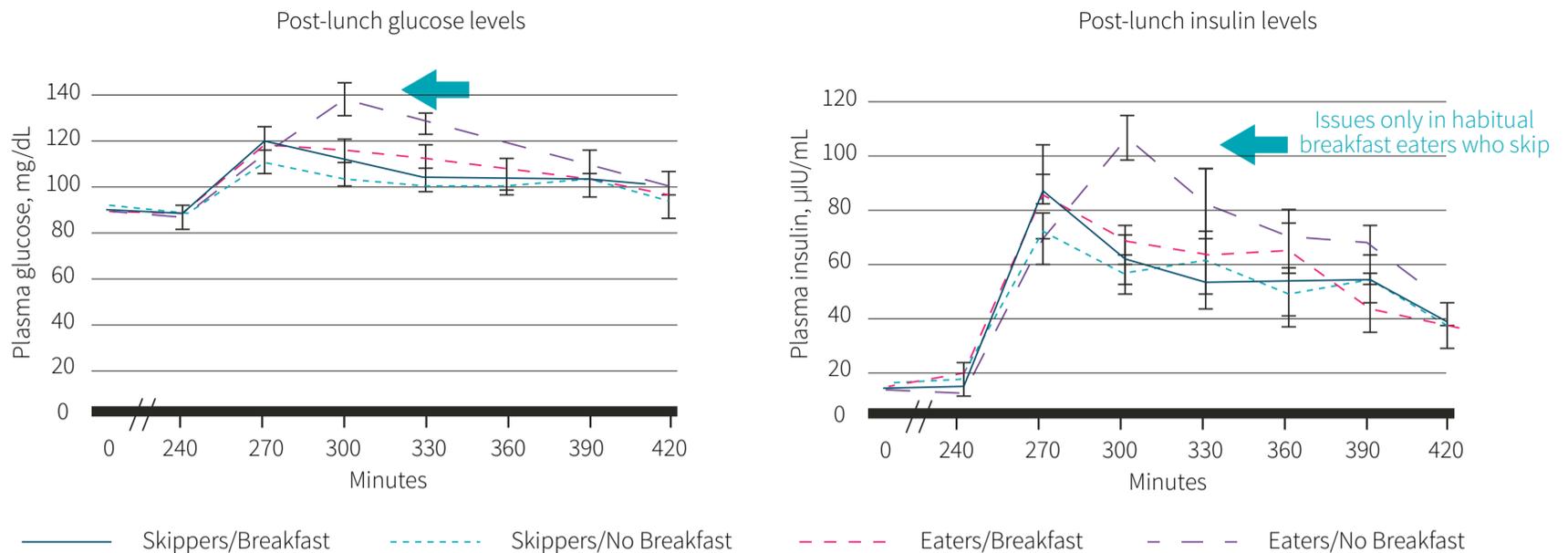
Much of the focus on the topic of breakfast and health has been on the consumption of the meal *per se* instead of its composition. Typical breakfast items include energy-dense foods rich in refined flour, sugar, and fat—a combination that is not just nutrient-poor but also hyperpalatable and thus prone to trigger overeating. Conversely, consumption of a breakfast rich in protein might promote longer satiety and therefore lead to fewer calories eaten later in the day. For instance, consumption of eggs for breakfast during an energy-restricted diet [promotes more weight loss](#) than consumption of an energy-matched breakfast consisting of bagels. This agrees with [other research](#)

showing higher satiety and lower daily energy intake after consumption of a breakfast higher in protein and fat, and lower in carbohydrates (eggs and toast), compared to an isocaloric breakfast higher in carbohydrates. Therefore, the consumption of a high protein breakfast might be advisable for weight loss.

Besides weight loss, breakfast consumption might influence other metabolic parameters that are important for overall health, like insulin sensitivity. Some data suggests that in participants with type 2 diabetes, skipping breakfast [worsens glycemic control](#). Similarly, one study showed that, in healthy women, skipping breakfast [increased](#) total daily energy intake and decreased post-meal insulin sensitivity. In addition, emerging research on the timing of food intake and its relationship with health parameters has suggested that breakfast consumption [might be of importance](#) for maintenance of a healthy circadian rhythm (the oscillatory patterns observed in distinct physiological metrics that occur during 24 hours)—with all its potential [downstream effects on human cardio-metabolic health](#).

In sedentary conditions, insulin sensitivity follows a [circadian pattern](#), in that it is higher in the morning and declines nearer to night. Hence, some authors [have suggested](#) that skipping breakfast might negatively affect the circadian rhythm and therefore health. However, most of these studies have assessed the effects of breakfast omission acutely on one test day, without taking into account the breakfast habits of the participants. Indeed, it [has been observed](#) that the metabolic issues seen after skipping breakfast occur only in habitual breakfast eaters. Therefore, research must take into account the breakfast eating habits of participants when assessing the effects of skipping breakfast. Over time, the body appears to adapt to different eating patterns, such as one which regularly skips breakfast.

Figure 3: Metabolic effects of breakfast eating versus skipping



Reference : Thomas et al. Obesity (Silver Spring). 2015; 23(4): 750-9

The putative healthy effect of breakfast may be an example of over-reliance on observational data (that can determine associations but is generally insufficient for establishing causation) for making nutritional guidelines and recommendations. As such, [some authors have suggested](#) that the “proposed effect of breakfast on obesity” is not supported strongly by scientific evidence and constitutes a “belief beyond the evidence.” As observational data can only be hypothesis-generating, it is important that observational associations are tested under controlled conditions.

Although much of the research has focused on the influence of breakfast eating *per se*, an important parameter that has to be taken into account is the composition of the meal. Specifically, it appears that a breakfast rich in protein and fat, and lower in carbohydrate, increases satiety and reduces subsequent calorie intake. Moreover, most evidence showing negative effects of breakfast skipping have been performed acutely, and it appears that these effects are observed only in habitual breakfast eaters.

Frequently asked questions

Is there any evidence regarding the effects of breakfast on cognition or mental tasks?

Evidence in this regard is equivocal and methodologically heterogenous. In healthy adults, [some studies](#) suggest a small benefit of consuming breakfast for memory (particularly delayed recall, which involves reproducing information learned about 15-45 minutes before), but overall, no differences after skipping breakfast are observed.

However, as with other research on breakfast consumption, these studies are acute and do not differentiate between people who habitually eat breakfast or not. Thus, it’s possible that the memory effects are simply due to the fact that people who habitually eat breakfast are not physiologically adapted to skipping it. Nevertheless, it is worth pointing out that there is no strong evidence favoring breakfast for cognition, as it is commonly believed.

What should I know?

Breakfast consumption has been considered an important part of a healthy lifestyle that promotes weight

loss. However, this idea has been derived mainly from observational evidence and there is a discordance with RCTs on the subject. Therefore, the authors of this study performed a systematic review and meta-analysis of RCTs examining the effects of breakfast on weight loss and energy intake in overweight and obese participants from high-income countries.

The results show that breakfast consumption increases total daily energy intake and bodyweight relative to

skipping breakfast. Thus, contrary to current suggestions, consumption of breakfast could promote weight gain over time. However, personal breakfast habits and the nutritional composition of breakfast might influence the effects of breakfast on weight and energy intake. As the available studies are short-term and of low quality, longer term experiments with higher quality are needed to determine if the observed effects are maintained. ♦

The discussion about breakfast happening over at the [ERD Facebook forum](#) is calorie free, so don't skip it!

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