ERD

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Research Digest

ERD Anniversary Edition

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From the Editor

Welcome to the 2017 ERD anniversary edition! November marks the third year of the ERD. During that time, we've covered quite a few major topics in the health and nutrition world. Some of the topics we've tackled over the past year include red meat's impact on cardiovascular disease, how well mindfulness interventions work for weight loss, and magnesium's impact on depression. You'll find our reviews of all that research, and more, in this edition.

We've also gone through a few changes in the past year. I've taken the reins as editor-in-chief of ERD from Kamal, who's currently working on new, great projects for Examine.com. We're also pulling in some new writers to add new voices and perspectives and to keep the analysis tap flowing.

As ERD ages, changes are to be expected on the path to growth. To see how well we're doing, I took a peek at some child development milestones for comparison. As ERD reaches the end of its toddlerhood, I think it's meeting, if not exceeding, expectations. It uses clear language. Our articles can also string words together into sentences - lots of them, in fact! And ERD can even choose correct words. Right exactly where a three-year old should be!

Fine. My choice of metric did not set a high bar. However, there can be some wisdom to be gained even from inappropriate comparisons. Because three-year olds can also take requests, and I think that's one area where we can improve.

After all, we exist for one reason: to provide our readers with unbiased, up-to-date analyses of the latest research in supplementation, nutrition, and health. However, that's a broad field. Furthermore, our readers have all sorts of backgrounds, ranging from nutrition enthusiasts to health professionals, And with a wider readership comes a wide range of interests.

As ERD enters its fourth year, more changes are likely to happen. And I'd like to ask you to be a part of it. I encourage subscribers to voice their preferences on the private ERD forum. And you can always contact us to tell us what they'd like to see for the ERD in the future. Over the next year, we hope to learn more about what you want. So feel free to get in touch!

But for now, happy reading!

Gregory Lopez, *Editor-in-Chief*

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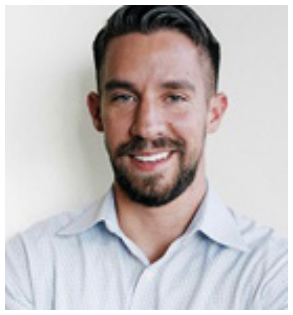

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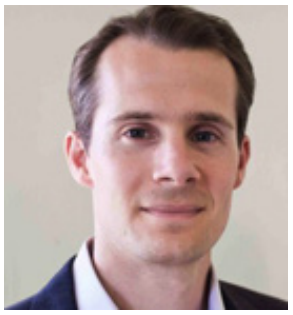

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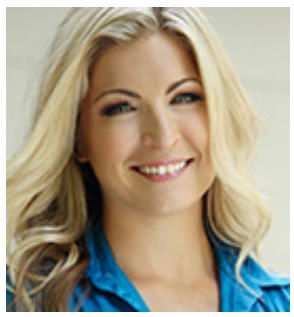

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Cut out FODMAPs, cut out IBS symptoms?

Does a diet low in FODMAPs reduce symptoms associated with functional gastrointestinal disorders? A comprehensive systematic review and meta-analysis

Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder that affects approximately 11% of the global population. It is associated with abdominal pain, bloating, excessive flatulence, and altered bowel habits, severely lowering a person's quality of life. Functional gastrointestinal disorders like IBS are not caused by structural abnormalities such as ulcers or tumors. Rather, they occur as a result of an abnormally functioning GI tract. This makes it difficult to accurately diagnose a person because no biomarker can indicate whether or not someone is suffering from IBS. Thus, clinicians have to rely on the reports of patients and on a set of criteria that have evolved over time for diagnosis.

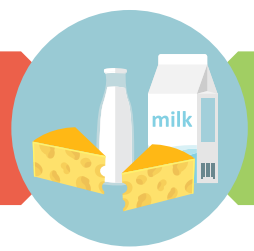
Although the cause of IBS is still not well understood, researchers have put forth several hypotheses. Some of these theories include infections of the GI tract, psychological stress, abnormalities in gut motility, and gut-brain axis problems. Unfortunately, no cures currently exist for IBS. It is managed through various treatments such as 5-HT agonists/antagonists, antispasmodics, and antidepressants. These drugs can improve primary symptoms in some people, but they are unable to fully resolve disorders like IBS that are characterized by multiple symptoms. In addition to their limited use, there are several side effects associated with these drugs, so long-term use is not ideal.

As a result of these issues, researchers have investigated several alternative treatments as potential treatments for IBS. Patients suffering from IBS often report that particular foods worsen their symptoms more than others. Therefore, researchers have investigated various dietary interventions.

Dietary interventions that restrict specific food components, such as low-FODMAP diets, have been explored in several trials. FODMAP is an acronym that stands for "Fermentable, Oligo-saccharides, Di-saccharides, Mono-saccharides, and Polyols." These are short-chain carbohydrates that are poorly digested and absorbed in the small intestine. As a consequence, they travel to the large intestine, where they are fermented by the bacteria that colonize it. This breakdown of carbohydrates by bacteria results in the formation of gasses such as hydrogen and methane in all individuals. However, this phenomenon seems to be excessive in IBS sufferers. Therefore, restricting foods that are rich in these short-chain carbohydrates (some of these are listed in Figure 1) can potentially alleviate many of the symptoms prominent in people with IBS.

"Unfortunately, no cures currently exist for IBS. It is managed through various treatments such as 5-HT agonists/antagonists, antispasmodics, and antidepressants."

Figure 1: Food FODMAP content

High FODMAP Foods		Low FODMAP Foods
Asparagus, onions, garlic, legumes/pulses, sugar snap peas, beetroot, celery, sweet corn		Bean sprouts, green beans, bok choy, carrot, bell pepper, fresh herbs, cucumber, lettuce, tomato, zucchini
Apples, pears, mango, nashi pears, watermelon, nectarines, peaches, plums		Banana, orange, mandarin, grapes, melons
Cow's milk, yoghurt, soft cheese, cream, custard, ice cream		Lactose-free milk, lactose-free yoghurts, hard cheese
Rye, wheat-containing breads, wheat-based cereals with dried fruit, wheat pasta		Gluten-free bread, sourdough spelt bread, rice bubbles, oats, gluten-free pasta, rice, quinoa

Source: The Monash University Low FODMAP diet

A previous systematic review conducted in 2015 showed that a low-FODMAP diet was somewhat effective in reducing the severity of symptoms associated with IBS. Six studies were included in that review and of those six, three were randomized controlled trials. The authors concluded that although a low-FODMAP was somewhat effective in treating IBS symptoms, more controlled trials with longer durations were needed to gauge the efficacy and safety of a low-FODMAP diet in treating IBS symptoms. The current study extends upon that review with further research, and also performs a meta-analysis to quantitatively summarize the findings.

Irritable bowel syndrome is a functional gastrointestinal disorder associated with abdominal pain, distension, and altered bowel habits. It is theorized to have a variety of causes. It is currently considered incurable by most medical practitioners, and is most commonly managed through the use of pharmaceuticals. Several alternative treatments have been explored as a result of this and one of these treatments, a low-FODMAP diet, has shown some effectiveness in reducing the severity of the symptoms associated with IBS.

Systematic reviews

Systematic reviews of the scientific literature are highly useful for clinicians and researchers because they compile the findings of many studies and allow the reader to stay up to date with scientific research. Unlike narrative reviews, where the author chooses which studies he/she wants to report on, systematic reviews are less likely to be impacted by selection bias because the author has a comprehensive search strategy beforehand, with the goal of reducing bias when digging through the scientific literature. Thus, systematic reviews generally report on the most relevant studies on a particular topic and are far more comprehensive than narrative reviews.

A systematic review is often accompanied by a meta-analysis, a statistical technique in which the findings of multiple studies are pooled to produce a single quantitative result. They are far more objective than narrative reviews and they allow one to assess the quantitative strength of a relationship between two variables. In the previous systematic review on this topic, the authors did not conduct a meta-analysis to see the relationship between a low-FODMAP diet and reduction of IBS symptom severity, whereas the current study did.

Who and what was studied?

This study was a systematic review and meta-analysis of six randomized controlled trials and sixteen non-randomized studies, which evaluated the effectiveness of a low-FODMAP diet in reducing symptoms associated with IBS. In the controlled trials, a low-FODMAP diet was generally compared to a control diet, which varied from study to study. In some studies, the control diet was a diet typically prescribed to IBS patients by healthcare professionals. In other studies, the control diet was the normal diet of the participants.

The duration of the RCTs ranged from three to six weeks. The age of the participants ranged from 18 to 74 and most were female. The duration of the non-randomized studies ranged from two days to 35 months, with the number of participants ranging from 19 to 82.

The three primary outcomes in both the randomized and non-randomized interventions were the number of participants with symptom improvement after the intervention, IBS Severity Scoring System (IBS-SSS) scores, and/or the IBS Quality of Life (IBS-QOL) scores, which were measured pre- and post-intervention.

Pooled odds ratios and confidence intervals were calculated for the reduction in IBS-SSS scores, the increase in IBS-QOL scores, and for the number of patients who reported improved functional gastrointestinal symptoms for both randomized and non-randomized interventions.

The goal of a meta-analysis is to pool together the results of multiple studies. It is impossible for all of the studies to be identical because there will always be differences in the study designs, measured outcomes, and results. This is known as heterogeneity. When there is high heterogeneity amongst the studies, a meta-analysis is usually not appropriate. Therefore, researchers usually quantify the heterogeneity amongst the studies before proceeding with a meta-analysis. In this meta-analysis, heterogeneity was calculated using the I2 statistic, study quality was assessed using the Jadad scale for reporting RCTs, and publication bias was measured using the Egger's regression model.

This meta-analysis and systematic review investigated the effectiveness of a low-FODMAP diet in reducing symptoms associated with IBS. The analysis included six randomized trials and sixteen non-randomized trials. The main outcomes of the studies were IBS-SSS scores, IBS-QOL scores and the number of participants who reported improved gastrointestinal symptoms.

Measuring IBS improvements

The IBS Severity Scoring System (IBS-SSS) questionnaire measures the severity of IBS symptoms on a scale from 0-500. The higher the score, the more severe the symptoms. Mild IBS is characterized by a score less than 175; moderate is marked by a score ranging from 175- 300, and severe IBS is characterized by a score of 300 and greater. A decrease in 50 points is considered to be clinically significant.

The IBS Quality of Life (IBS-QOL) questionnaire gauges a person's health-related quality of life. It is composed of 34 statements, each with a five-point Likert response scale. The questionnaire standardizes the total scores from 0 (poor quality of life) to 100 (maximum quality of life) using a formula. An IBS-QOL score change that is greater than 14 is considered to be clinically meaningful.

What were the findings?

In the randomized controlled trials, participants in the experimental groups reported abdominal pain and abdominal bloating as the symptoms with the greatest improvement. The low-FODMAP diets were found to be superior in providing overall relief of gastrointestinal symptoms compared to the diets in the control groups. In the non-randomized interventions, abdominal pain was reported to be the symptom with the greatest amount of improvement, followed by gas, diarrhea, nausea, and constipation.

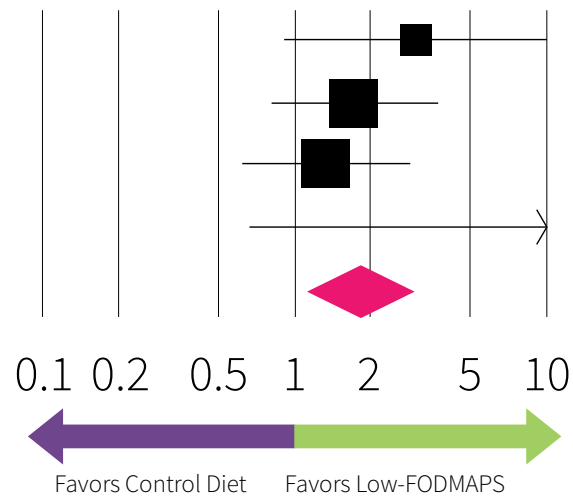
All participants had a baseline IBS-SSS score that was greater than 232, which is considered to be moderate. In the RCTs, the average decrease in IBS-SSS scores for the low-FODMAP groups was 122.64. In the control groups, the average decrease was 69.64. In the non-randomized interventions, the average decrease in the IBS-SSS scores was 118.7. For a change in IBS-SSS score to be designated as clinically meaningful, it must be over 50 points. So, both the control diets and the low-FODMAP diets led to clinically meaningful decreases in IBS-SSS scores. However, it is also important to note that the difference in the mean decrease in scores between the experimental and control groups was over 50 points. Thus, the low-FODMAP diets were far more effective in reducing IBS-SSS scores than were the control diets, as shown in Figure 2.

In the randomized trials, the experimental group had an average improvement of 10 points in IBS-QOL scores while the control group had an average increase of 0.4 points. In the non-randomized trials, there was an average improvement of 10.5 points. While none of these improvements were deemed clinically meaningful (due to being less than 14), there was a difference in the mean increase in scores between the experimental groups and the control groups.

The authors did not find any evidence of publication bias. The authors also did not find any statistically significant heterogeneity in the RCTs. However, there was large heterogeneity in the non-randomized interventions.

Figure 2: Low-FODMAP diets reduced overall gastrointestinal symptoms

Study name	Odds ratio	Lower limit	Upper limit	p-Value
Staudaucher et al	3.01	0.91	10.00	0.07
Pedersen 2014	1.73	0.80	3.74	0.16
Pedersen 2014a	1.33	0.61	2.89	0.47
Halmos et al	11.98	0.66	218.90	0.09
	1.81	1.11	2.95	0.02



In this analysis, the authors pooled together the results from multiple other studies, and found that adhering to a low-FODMAP diet resulted in clinically meaningful changes in IBS-SSS scores and led to a reduction in abdominal pain and bloating. Adhering to a control diet also resulted in symptom improvement. However, the low-FODMAP diet was superior in reducing symptom severity.

What does the study really tell us?

This is the first meta-analysis to investigate the effectiveness of a low-FODMAP diet in reducing symptoms associated with IBS. The analysis shows that low-FODMAP diets are effective and superior to control diets in reducing gastrointestinal symptoms.

The results also indicate that even though the low-FODMAP diets were associated with better outcomes, adhering to a control diet still resulted in improved outcomes. This suggests that simply adhering to any diet may offer symptom relief in certain individuals. However, this could also be a result of patients adhering better to diets while enrolled in trials.

Meta-analyses are only as good as the studies they include. When there are significant differences between the studies being analyzed, also known as heterogeneity, a meta-analysis is not always appropriate. While the authors of this meta-analysis tested the RCTs for heterogeneity using the I2 statistic and found low to no heterogeneity, they noted that there were differences in the RCTs that could be confounding factors and that quality assessment of the RCTs yielded mixed results.

For example, the durations of the randomized interventions differed, ranging from three to six weeks. The blinding techniques of the RCTs also tended to vary, with four randomized trials being single-blinded and two being unknown, due to the original study authors not providing this information.

The authors also noted that the control diets in the RCTs varied, with some comparing low-FODMAP diets to the standard diets of IBS patients, while others compared a low-FODMAP diet to dietary advice that is prescribed to IBS patients. However, each of these studies has shown the low-FODMAP diet to be superior to the control diets. Another limitation of the RCTs included was that the longest RCT was only six weeks in duration. In the context of a chronic disorder like IBS, six weeks may not be long enough to determine how a diet would affect symptoms in the long-term.

An important shortcoming of this meta-analysis was that most of the studies included did not report on IBS subclassification such as diarrhea predominant (IBS-D), constipation predominant (IBS-C), both diarrhea and constipation (IBS-M) and neither diarrhea or constipation (IBS-U). Thus, it remains unclear how a low-FODMAP diet affects these particular symptoms.

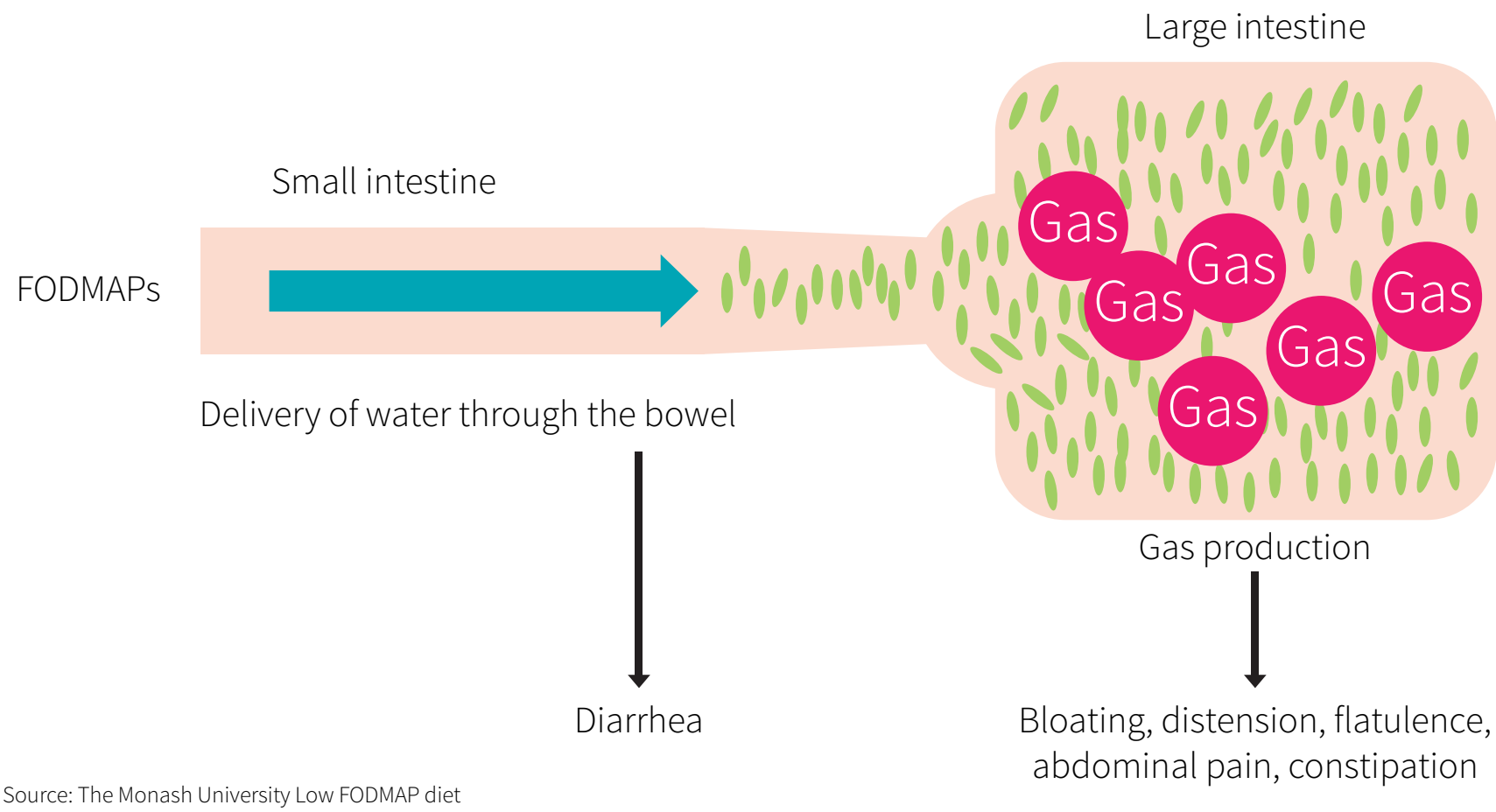
This meta-analysis provides strong evidence to support the use of a low-FODMAP diet in treating IBS symptoms. Both the low-FODMAP diets and the control diets resulted in improved symptoms. Unfortunately, the control diets between the studies differed, thus it is difficult to accurately determine how effective each one is in reducing IBS symptoms. The RCTs included were also not very long in duration, which limits conclusions about long-term efficacy.

The big picture

The conclusions that the authors arrived at fall in line with the results of previous reviews of low-FODMAP diets, showing that they are effective for treating IBS symptoms. Previous reviews were not able to pool together the results of multiple studies due to high heterogeneity and because many of the trials at the time were quite short in duration. Thus, researchers were unable to quantify how effective a low-FODMAP diet was when compared to other interventions. However, dozens of trials investigating low-FODMAP diets have been conducted since then, many with similar study designs. Many researchers have proposed that a low-FODMAP diet be the first line of treatment for IBS. This is the first meta-analysis to examine the effectiveness of a low-FODMAP diet, and it provides strong evidence to support the use of a low-FODMAP diet in reducing gastrointestinal symptoms associated with IBS.

The results from this meta-analysis also provide further evidence that diets high in fermentable substrates can be problematic for people with gastrointestinal disorders. By restricting these short chain carbohydrates, bacteria in the intestines have less substrate and create fewer byproducts such as gas (as shown in Figure 3),

Figure 3: FODMAP effects in the intestines



Source: The Monash University Low FODMAP diet

> “ [...] different people can react quite differently to both FODMAPs and different specific fibers and foods.”

so symptoms such as abdominal pain and abdominal bloating are less likely to be problematic. In fact, this meta-analysis showed that abdominal pain and abdominal bloating were reported to be the two symptoms with the greatest improvement in the RCTs by the low-FODMAP group. This theory is further supported by studies that have shown low-FODMAP diets to be superior to gluten-free diets in treating IBS. However, the results of this meta-analysis also showed that the control groups experienced some relief. Thus, it is very likely that any dietary intervention will result in some form of relief whether it be due to placebo or to biochemical reasons.

It is quite clear at this point that diet plays a large role in how a person's microbiome is shaped. Although research into the microbiome is fairly new, the results of this study show that manipulating one's diet can have a substantial effect on their health-related quality of life.

Now that there is substantial evidence to support the use of a low-FODMAP diet in reducing IBS symptom severity, it is possible that it may become a first line of treatment. The results of this meta-analysis and the results of other RCTs may convince physicians and researchers to focus more on the microbiome when developing new interventions for gastrointestinal disorders.

Frequently asked questions

How will a low-FODMAP diet affect the microbiota?

Unfortunately, there is a lack of long-term RCTs that have examined this phenomenon. Short-term RCTs have shown that following a low-FODMAP diet for over a month reduces luminal bifidobacteria and reduces total bacteria counts in the colon when followed for an extended period of time. However, it is difficult to speculate how adopting a low-FODMAP diet will impact the gut microbiome in the long-term.

Fiber consumption can be more difficult on a low-FODMAP diet, but there are still many plant foods that are low in FODMAPs and high in fiber (such as several types of berries). The consumption of fibrous foods without FODMAPs, that a given individual can handle without symptoms, isn't something that has been well studied. Part of the reason may be that different people can react quite differently to both FODMAPs and different specific fibers and foods.

What impact will a low-FODMAP diet have on constipation?

Interestingly enough, this meta-analysis found that following a low-FODMAP diet resulted in significant improvements in almost all symptoms associated with IBS with the exception of constipation. Although there was some degree of improvement in constipation, it was the symptom with the least amount of improvement.

It is often believed that constipation is caused by a lack of fiber and that low-fiber diets will exacerbate constipation. So, it is commonly thought that a low-FODMAP diet, which is often a bit low in fiber, will likely worsen constipation. One meta-analysis concluded that the available evidence supports fiber for the treatment of constipation; however the evidence was not strong. Thus, it is quite difficult to know how a low-FODMAP diet will affect constipation.

What other evidence-based strategies are available for managing IBS?

Peppermint oil has been found in multiple RCTs to be effective in reducing abdominal pain in people with IBS. One systematic review and meta-analysis also found certain probiotics to be effective in reducing abdominal pain associated with IBS. A low-FODMAP diet and probiotic supplementation may be an effective strategy in dealing with IBS, since previous studies reported reduced counts of bifidobacteria in people who adhered to a low-FODMAP diet for a month.

What should I know?

IBS is a very difficult chronic disorder to manage. In the past, no one treatment had substantial evidence behind it, and thus first-line dietary treatments were in question. However, this meta-analysis and several other RCTs have shown that a low-FODMAP diet is effective in reducing not just one or two symptoms but many of the symptoms that are associated with IBS. Low-FODMAP diets have the potential to be a first line of treatment utilized by evidence-based clinicians. However, more research is needed to evaluate potentially detrimental effects on gut microflora from long-term diet adoption. ◆

The general public may not be aware of the ins and outs of FODMAPs and IBS, but they probably should be. Discuss this paper over at the ERD Facebook forum.

Can diet soda ruin your diet?

Beneficial effects of replacing diet beverages with water on type 2 diabetic obese women following a hypo-energetic diet: A randomized, 24-week clinical trial.

Introduction

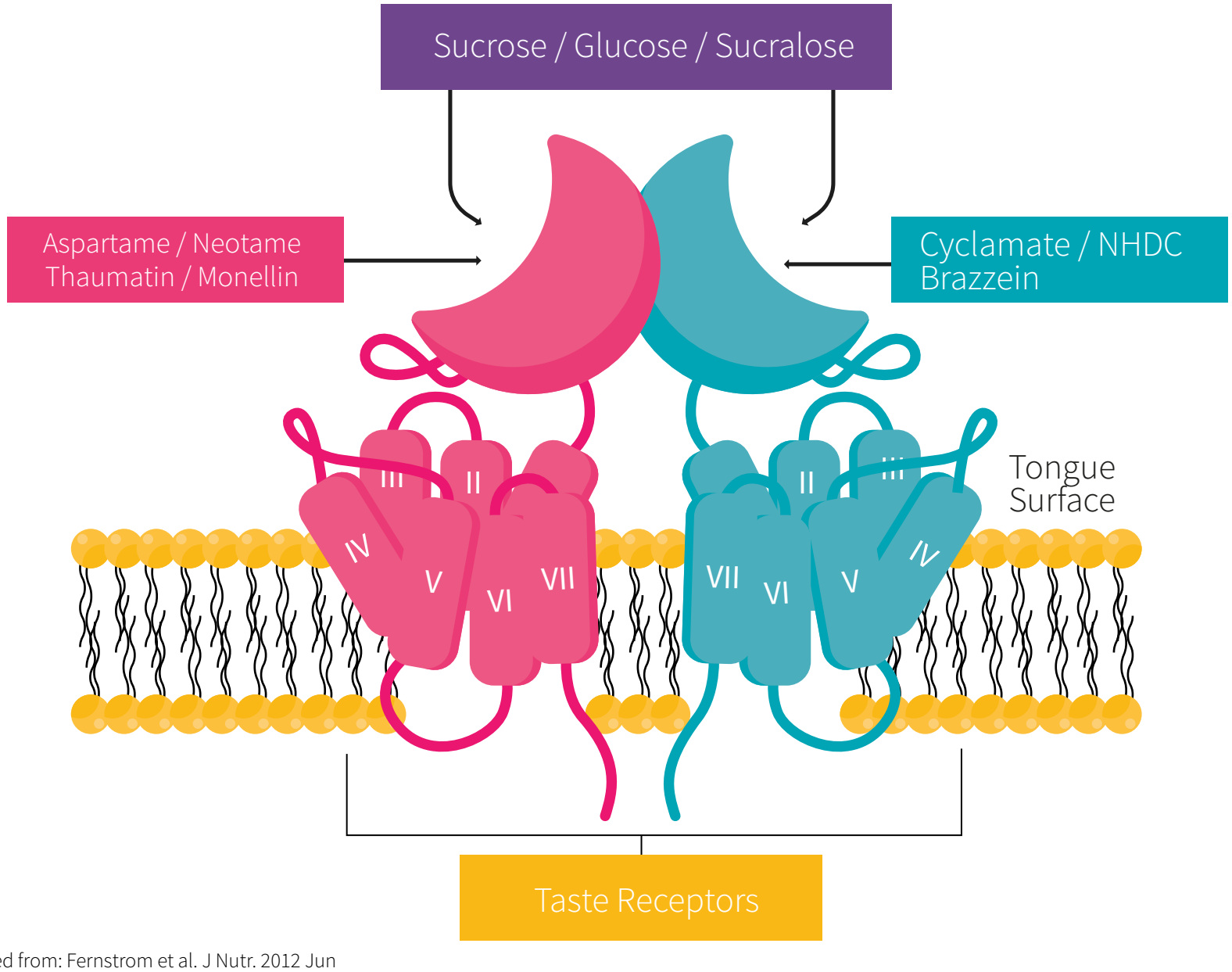
When it comes to weight loss, eliminating sugar-sweetened beverages (SSBs) is low-hanging fruit. However, researcher isn't clear on the impact of replacing these with diet beverages flavored with artificial sweeteners. As shown in Figure 1, these sweeteners interact with taste buds to produce a sweet sensation, yet they don't provide substantial energy to the body like sugar would.

Artificial sweeteners, like aspartame, saccharin, and sucralose, have been the subject of nutrition debates for years. Trials that examine the effect of diet beverages versus water on weight regulation show mixed results, with at least one showing a benefit for diet beverages, while another shows no difference. Observational studies on artificial sweeteners, also called non-nutritive sweeteners or NNS, frequently show associations between NNS and obesity or diabetes.

So, other researchers have tried to determine why artificial sweeteners aren't a surefire trick for easier weight loss. Some theorize that artificial sweeteners act on the brain and increase our desire for sweeter foods. Others theorize that dieters reward themselves with more calorie-dense treats when they choose diet sodas rather than sugary treats. Recently, scientists have questioned whether artificial sweeteners affect the microbiome and prevent weight loss by affecting gut bacteria.

But the varied scientific outcomes still leave questions unanswered. What's the bottom line ... are diet drinks a poor choice for weight loss? And if they are, why? Like everything else, it may depend on the context.

Figure 1: Sweetener and taste bud interactions



Adapted from: Fernstrom et al. J Nutr. 2012 Jun

In the study under review, researchers wanted to examine how diet soda may differentially affect the weight loss of adult women with diabetes. Researchers assigned one group of women to a diet that included diet soda and a second group that did not. Weight loss, metabolic markers, and other surrogate health markers were examined.

In a previous study, researchers found a slight beneficial effect of replacing diet beverages with water in obese women without diabetes on a low calorie diet plan. In the current study, researchers wanted to examine whether they would see the same effects in women with obesity and type II diabetes.

Artificial sweeteners, and diet beverages in general, remain controversial in the nutrition community, despite the low calorie count. Observational studies show correlations between diet soda intake, weight gain, and metabolic syndrome that could prevent health professionals from recommending them. A previous study by the same authors found that obese women who replaced diet beverages with water had improved weight loss. The current study examines whether the addition of diet soda or water has an effect on women with diabetes enrolled in a weight loss study.

Who and what were studied?

The study, a randomized controlled trial (RCT), enrolled 81 overweight-to-obese (BMI ranging from 27 and 35) diabetic women between the ages of 18 and 50, who regularly drank diet soda. All women were enrolled in the same weight loss program, but half of the women were assigned to drink a single 250 milliliter (mL) diet soda after lunch, whereas the other half drank a glass 250 (mL) of water for 24 weeks. Sixty-five women completed the 24 week intervention and 16 women dropped out. Results from all women were included using an intention-to-treat analysis.

The primary measured outcome was body weight. Researchers also measured secondary outcomes of waist circumference and carbohydrate and lipid metabolism. They collected blood samples and assessed lipid panels, fasting and two-hour postprandial blood glucose, Hb A1C, fasting insulin, and insulin resistance.

All women were habitual soda drinkers, and researchers required all participants to undergo a two week "washout period" before the intervention. None of the participants could drink diet soda or use artificial sweeteners of any kind leading up to the start of the study.

Once the study commenced, all participants were enrolled in the same weight loss program, the NovinDiet protocol. The NovinDiet protocol is a hypocaloric diet that is individualized to each participant based on their food diaries and requires participants to track their intake and record their progress. It also encouraged increasing physical activity to 60 minutes per day, 5 days per week. In addition to the protocol, participants were provided with online support through a website and weekly magazines, and individual counseling as needed.

Participants' diets were measured at baseline, during week 11, and during week 23 using a detailed four-day food recall. Anthropometric and biochemical measures were taken at baseline, 12, and 24 weeks.

The study consisted of 81 women randomized to two groups: diet beverages and water. The diet beverage group was instructed to drink one diet soda after lunch each day. The water group was instructed to drink the same amount of water after lunch each day. All participants were enrolled in the same weight loss program.

What were the findings?

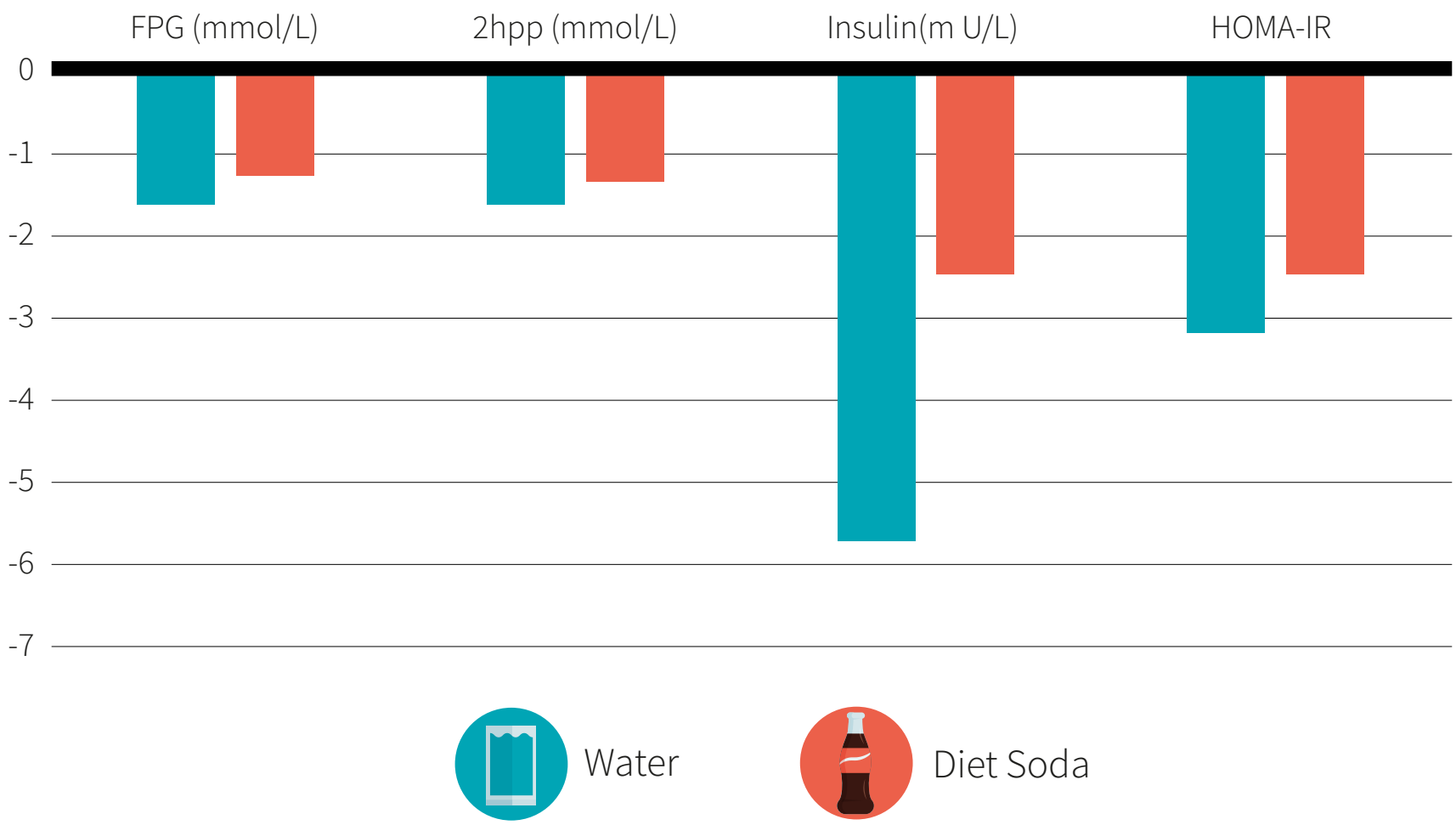
At 24 weeks, both groups lost significant weight compared to baseline; however, women in the water-only group lost significantly more weight than women in the diet beverage group. At 24 weeks (approximately six months) the water group had lost an average of 6.4 kilograms (14.1 pounds), whereas the diet beverage group lost 5.25 kilograms (11.6 pounds). Weight loss also affected the BMI outcomes of course, where the water group also outstripped the diet beverage group.

There were several significant results among secondary outcomes: central adiposity and markers of carbohydrate and lipid metabolism. While both groups saw beneficial decreases in FPG, 2hpp, fasting insulin, and HOMA-IR, the water-only group saw a significantly greater change when compared to the diet beverage group (as shown in Figure 2). For example, average FPG decreased from 8.49 to 6.86 mmol/L (153.0 to 123.6 mg/dL) in the water group and from 8.48 to 7.19 mmol/L (152.8 to 129.5 mg/dL) in the diet beverages group. Changes in other metabolic markers were of a similar magnitude. Differences between groups in Hemoglobin A1C, a measure of average blood sugar over time, were not significant.

Further, waist circumference, total cholesterol, HDL, LDL, and TGs showed significant improvement over time for both groups, but differences between the two groups were observed.

Researchers also observed differences in each group's dietary recalls. While both groups reported an overall drop in calories consumed each day, the women in the diet beverages group reported eating significantly more calories per day than the women in the water group. Specifically, women in the diet beverages group reported eating on average 16 more grams of carbohydrates (approximately 64 kcals) than the water group. This discrepancy could explain the 42 kcal per day average difference that researchers observed between the two groups' recalls. Both the between-group differences in reported carbohydrate and reported energy intake were statistically significant.

Figure 2: Diet vs water - significant results



The group assigned to drink water instead of diet soda experienced a greater reduction in weight and greater improvements in fasting plasma glucose, postprandial glucose, fasting insulin, and measures of insulin resistance than the group drinking diet soda. Both water and diet soda groups saw significant improvements in in total cholesterol, LDL and HDL cholesterol, TGs, and Hb A1C, but there were no statistically significant differences between the two groups. The diet recalls of both groups indicate that the women assigned to drink diet soda consumed more calories per day, on average, than the women drinking water.

What does the study really tell us?

The results of this study indicate that, all else being equal, women with diabetes assigned to drink a diet soda as part of a weight loss regimen may not lose as much weight as those who replace diet drinks with water. Evidence from this study suggests that diet beverages influenced the number of calories the women ate, causing them to eat more and lose less weight than their water-drinking counterparts.

While markers of glucose control (FPG, 2hpp, fasting insulin, HOMA-IR) improved more in the group drinking water, these improvements may be due to the greater weight loss of the water group or the greater carbohydrate intake of the diet soda group, rather than an independent biochemical effect of the diet beverage.

The authors note that further study is required "…in order to elucidate the mechanism that might explain the better rate of weight loss in the water group compared to the DBs [diet beverages] group…"

It is important to keep in mind, however, that the differences between the two groups amounted to an average of a 2.5 pound difference over a six-month trial. This equates to the water group achieving an additional weight loss of 1.35% of their original body weight. While the results are statistically significant, the clinical significance is open to interpretation.

Though the results indicate that the fasting plasma glucose of the water group was significantly better than that of the diet soda group, both groups managed to gvet average fasting plasma blood glucose ranges into the "goal range" of 70-130 mg/dL for people with diabetes. Additionally, while the HbA1C of the water group appears significantly lower (at 5.8%) than the diet soda group, the variation around that average is much larger, making the measurement statistically insignificant. Both groups also moved their LDL, HDL, and triglyceride levels into the goal ranges, on average.

Therefore, while the water group saw a statistically significant change in weight and some markers of glycemic control, it is not clear whether this difference would continue to grow over the course of a longer trial and become clinically significant.

The study relied on self-reported dietary information to assess how well participants adhered to the diet. While self-reported intake can be notoriously faulty, researchers did find significant increase in carbohydrate intake in the group assigned to diet beverages. This finding - that drinkers of diet beverages ate more carbs - was consistent with the results of their 2015 trial, which also found that women assigned to drink diet sodas ate more carbohydrates. The increased intake of carbohydrates in both studies contributed to the diet beverages groups reporting a slightly greater overall intake.

So the study showed that drinking a diet beverage after lunch in place of water leads to greater carbohydrate and energy consumption. The study illuminates that diet soda consumption changes eating patterns and though the design cannot tell us why, it certainly opens the door to further research.

The study design cannot determine what about diet soda or artificial sweeteners caused the women in the diet beverage group to eat slightly more carbohydrates, and therefore lose less weight and show less improvement in some metabolic markers. However, it does show that in a study where two groups are given exactly the same treatment, including diet soda in the regimen led to less weight loss, although this difference may not be strongly clinically significant. Additionally, women in the group assigned water saw greater beneficial effects in some markers of glycemic control including fasting plasma glucose, 2 hour postprandial glucose, fasting insulin, and HOMA-IR.

The big picture

The authors of the present study authored a previous study in 2015 with similar methodology examining the effects of diet soda on weight loss in obese women without diabetes. Interestingly, the current study shows remarkably consistent results, with the diet soda group losing less weight and showing less improvement in certain glycemic markers. Further, the diet beverages group in the original study also showed a slightly greater intake in carbohydrate and energy. This seems like good evidence that researchers are onto something and that the effect of diet soda is similar in obese women with and without diabetes.

Why would researchers observe less weight loss in participants drinking diet sodas, especially since they contain no calories? This is not the first time ERD has examined this issue. ERD #22 discussed how sucralose (brand name Splenda) may promote energy imbalance.

Higher body weight in artificial sweetener users is commonly seen in observational studies, including one published recently (November 2016), which found that men and women who report using low-calorie sweeteners had a BMI 0.8 kg/m^2 higher, a waistline 2.6 cm larger, and a 53% higher incidence of abdominal obesity than those who abstained. A Japanese study from 2014 following participants for seven years found that people who drank diet sodas were more likely to develop diabetes. Even a study from Harvard found a correlation between artificially-sweetened soda and diabetes, though once results were adjusted for existing risk factors the correlation went away. One major difficulty in assessing the effect of artificial sweeteners in observational studies is the tendency for people trying to use artificial sweeteners to manage weight. Rather, people who are heavier will use artificial sweeteners, artificial sweeteners don't make people heavy.

Even including the current study, the effect of diet sodas on weight change in RCTs has been a mixed bag. In a study done on 318 overweight and obese participants and consisting of three arms, a diet beverage, a water, and a control arm, researchers found that the weight loss was not statistically significant between the three groups, though all reported weight loss. In a 2014 study on 308 adults assigned to water or diet beverages, researchers found a significantly greater weight loss in the group assigned to diet beverages.

A 2014 meta-analysis that examined 15 RCTs and nine prospective cohort studies concluded that in RCTs, artificial sweeteners came out ahead, but in cohort studies artificial sweetener use was correlated with a BMI 0.03 kg/m2 higher.

So, it seems the answer is that there is no definitive answer. Perhaps artificial sweeteners have differential effects when they are used as part of daily living and when they are meant to function as a weight loss tool. For now, the science is certainly not settled.

While the current study, as well as a 2015 study published by the same authors, found that diet soda consumption consistently reduced the amount of weight lost, the body of literature on artificial sweeteners is still ambiguous. Though observational studies tend to show that people using artificial sweeteners are heavier, RCTs have mixed results.

Frequently asked questions

Can diet soda make me crave sugar?

Research (including the current study) does suggest that people drinking diet sodas are also consuming more calories. There is some evidence that regular drinkers of diet soda may experience differential food reward responses in the brain in response to artificial sweeteners. However, it is not clear whether diet drinks themselves cause this difference or whether people who have a natural "sweet tooth" are more likely to seek out both artificially sweetened foods and beverages, as well as other energy-dense sweet foods.

One persistent myth is that artificial sweeteners are so much sweeter than table sugar, that they create a craving for sweets above and beyond normal sugar. As explained in Figure 3, this is simply untrue.

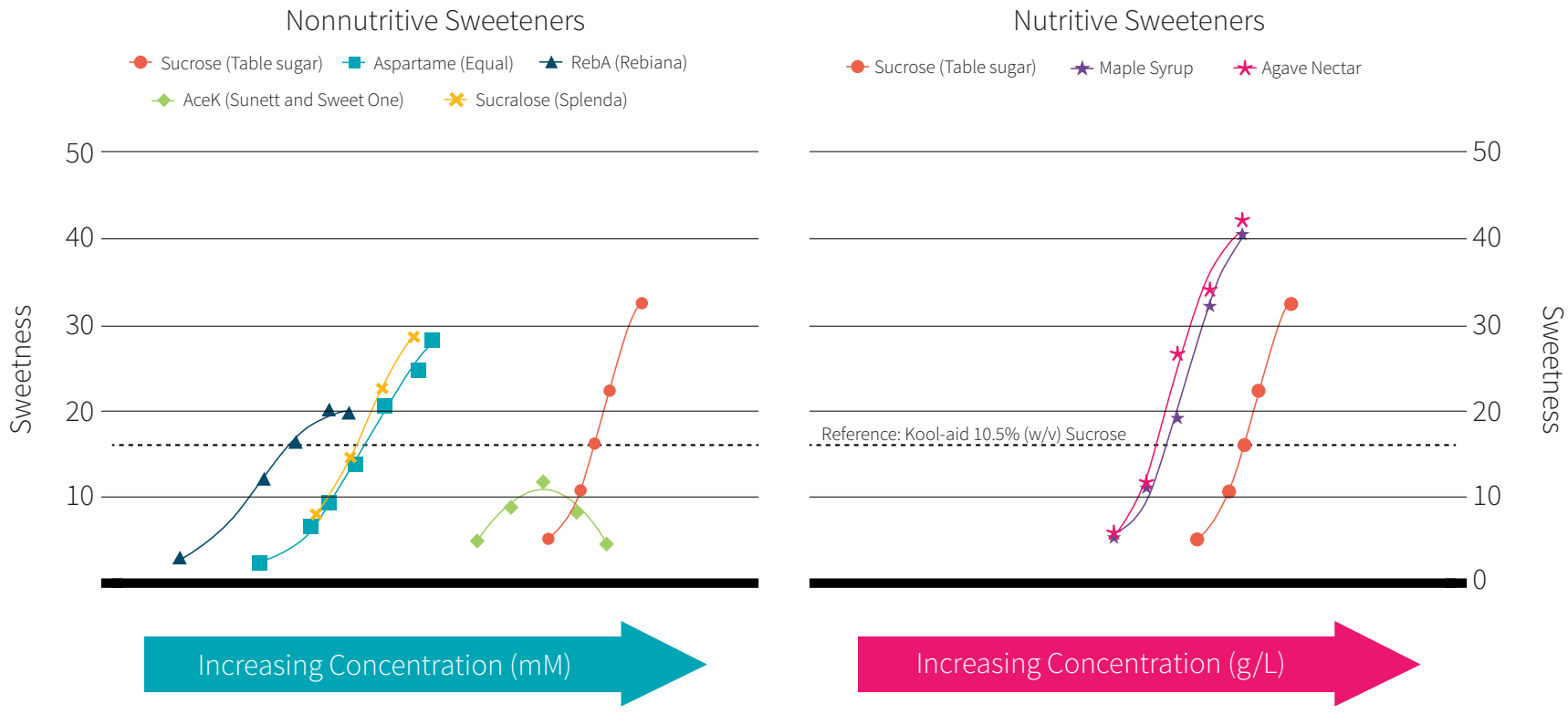
What do I need to know?

The benefits or detriments of diet soda compared to water for weight loss remain up in the air, though the current study puts a tick in the "cons" column.

The current study showed that dieters drinking diet soda showed less improvement in weight loss and glycemic markers, including fasting plasma glucose, two-hour postprandial glucose, fasting insulin, and HOMA-IR. This difference is likely due to the fact

Figure 3: Nonnutritive sweeteners

100's of times sweeter than sugar? Think again.



Nonnutritive sweeteners (NNS) are often talked about as being "hundreds of times sweeter than sugar". This stems from a misunderstanding of how sweetness is measured. In reality, NNS are hundreds of time more potent than table sugar because you can use a much smaller dose to obtain the same perception of sweetness as a nutritive sweetener. However, as you can see above they are often less sweet than table sugar.

Adapted from: Antenucci et al. Int J Obes (Lond). 2015 Feb.

Gelatin + vitamin C + exercise = joint benefits?

Vitamin C–enriched gelatin supplementation before intermittent activity augments collagen synthesis

Introduction

The collagen-rich extracellular matrix may be among the most underappreciated parts of the musculoskeletal system. It is required for proper functioning of the tendons, ligaments, cartilage, skin, and bone. For this matrix to function, an adequate amount of collagen and collagen crosslinking, along with water and minerals inside the tissue, is needed. Nutritional inadequacy and disease states can weaken connective tissue and leave it prone to breaking down from normal mechanical demands such as walking and even moderate exercise. In contrast, adequate nutrition and exercise are able to improve the functioning of the extracellular matrix, and collagen synthesis can be increased by an acute bout of exercise. The purpose for increasing collagen synthesis is to create denser and stiffer tissue, which can withstand higher loads.

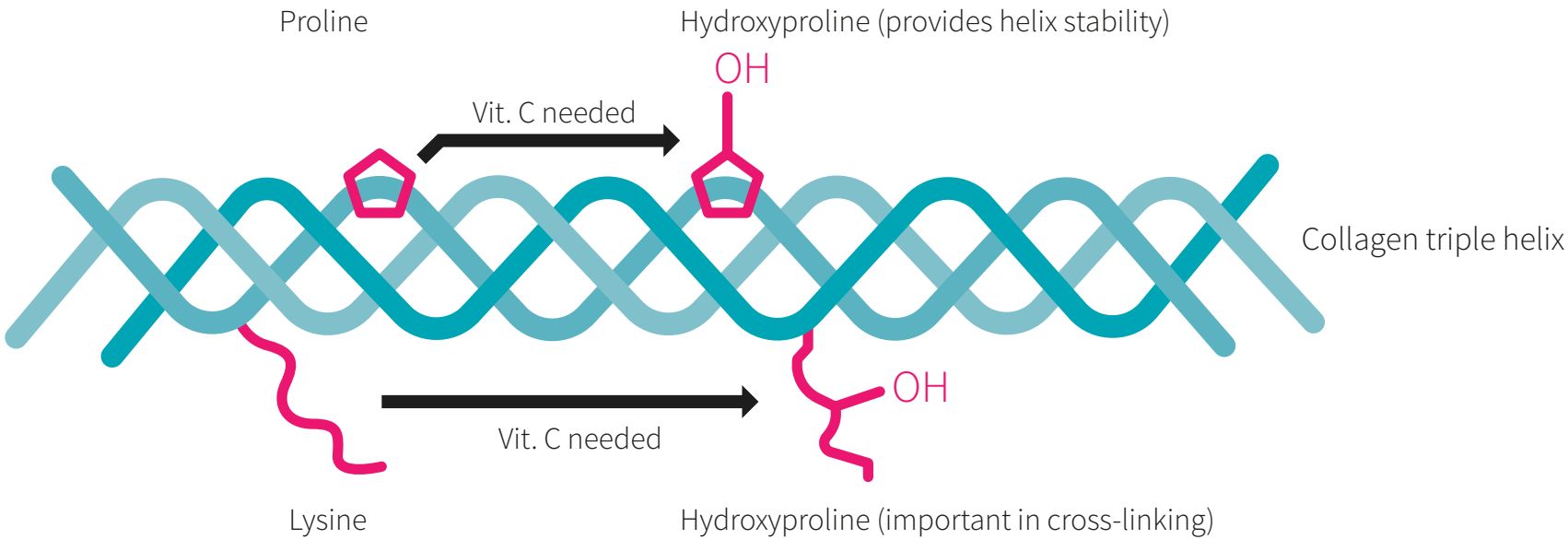
In vitro studies from engineered models of tendons and ligaments have shown that the presence of vitamin C and the amino acid proline can increase collagen production (shown in Figure 1), while increasing the amino acid glycine can improve tendon recovery from inflammation and make tendons more resistant to rupture. Up until this point, the combination of nutritional intervention and acute exercise bouts have not been studied with regard to their synergistic effects on collagen synthesis. With this in mind, researchers set up a study in humans to determine if consuming gelatin (a food derived from collagen and rich in proline and glycine) and vitamin C combined with exercise could increase collagen synthesis in healthy adult males.

A collagen-rich extracellular matrix is a critical part of a healthy musculoskeletal system. In addition to exercise, nutritional components such as vitamin C and the amino acids proline and glycine also play a role in collagen synthesis. This study was setup to determine whether gelatin supplementation (rich in proline and glycine) with vitamin C could increase collagen synthesis when taken before an acute bout of exercise.

Who and what was studied?

Eight recreationally active men participated in this double-blind crossover study (average 27 years old, 79.6 kilograms or 175 pounds), which provided them with 0, 5, or 15 grams of gelatin dissolved in a low-calorie drink that included 48 milligrams of vitamin C (about 80% of the recommended dietary allowance for men). One hour after ingestion, participants performed six

Figure 1: Vitamin C's role in collagen structure and function



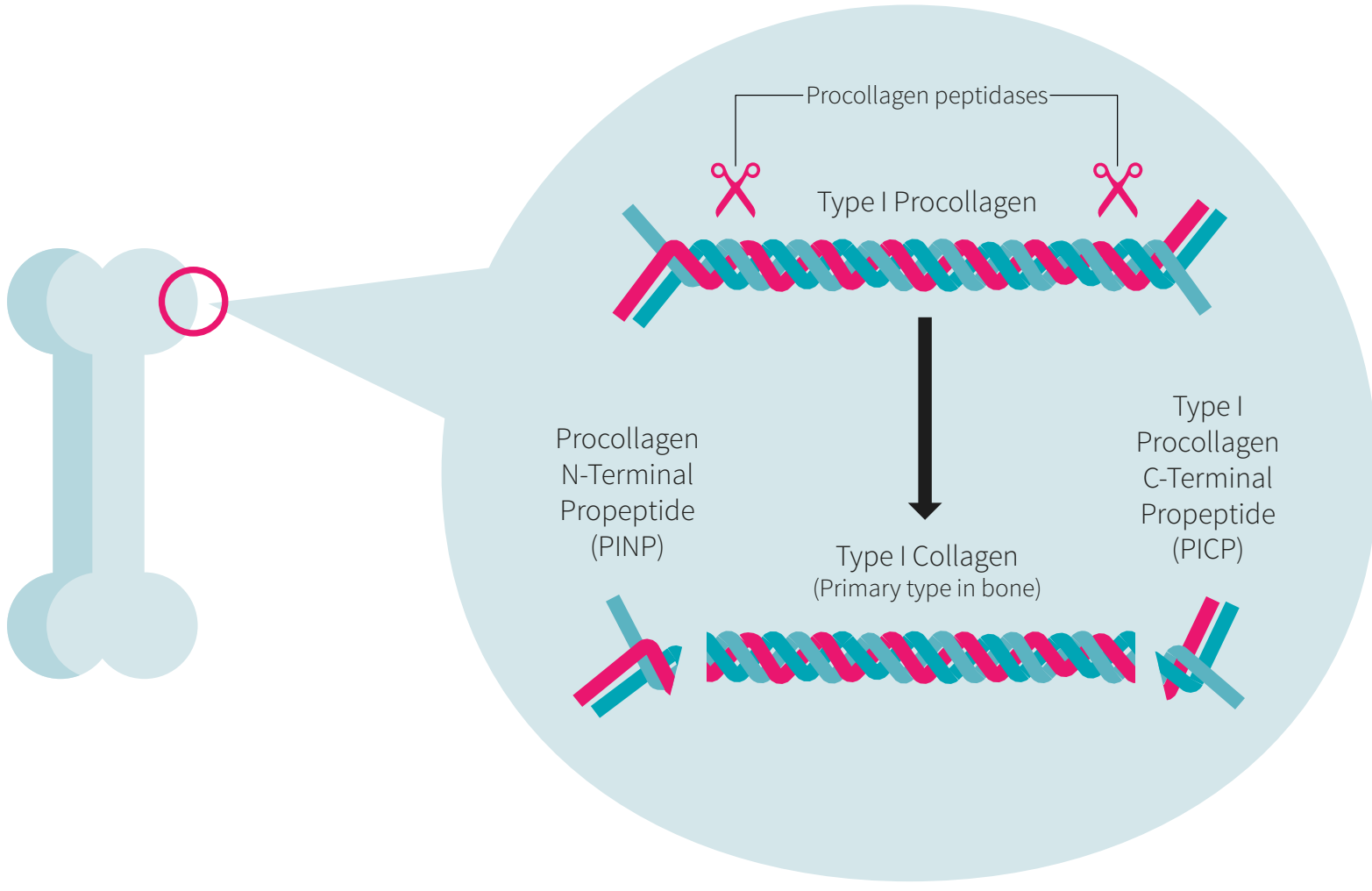
Reference: Shoulders et al. Annu Rev Biochem. 2009.

minutes of jump-rope activity in order to load the musculoskeletal system. This process was repeated two more times that day outside of the lab, and six more times over the following two days. There was a minimum of six hours between sessions. Blood samples were collected at multiple time points during the initial lab visit, and again on each day of the study. Blood was processed for N-terminal peptide of pro-collagen I (PINP, shown in Figure 2), which is a marker of collagen synthesis and bone formation. Supplement groups (0, 5, or 15 grams of gelatin) were randomly assigned, and there was a four-day washout period between treatments. The washout period was confirmed to be adequate because baseline PINP levels were not different among trials.

Engineered ligaments were also used in this study to determine the effects of gelatin on collagen synthesis. Ligaments were formed from human cells of the anterior cruciate ligament (ACL). Blood samples from four of the eight study participants were used, taken both before and one hour after supplementation. The ligaments were treated with the blood plasma samples for six days, and then tested for length, maximal tensile load (MTL), and cross-sectional area (CSA). This allowed stiffness and overall tensile stress resistance to be determined.

This double blind, randomized crossover-design study had eight healthy male participants consume either 5 or 15 grams of vitamin C–enriched gelatin or a placebo control, followed one hour later by six minutes of jumping rope to stimulate collagen synthesis. Engineered ligaments were also studied using samples of blood collected from a portion of the study participants.

Figure 2: Where PINP comes from



Bone extracellular matrix

Reference: Krege et al. Osteoporos Int. 2014 Sep

What were the findings?

As expected, blood levels of the amino acids that are present in significant amounts in collagen, such as glycine, proline, hydroxyproline, and hydroxylysine increased in a dose-dependent manner (meaning the higher the dose of collagen, the higher the amount of each amino acid was present in the blood). The amino acids peaked one hour after taking 15 g of supplemental gelatin, with the exception of amino acids having a lower concentration in the supplement, such as lysine, which peaked after 30 minutes. When given 5 g of gelatin, most amino acids peaked in the blood after 30 minutes.

Collagen synthesis after exercise (as measured by PINP levels) increased by 54-59% in both the placebo and five-gram gelatin groups, and by 153% in the group receiving 15 grams of gelatin. These changes were observed after four hours and maintained throughout the entire 72-hour treatment duration. The area under the curve (the total amount of PINP over the measurement duration) was doubled in the 15-gram group.

After six days of treatment with serum drawn from the participants, engineered ligaments showed an increase in collagen content and percent of collagen relative to dry mass. These increases were larger when treated with the serum from participants taking higher doses of collagen. They also occurred without a change in the cross-sectional area, which implies that the density of the collagen is what was increased (which is thought to be favorable). In order to test whether this could lead to any functional changes, the ligaments were mechanically tested to failure. The maximal tensile load (MTL) is a way to measure how much stress something can withstand before breaking. This value increased with all treatments, compared with the baseline sample, including the placebo group, with no differences among treatments. That the effect was observed even in the placebo group was somewhat unexpected, but likely is due to the vitamin C content of the drink.

Supplementation with gelatin increased circulating glycine, proline, hydroxyproline, and hydroxylysine in a dose-dependent manner, peaking in the blood one hour after the ingestion. Ingestion of 15 grams of gelatin one hour before jumping rope for six minutes led to an increase in collagen synthesis, measured by a doubling of PINP in the blood.

What does the study really tell us?

This study shows that consuming 15 grams of gelatin along with a small amount of vitamin C, prior to a short bout of moderate-impact exercise, can increase collagen synthesis, which could potentially play a beneficial role in both injury prevention and tissue repair. In addition to the potential benefits observed, many people should be able replicate the design of this study fairly easily. This would be in contrast with other studies that use interventions which might be quite challenging to follow.

Participants were ingesting the supplement and exercising three times per day for three days, and measures of collagen synthesis were taken after the first exercise bout (hour six) as well as hours 24, 48, and 72. Noteworthy is the fact that the increase in collagen synthesis observed at the six-hour mark was maintained throughout the study. This means that not only can an acute dose have a beneficial effect, but the benefits can be maintained for at least three days. Longer studies would obviously be needed to determine if there is any compensatory effect where either more gelatin or more exercise might be needed to stimulate the same response. Keep in mind that this study used very small sample, that was also fairly young. Future research is needed to see if the response in an older population would be similar.

This study also showed that consuming a lower amount of gelatin led to blood levels of amino acids that peaked 30 minutes after ingestion. This means if someone is taking in a smaller amount (about five to 10 grams), exercise should be performed a bit closer to the time of ingestion. This is particularly relevant because recipes that use gelatin often call for smaller amounts per serving. For instance, one cup of bone broth often contains less than 5 grams of total protein.

Consuming 15 grams of gelatin one hour before an acute bout of exercise appears to be an effective way of increasing collagen synthesis.

The big picture

These findings are in line with the limited previous research in what is seemingly an under-researched field. PINP in the blood is often used as a marker of bone metabolism because of its higher turnover rate, though it can also be increased from exercise. Bone responds most dramatically to short periods of exercise, separated by about four to eight hours of rest. This pattern offers a greater osteogenic (bone building) stimulus than a single sustained session of exercise, as the sensitivity of bone cells to loading quickly becomes saturated. While a number of studies have shown mechanistic benefits and pain reduction with gelatin supplementation, this is the first study that shows the increase in bone collagen synthesis from mechanical stress could be supported and enhanced by a nutritional intervention.

The kinetics seen in this study are similar to those seen elsewhere, with another study showing that the peak of hydroxyproline in the blood was delayed as the gelatin dose increased. While this study didn't measure functional outcomes, other studies have. An increase in collagen within the knee as well as reduced knee pain was shown after the consumption of 10 grams per day of collagen hydrolysate (a differently-processed version of gelatin) for 24 weeks. Animal research has shown that gelatin hydrolysate was more effective at being incorporated into the collagen of cartilage and muscle compared with individual amino acids.

The in-vitro model of engineered ligaments has been previously used to look at the effects of menstrual cycle hormones, showing that estrogen decreases the activity of a key enzyme involved in collagen cross-linking which could potentially explain the elevated rate of ACL rupture in women. This model has also looked at resistance training and the accompanying hormonal rise in the post-exercise window, showing that collagen content and tensile strength are enhanced after exercise.

> “ […] this is the first study that shows the increase in bone collagen synthesis from mechanical stress could be supported and enhanced by a nutritional intervention.”

Also noteworthy is the effect of the exercise intervention itself, six minutes of jumping rope followed by six hours of rest, which was able to increase collagen synthesis in the placebo group (to a smaller degree than the 15 gram gelatin group). Research in engineered ligaments has shown a greater increase in collagen synthesis from 10 minutes of activity followed by six hours of rest compared with continuous activity. This is supported by animal research showing that low volume, high impact activity can increase bone mass and mineralization, and a human study that showed improved bone mineral density after just 10 vertical jumps per day, three times per week. Together, the available data overwhelmingly supports the idea that musculoskeletal tissues can be maximally stimulated for collagen synthesis from short periods of activity with long rest periods.

> “Research in engineered ligaments has shown a greater increase in collagen synthesis from 10 minutes of activity followed by six hours of rest compared with continuous activity.”

An unexpected finding was that the engineered ligaments showed a similar increase in mechanical strength in all of the supplement groups, *including the placebo*. This may be due to the vitamin C content of the drink used in the study, which contained 48 milligrams of vitamin C. Vitamin C may help increase collagen synthesis and/or increase cross-linking between the collagen molecules. Because the collagen concentrations in the *in vitro* model only increased with gelatin (and not with vitamin C alone in the placebo condition), it is likely that the increase in collagen concentration is due to an increase in cross-linking. This would also be consistent with the increase in tensile strength without an increase in cross-sectional area that was observed in the engineered ligaments supplemented with blood of individuals who consumed gelatin. Future studies should also measure serum concentrations of vitamin C.

This study is in line with previous human studies, as well as research using engineered ligaments and animals, showing improvements in bone and joint function as a result of acute exercise bouts, gelatin supplementation, and vitamin C.

Frequently asked questions

Would the participants have seen a benefit with less than three sessions per day?

There would likely be some benefits even from single doses of gelatin followed one hour later by a short bout of ballistic exercise. In this study, increased collagen synthesis occurred as early as four hours after the first bout of exercise.

Would the study results be different in women?
Possibly. It appears that in females the increase in collagen formation in connective tissue after exercise is less than that of males. It was speculated that this could possibly be due to the effects of estrogen. However, no effects of menstrual phase on collagen synthesis at rest or after exercise have been observed. It is unknown (but conceivable) that a greater dosage of gelatin would be required to see a similar increase in collagen formation in women.

Why take gelatin at all? Isn't it just made of amino acids like other protein?
It's true that gelatin is essentially a protein. However, it has a different amino acid profile compared to typical protein supplements such as whey, with specific profiles broken out in Figure 3. Specifically, it is much higher in proline, glycine, hydroxylysine, and hydroxyproline, all of which are found in higher amounts in collagen, which may make a difference. In fact, the inspiration for this study came about from two previous studies that found that some of these amino acids matter. In one of these, the engineered tissue used in this study was seen to synthesize more collagen in the presence of proline plus vitamin C. In the other study, glycine intake was seen to improve Achilles tendon mechanics after injury.

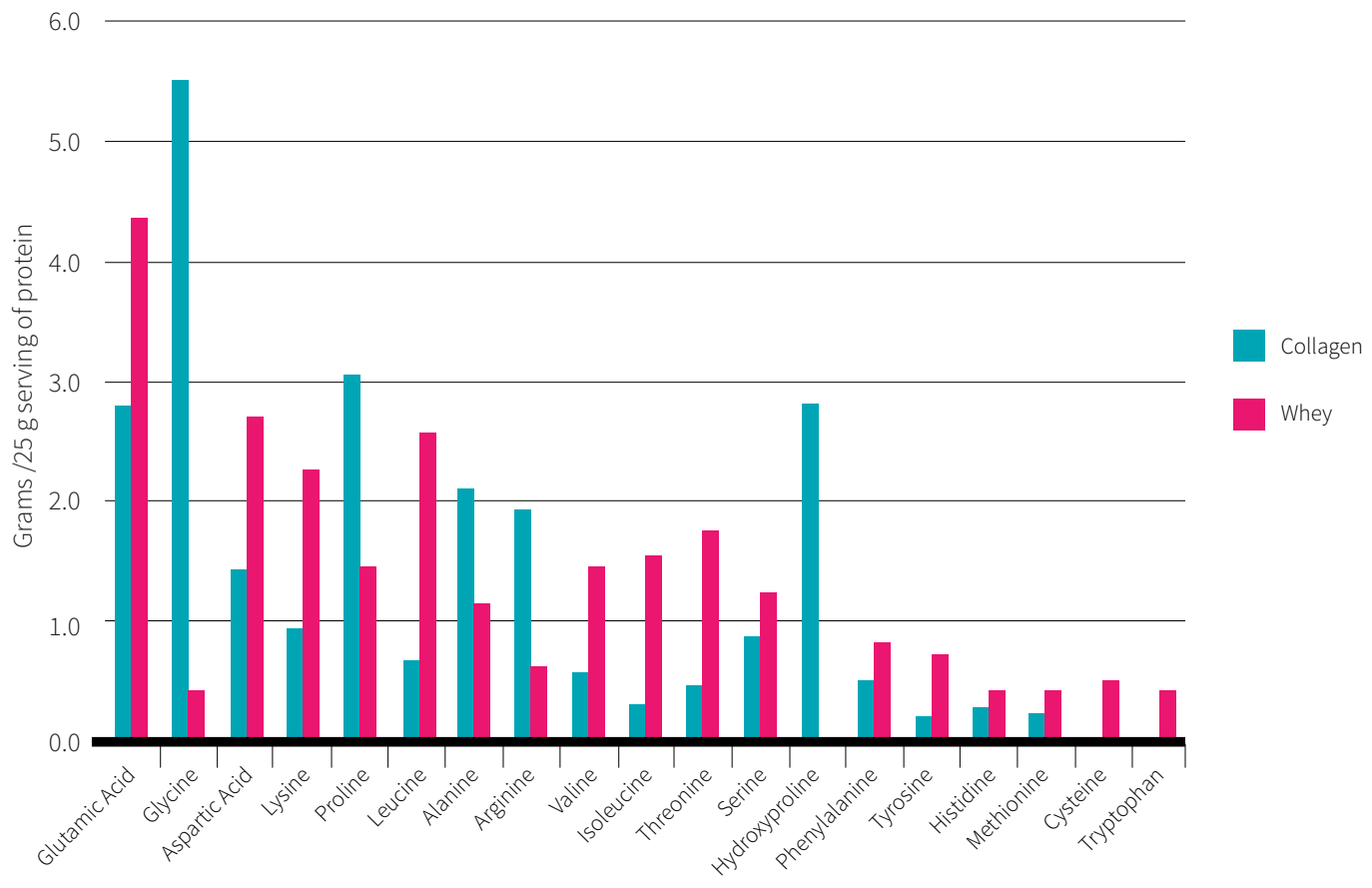
Can I consume Jell-O and get the same effect?
Unfortunately not. Individual packs of "Jell-O" contain about 1 g of protein. This means you would need to consume about 15 packs to get a similar amount of protein, which would provide over 240 grams of sugar and 1000 kcals! But if you were to make your own gelatin dessert out of a more protein-rich gelatin, that could be different.

What should I know?

Collagen synthesis can be modulated by an acute bout of exercise and provision of certain amino acids alongside vitamin C. This study is the first to show that supplementation with 15 grams of gelatin one hour prior to a six minute bout of rope skipping can enhance collagen synthesis after exercise, potentially having benefits for injury prevention and tissue repair. ◆

Finally, you are aware of the true nature of The Matrix (the extracellular matrix, that is). Discuss supplementation for The Matrix at the ERD Facebook forum.

Figure 3: Amino acid profile of whey vs. collagen



SCD for IBD?

Clinical and Fecal Microbial Changes with Diet Therapy in Active Inflammatory Bowel Disease.

Introduction

Inflammatory bowel disease (IBD) refers to a group of chronic inflammatory conditions that affect the gastrointestinal tract. The two most common types of IBD are Crohn's disease, which can impact any portion of the digestive system from mouth to anus, and ulcerative colitis, which is restricted to the colon and rectum. Up to 0.5% of the Western world is estimated to suffer from IBD and associated medical costs may exceed $6 billion annually.

There is no known medical cure for IBD, with the most common treatment option being surgery to remove affected areas of the intestinal tract. Individualized drug therapies, including immunosuppressant drugs and steroids, are also used to help control symptoms and reduce inflammation. But side effects can be substantial from some of these medications.

One reason for the lack of a full-blown cure is the complicated etiology of IBD. For instance, there is a clear genetic predisposition for developing IBD that shares similarities to type 1 diabetes and other autoimmune conditions. In addition, IBD is associated with a reduced diversity of bacteria in the gut microbiome, including a reduction of bacteria with anti-inflammatory properties and an increase in bacteria with pro-inflammatory properties. It is likely that IBD arises from an interaction between environmental and genetic factors that ultimately leads to an inappropriate immune response against the gastrointestinal tract.

The role of the microbiome in the pathology of IBD has spurred an interest in dietary strategies to manage IBD. Enteral nutrition (tube feeding) is currently the first line therapy in children with IBD and in adults who do not tolerate treatment with steroids. However, a major problem of enteral feeding as primary therapy for IBD is the high relapse rate when patients return to a normal diet: approximately 50% within six months. Moreover, the low palatability of feeds, going for long periods without solid food, the cost of the enteral formulas, and the social inconvenience make staying on enteral therapy difficult over the long term.

Aside from enteral therapy, there are several diets promoted in the lay literature for managing IBD. One of the most commonly recommended is the specific carbohydrate diet (SCD), which postulates that disaccharides and starch are poorly absorbed in the intestinal tract, causing an overgrowth of bacteria that exacerbate mucosal damage. Accordingly, the SCD excludes several types of food (shown in Figure 1), including all grains and sugars except for honey, processed foods, and lactose-containing dairy products.

Figure 1: Prohibited foods in the Specific Carbohydrate Diet

Canned fruits and vegetables

Foods high in sugar alcohols

Foods high in starch

Dairy high in lactose

Foods and drinks with added sugars

Non-distilled alcohols

Reference: Gottschall, E. Breaking the vicious cycle: intestinal health through diet. Kirkton, Ont Kirkton Press, 1994.

To date, there is limited evidence supporting the use of the SCD in managing IBD. Three case studies, two retrospective analyses, an online survey, and a single small-scale clinical study have documented clinical and symptomatic improvements, including mucosal healing of the intestinal tract, in patients with IBD following the SCD. The study under review sought to add to the currently available literature by examining the effect of the SCD on clinical disease activity, markers of inflammation, and microbiome composition in patients with IBD.

Inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, is a chronic inflammatory condition of the gastrointestinal tract with no known medical cure. Current treatment options include surgery, steroids, and tube feeding, none of which are popular. The specific carbohydrate diet (SCD) is a common recommendation in the public domain for managing IBD, but it lacks scientific rigor to support its efficacy. The study under review sought to evaluate the effect of the SCD on clinical disease activity, markers of inflammation, and microbiome composition in patients with IBD.

Who and what was studied?

This was a 12-week, open-label, multicenter (Seattle, WA and Atlanta, GA) clinical study that recruited people 8 to 21 years old with mild to moderate Crohn's disease or ulcerative colitis (10-45 on the pediatric Crohn's disease activity index [PCDAI] or 10-60 on the pediatric ulcerative colitis index [PUCAI]). Ultimately, 12 children and adolescents aged 10-17 years (average: 13 years) with an average disease duration of 1.3 years (range: 0-5 years) began the intervention. Nine participants had Crohn's disease and three had ulcerative colitis.

All participants followed the SCD as the sole intervention for the entire 12 weeks. They received one-on-one education and counseling from a registered dietitian

What are the PCDAI and PUCAI?

The PCDAI and PUCAI are symptomatic questionnaires developed to assess disease severity in children. The questionnaires were developed to be non-invasive and avoid the need for endoscopy (viewing the intestines with a camera tube through the rectum or down the throat). Both ask questions about gastrointestinal pain and function, while the PCDAI also has questions about weight, growth, and a few bloodborne variables.

For the PCDAI, remission is considered a score below 10, which indicates an inactive disease state, while a mild disease state is between 10 and 30 points. Anything above thirty is considered moderate to severe, with a poor ability to accurately differentiate between the two. A PCDAI decrease of at least 12.5 points is considered to reflect a clinically meaningful improvement in patient condition.

For the PUCAI, categorical scores are less than 10 for inactive, 10-34 for mild, 35-64 for moderate, and greater than 65 for severe disease states. All cut-off points using the PUCAI are highly sensitive and specific for the condition. A clinically meaningful response to treatment is considered to be a reduction of 20 points in the PUCAI.

and were provided several resources to help with meal planning, including a recipe book and meal/snack recommendations. The participants met with the dietitian at each study visit and completed a three-day food log beforehand to help ensure compliance to the SCD. Additionally, the patients could contact the dietitian, research assistant, and primary gastroenterologist at any time if they had questions or concerns.

Study visits were performed at baseline, two, four, eight, and 12 weeks, when the PCDAI/PUCAI, blood samples, and stool samples were collected for analysis. The primary outcome was the change in the PCDAI/PUCAI at 12 weeks, while secondary outcomes included 12-week changes in C-reactive protein (CRP), sedimentation rate (another marker of inflammation), albumin (the main protein in the blood), and fecal calprotectin levels (a protein that indicates intestinal inflammation). Descriptive statistics for changes in fecal microbiome compositions were also compiled.

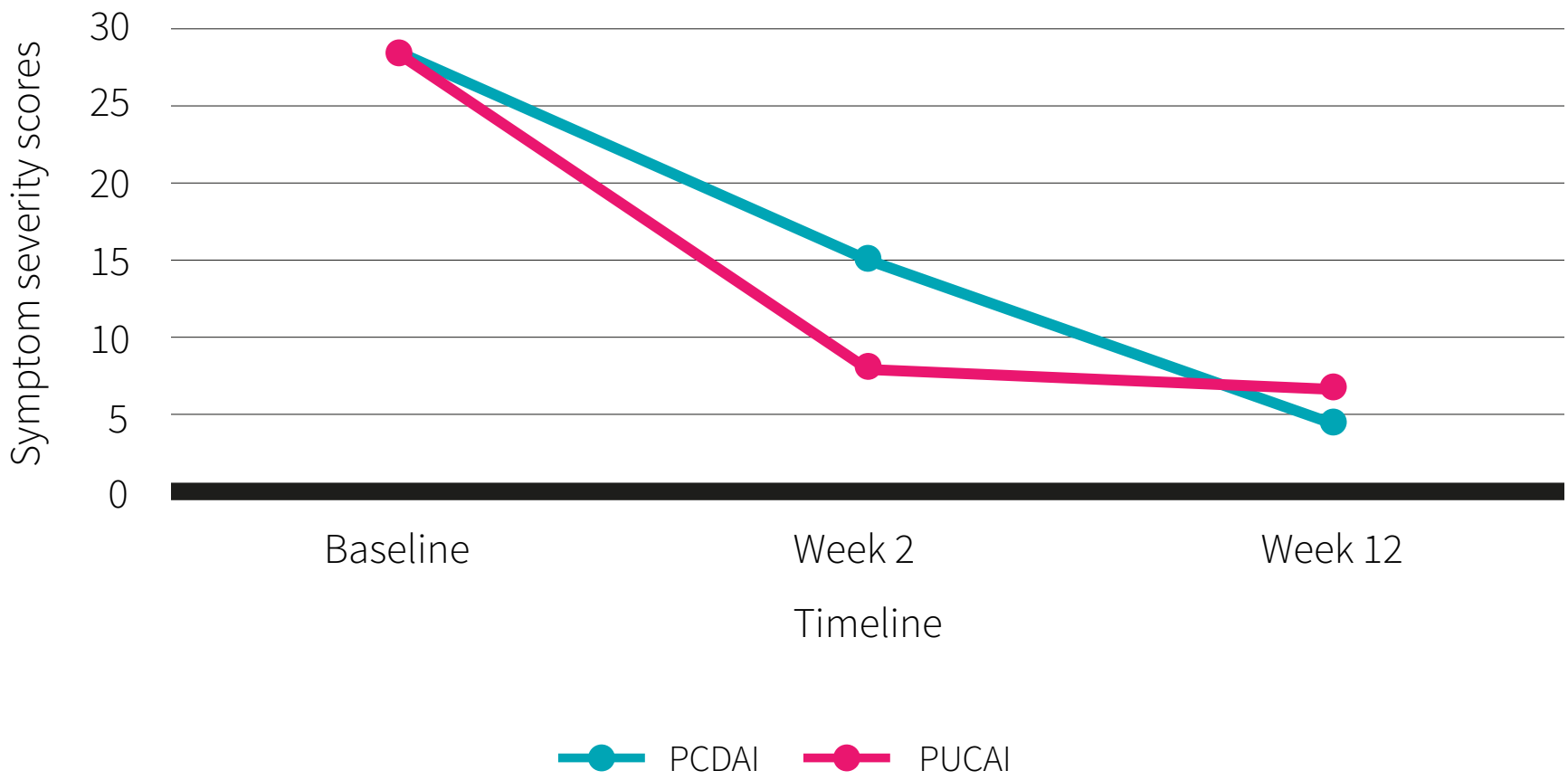
A group of 12 children and adolescents with mild to moderate Crohn's disease or ulcerative colitis followed the SCD for 12 weeks. Changes in the PCDAI/PUCAI were the primary outcome, while changes in CRP, sedimentation rate, complete blood count, and fecal calprotectin levels were secondary outcomes. Descriptive statistics were used to assess changes in participant microbiomes.

What were the findings?

Although no adverse events to the SCD intervention were reported, two participants dropped out of the intervention due to difficulty maintaining the diet (at two and eight weeks). One participant had Crohn's and the other had ulcerative colitis.

Of the remaining ten participants, five had achieved clinical remission after two weeks and eight achieved clinical remission by week 12. As illustrated in Figure 2, the average PCDAI score at baseline was 28, which

Figure 2: Effects of SCD on symptom severity scores



Reference: Suskind et al. J Clin Gastroenterol. 2016 Dec.

declined to 15 after two weeks and to 4.6 after 12 weeks. Similarly, the average baseline PUCAI score was 28 and declined to 8 after two weeks and to 6.7 after 12 weeks.

Levels of the two tested inflammatory markers, CRP and sedimentation rate, followed a similar pattern as the PCDAI/PUCAI scores. All participants significantly reduced their CRP by week 12, with all but one showing a reduction after the first two weeks. Average CRP at baseline was 21-24 milligrams per deciliter, which significantly declined to five to seven milligrams per deciliter after 12 weeks (71-76% reduction). The sedimentation rate was also reduced by 51-66% after 12 weeks, although this reduction only reached statistical significance in the Georgia-based children.

Neither serum albumin nor fecal calprotectin were significantly changed during the intervention. However, serum albumin was improved or maintained in all but one participant. Additionally, calprotectin was reduced by 68% in the Seattle cohort and nearly doubled in the Georgia cohort, which the authors state was largely driven by a single participant who ate non-SCD foods before the test.

Metagenomic sequencing of the participants' fecal samples revealed a modest 7% increase in the average diversity of bacterial species within the microbiomes (called "α-diversity") after 12 weeks. Proteobacteria, a phylum that includes many pathogenic bacteria such as E. coli and has been implicated in the chronic inflammation of Crohn's disease, decreased in all but two participants who began the study with the highest and lowest abundance. However, there were no changes in other phyla of bacteria.

The SCD was associated with clinical remission of IBD in most patients who adhered to the diet. It was also associated with a reduction in markers of inflammation (CRP and sedimentation rate) and modest changes in the composition of the participants' microbiomes.

What does the study really tell us?

The current study strengthens the small base of evidence reporting on the effect of the SCD in patients with IBD by suggesting that following the SCD for 12 weeks leads to clinically meaningful reductions in disease severity and inflammation. In addition, the study under review adds to the literature by reporting on the changes of the patients' microbiomes while following the SCD.

The only other clinical study to follow IBD patients consuming the SCD was published in 2014. This study used the same design and recruitment criteria as the study under review, ultimately involving nine adolescents who were followed for 12 weeks. The PCDAI significantly decreased from 21 points at baseline to 8 points after 12 weeks. Moreover, capsule endoscopies revealed that the intestinal ulcers of four patients at baseline were no longer present by week 12. Seven of the nine patients continued with the diet for one year and showed a further small reduction in the PCDAI, down to 5.4 points on average.

Both clinical trials suggest that the SCD may be a worthwhile pursuit for managing IBD. However, the diet is strict and adherence was a documented problem. One retrospective analysis of 11 adolescents with IBD suggests that regularly eating some non-SCD foods after an initial strict SCD period does not significantly affect hematocrit, sedimentation rate, albumin, or growth parameters. This suggests that the SCD, even with mild liberalization, may offer a sustainable real food therapeutic intervention. However, disease severity and remission on the liberalized SCD were not assessed. Follow-up research is necessary to determine if a less strict SCD can increase dietary adherence while maintaining the diet's clinical benefits.

The observations regarding the participants' microbiomes suggest that the SCD does influence the diversity

and composition of our gut bacteria. However, the implications of these observations remain to be determined. An increase in microbial diversity and a reduction in pro-inflammatory bacteria seems beneficial, but how these changes influence disease severity or other aspects of wellbeing are unknown.

The methodology of the study under review is its greatest limitation. Without a control group for comparison, we cannot say that the observations were owed exclusively to the SCD. This is especially so considering that the children and parents being recruited had a strong personal belief that the SCD would provide a benefit. An online survey of people with IBD who followed the SCD reported that more than one-third of the respondents perceived that they achieved clinical remission of the disease, despite most participants not maintaining a strict SCD. A placebo effect benefit of the SCD cannot be excluded. Some research suggests that stress is associated with IBD symptoms, and the patients could therefore have experienced some reduction in the PCDAI and PUCAI through a reduction in stress from medical care.

Other limitations include the small sample size of children and adolescents, the lack of an objective marker to determine dietary compliance, and variation in treatment from the two study sites (Seattle and Atlanta).

Most research investigating the SCD in IBD to date has involved pediatric populations. The online survey above involved people aged between 1.5 to 70 years, with an average age of 35 years, suggesting that adults with IBD may benefit from the SCD. However, clinical trials using an adult population will be necessary to paint a more complete picture of how the SCD interacts with IBD pathology.

The SCD may benefit pediatric patients with IBD, but follow-up research using a stronger methodology (such as including a control group) is necessary before firm conclusions can be made. Nonetheless, the current findings support those of the only other clinical trial to date and provide a promising foundation for further investigation into using the SCD as a dietary therapy for managing IBD in children and adolescents.

“An increase in microbial diversity and a reduction in pro-inflammatory bacteria seems beneficial, but how these changes influence disease severity or other aspects of wellbeing are unknown.”

The big picture

Most people with IBD pursue the SCD to manage the disease, avoid medications, or achieve a level of health that medications alone could not provide. Aside from the SCD, there are limited case reports of other diets reporting positive results with various levels of carbohydrate restriction.

A retrospective analysis from 1979, in which IBD patients were encouraged to reduce their consumption of added sugars and refined carbohydrates while increasing their consumption of fruits and vegetables, reported reductions in hospital visits and time spent in hospitals compared to a control group that received no special dietary instructions. The diet-treated patients consumed an average of 33 grams of fiber per day and much less sugar than the controls (39 vs. 90 grams per day, on average).

However, the above study is directly contradicted by a randomized controlled trial showing no difference in clinical endpoints, including disease relapse and the need for surgery, between two groups given opposing dietary advice. Participants in one group were advised to "eat carbohydrate in its natural unrefined state only, avoiding all products containing sugar or white flour." Participants in the second group were "advised to eat carbohydrate in its refined form using white flour and rice and to avoid unrefined carbohydrate foods; sugar intake was unrestricted." These null findings held true when the analysis was restricted to participants who consumed more than 110 grams of sugar and less than 14 grams of fiber per day (refined carb group) and those patients who consumed less than 10 grams of sugar and more than 30 grams of fiber per day (unrefined group). However, these IBD patients had inactive or mildly active crohn's disease, which is in contrast to most other research involving people with moderately active or severe IBD.

A more recent study reported that a lacto-ovo-vegetarian diet led to a lower rate of IBD relapse over one and two years of follow-up compared to an omnivorous diet. Similarly, a case series reported benefits in IBD patients that followed an "anti-inflammatory diet" with similar dietary restrictions as the SCD (based on lean meats, poultry, eggs, fruits, starchy and fibrous vegetables, some dairy products, nuts, legumes, and oats as the only grain).

Although the evidence to date is mixed, the majority suggest that a minimally processed diet which eliminates added sugars and processed grains may have benefits for people with IBD. The SCD eliminates grains entirely, but other research suggests that it is the elimination of processed foods and refined grains rather than grains per se that benefit IBD.

An association between ingestion of incompletely absorbed fermentable carbohydrates (FODMAPs) and IBD has been postulated. However, the SCD encourages consumption of fruits and vegetables, some of which contain large amounts of FODMAPs.

The efficacy of a low-FODMAP diet for managing irritable bowel syndrome (IBS) was investigated in ERD #26, Volume 1, "Cut out FODMAPs, cut out IBS symptoms?". Based on 22 clinical trials included in this meta-analysis, adherence to a low-FODMAP diet resulted in clinically meaningful reductions in IBS symptom severity, such as bloating and abdominal pain. However, IBS is difference from IBD in that it is less severe and does not cause inflammation or damage to the intestinal tract. As such, the applicability of these findings to IBD is debatable and clinical trials are needed to test how FODMAP restriction in IBD patients performs, especially compared to other dietary therapies such as the SCD.

Several studies using diets that eschew processed foods, added sugars, and refined grains have reported clinical benefits in IBD patients, suggesting that a minimally processed diet is the centerpiece for the dietary management of IBD. Further research is necessary to figure out the nitty-gritty.

Frequently asked questions

What's the difference between IBD and IBS?

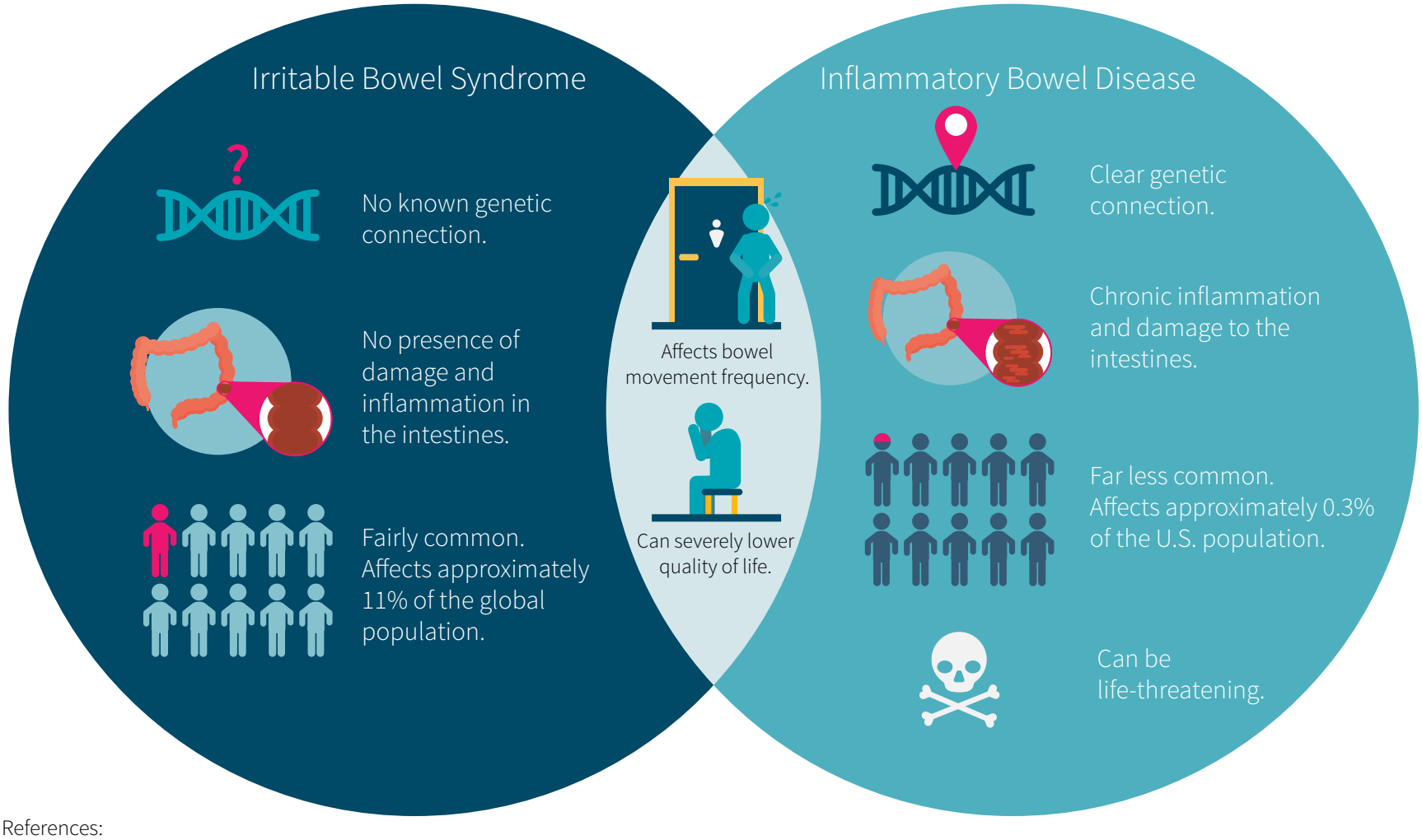
IBD and IBS are compared in Figure 3. They share several similarities, including gut-brain axis dysfunction, the involvement of genetic factors, and microbiome dysbiosis. Some evidence even suggests that the conditions have a similar impact on quality of life and psychological distress. However, there are a few key differences between the conditions that make them separate entities, the main one being that inflammation of the gastrointestinal tract is central to IBD pathogenesis. By contrast, IBS is a non-inflammatory condition and not currently classified as a true disease. Rather, IBS is classified as a "functional disorder," meaning that its symptoms don't have an identifiable cause.

What should I know?

Inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, is a chronic inflammatory condition of the gastrointestinal tract with no known medical cure. Current treatment options include surgery, steroids, and tube feeding, none of which are popular.

The specific carbohydrate diet (SCD) is a common recommendation in the public domain for managing IBD, and the current study supports that recommendation. The study under review found that following the SCD for 12 weeks in a pediatric population led to clinically meaningful reductions in disease severity, putting most

Figure 3: Irritable bowel syndrome



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patients into remission. The SCD diet therapy was also associated with reductions in inflammatory markers and changes in the microbiome, both of which require further investigation to determine their practical relevance. Other research to date has suggested that, overall, diets low in refined grains and added sugars (read: most processed foods) lead to improvements in IBD severity. ◆

The SCD may be the most popular single diet for addressing IBD. This study adds to the evidence base and delves into mechanisms, even though it doesn't get as far as using a randomized controlled design. Discuss options for IBD at the ERD Facebook forum.

The mindfulness-body connection

Mindfulness-based interventions for adults who are overweight or obese: a meta-analysis of physical and psychological health outcomes.

Introduction

Several studies have found an association between overweight and obesity and mental health issues like anxiety and depression in both adults and children.

Most weight loss approaches focus only on the behaviors of eating and perhaps exercise in order to lose weight. This approach tends to ignore the psychological and emotional issues that sometimes co-occur with overweight and obesity. One approach that has the potential to impact both weight and psychological well-being is mindfulness.

Mindfulness doesn't have a single agreed-upon formal definition, but the definitions which exist point to similar qualities. The founder of Mindfulness-Based Stress Reduction, Jon Kabat-Zinn, has described mindfulness as attending to the present moment intentionally and non-judgmentally. This form of awareness to the present moment cultivates curiosity and tends to lead to acceptance of what is happening internally and externally. This may help people lose weight; if a person feels hungry or has an urge to eat, they can accept the feeling by being mindful of it instead of automatically acting upon it.

This makes it sound like mindfulness could be helpful for people with overweight or obesity in theory. But does it work in practice? This question has been partially addressed in three previous systematic reviews, and the short answer to this question leans toward 'yes'. The reason these reviews only provide a partial answer, however, is because all three either included studies where BMI wasn't reported, or lumped people with BMIs above and below 25 into one big group. So, none of these reviews fully addressed the question of whether mindfulness is effective in people with a BMI greater than 25.

The present systematic review and meta-analysis attempted to address these concerns.

Mindfulness involves paying attention to present moment experiences intentionally and non-judgmentally. Cultivating this skill may help with people with overweight or obesity both lose weight and improve psychological well-being. Previous systematic reviews examining this issue have either included people with BMIs less than 25 or included studies where no BMIs were reported. The current study attempted to fill this gap by analyzing people whose BMIs were over 25.

Who and what was studied?

For this systematic review and meta-analysis, several databases were searched for both observational and interventional studies looking at mindfulness-based interventions in adults with a BMI greater than or equal to 25. The searches included studies up until mid-2015. Studies that involved only a single treatment session or included mindfulness as a minor component of treatment were excluded.

A total of 15 studies were ultimately included, with a total of 560 participants. Seven of the studies were randomized controlled trials (RCTs) and eight were prospective cohort (PC) studies. These are a type of observational study that doesn't involve a control group or randomization. Instead, you just take a bunch of people, do an intervention, and see what happens. Results from PC studies are less reliable since confounders can still exist due to lack of randomization, and also because there's no control group with which to compare results.

The included RCTs and PC studies used a variety of mindfulness techniques; seven used what the authors called a "multifaceted mindfulness approach" (e.g. being mindful of urges and pausing before giving in, or eating more slowly and paying attention to each

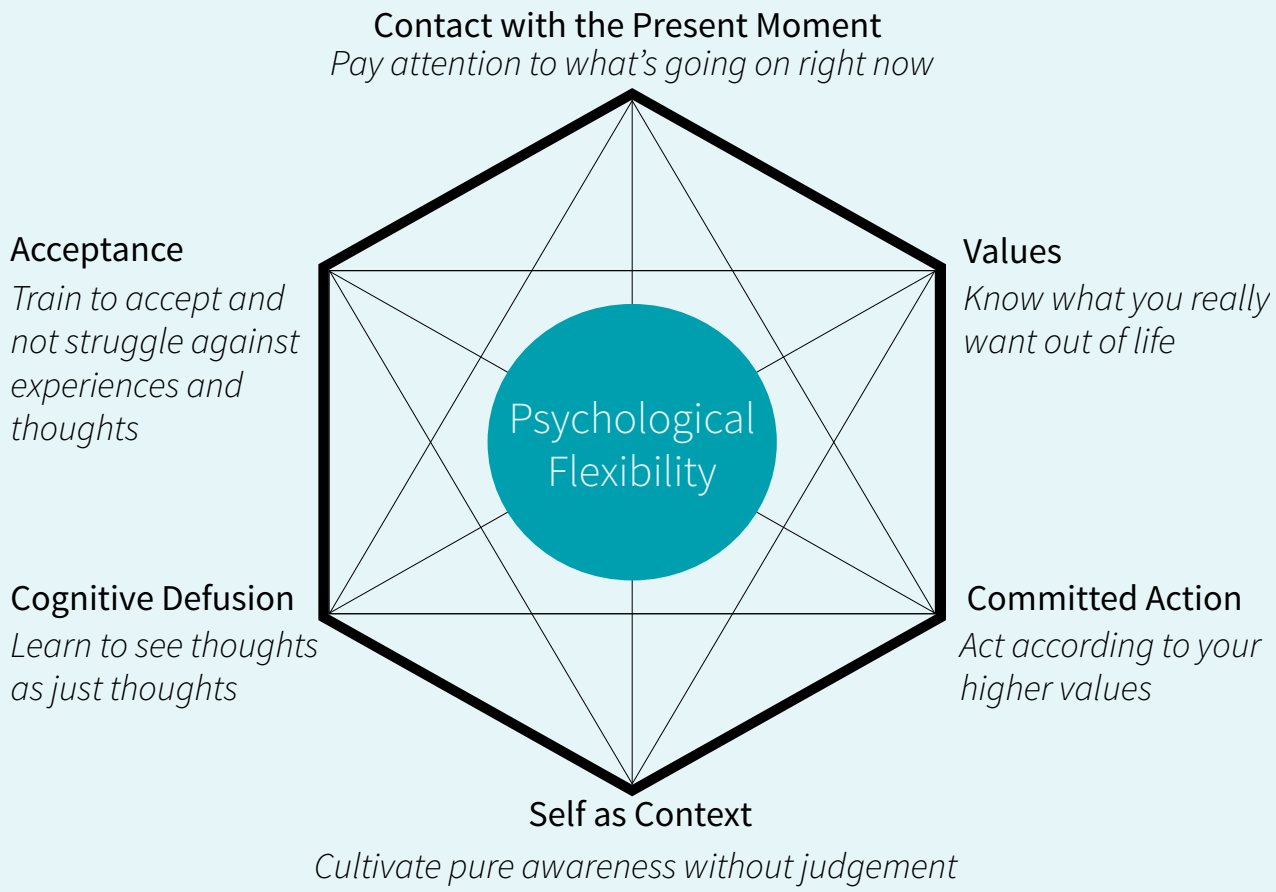
sensation involved with eating, perhaps mixed with meditation and other methods), six used Acceptance and Commitment Therapy (ACT - see the sidebar for more info), and two focused on meditation (e.g. sitting down, closing your eyes, and paying attention to the sensations of breathing). They also had wide variety in dose; four to 40 sessions were used, with a median of 9.5. Each session lasted 1.75 hours on average. In all, the median dose of mindfulness was 12 hours between the studies.

Acceptance and Commitment Therapy

Acceptance and Commitment Therapy is a third-wave behavioral therapy. The first wave consisted of changing behaviors. Techniques such as exposure therapy for phobias fall into this category. In exposure therapy, people are either gradually or suddenly exposed with consent to a feared object, and the fear tends to subside with repeated exposures. The second wave added thoughts to the equation, becoming cognitive-behavioral therapy (CBT). This family of therapies asked clients to change both behaviors as well as challenge irrational or harmful thoughts. Third-wave behavioral therapies take a different approach to thoughts: instead of challenging them, one is mindful of them, seeing them as just thoughts instead of necessary facts. Doing this allows the person to then act according to their higher values instead of responding mindlessly to emotion and circumstance.

ACT is one type of third-wave behavioral therapy whose name summarizes what it does. It teaches people to accept thoughts and feelings using mindfulness-based methods instead of fighting them, and then take committed action to one's higher values. ACT therapists tend to insist that the acronym be pronounced "act" instead of "A-C-T" to emphasize commitment to action. There are six areas of training in ACT, which can be seen in Figure 1.

Figure 1: The ACT Hexaflex



Eight different categories of data were then extracted from these studies: depression, anxiety, stress, mindfulness skill, quality of life, eating behaviors, eating attitudes, and BMI. Not all studies had every single measurement, though. Each of these measurements was converted to a standardized effect size (classified as large, medium, and small) so that studies using different assessment tools could be compared.

This systematic review and meta-analysis looked at the effect of mindfulness-based interventions on mood, eating behavior and attitudes, and weight loss for people with a BMI greater than 25.

What were the findings?

On average, the participants lost 4.2 kilograms (9.3 pounds) when both the PC and RCT data were taken into account. When PC studies and RCTs were looked at separately, though, the former tended to have larger effects than the latter. Participants in the RCTs lost 3.5 kilograms (7.7 pounds) on average, as opposed to the 4.6 kilograms (10 pounds) average lost in the PC studies.

Overall, a large effect size was observed for changes in eating behavior. Medium effects were seen for improving depression, anxiety, and eating attitudes, and low effects were seen for mindfulness skills. Effects on stress and quality of life were just outside of the range of statistical significance. As with weight loss, the observational PC trials tended to show larger effect sizes than the RCTs did in many of these areas. This tendency has been noted by other authors.

The authors also looked to see whether or not more mindfulness training produced better outcomes. To do this, they split the studies into those which had face-to-face mindfulness training time of 12 hours or less compared to more than 12 hours. Overall, they found no difference in all outcomes combined. They also saw no difference in BMI and eating attitudes. However, they unexpectedly did see better outcomes for depression in participants who had 12 hours or less of training. The researchers couldn't compare too many of the things they measured, though, since many of the categories (e.g. effect on anxiety when undergoing more than 12 hours of face time) only had one study that had such data. This precluded accurate comparison in all cases.

While the amount of mindfulness training didn't result in much difference, the type of mindfulness training did. The authors split the studies into those which used ACT, those which used meditation, and those that used mindfulness in general. The average weight loss was 7.6 kilograms (17 pounds) for ACT-based approaches, 1.8 kilograms (4.0 pounds) for meditative programs, and 1.7 kilograms (3.7 pounds) for mindfulness-based interventions. How other measurements responded to the three types of intervention are shown in Figure 2.

> "[...] they unexpectedly did see better outcomes for depression in participants who had 12 hours or less of training."

Figure 2: Effect sizes for outcomes by intervention type

	ACT	Meditation	Multifaceted mindfulness
Depression			●
Anxiety			●
Stress			—
Quality of life	—		
Mindfulness skills	—		●
Eating behaviors			●
Eating attitudes	●		●
Weight lost	7.6 kg	1.8 kg *	1.7 kg *

● = large effect
● = medium effect
● = small effect
— = not significant
Empty = not enough data
* = not statistically significant for BMI change

Three studies followed-up with the population for no more than six months after they stopped the mindfulness training to determine how they did. These studies found that participants were able to either maintain or slightly increase their weight loss, with an average total weight loss of 9.9 kilograms (22 pounds) after four to six months since the beginning of the mindfulness training.

Participants also varied in how well they stuck with their programs across the studies. The attrition rate ranged from 0%-34%, with ACT interventions tending to have the highest rates.

Mindfulness interventions for weight loss showed moderate effects for weight loss overall, with participants that used Acceptance and Commitment Therapy (ACT) showing the largest effect. Other side benefits of the mindfulness programs were sometimes observed. More than 12 hours of class time in mindfulness training did not seem to improve outcomes. Observational studies had a tendency to have larger effect sizes than randomized control trials.

What does the study really tell us?

Overall, this meta-analysis suggests that mindfulness-based interventions may help people with a BMI over 25 to lose weight. ACT-based methods seemed to have the strongest support behind them. However, ACT-based methods also tended to have higher attrition rates than the other methods, so they may be harder to stick to. Mindfulness also helped with emotional problems (anxiety and depression), and improved problematic eating attitudes and behaviors. Unsurprisingly, mindfulness training also improved mindfulness. The weight loss seemed to last for at least six months, although the the data for follow-up was very sparse. More research is needed to see if these effects really last.

How mindfulness training could lead to weight loss is unclear from this study. Changes in both mindfulness and weight were only seen in one of the three studies that reported both weight change and changes in mindfulness in this meta-analysis. This number should be

higher if mindfulness was causing the weight loss. But one study included here looked at whether mindfulness skills could explain weight loss, and they found that it did but only after six months of follow-up, and not before. This study was ACT-based.

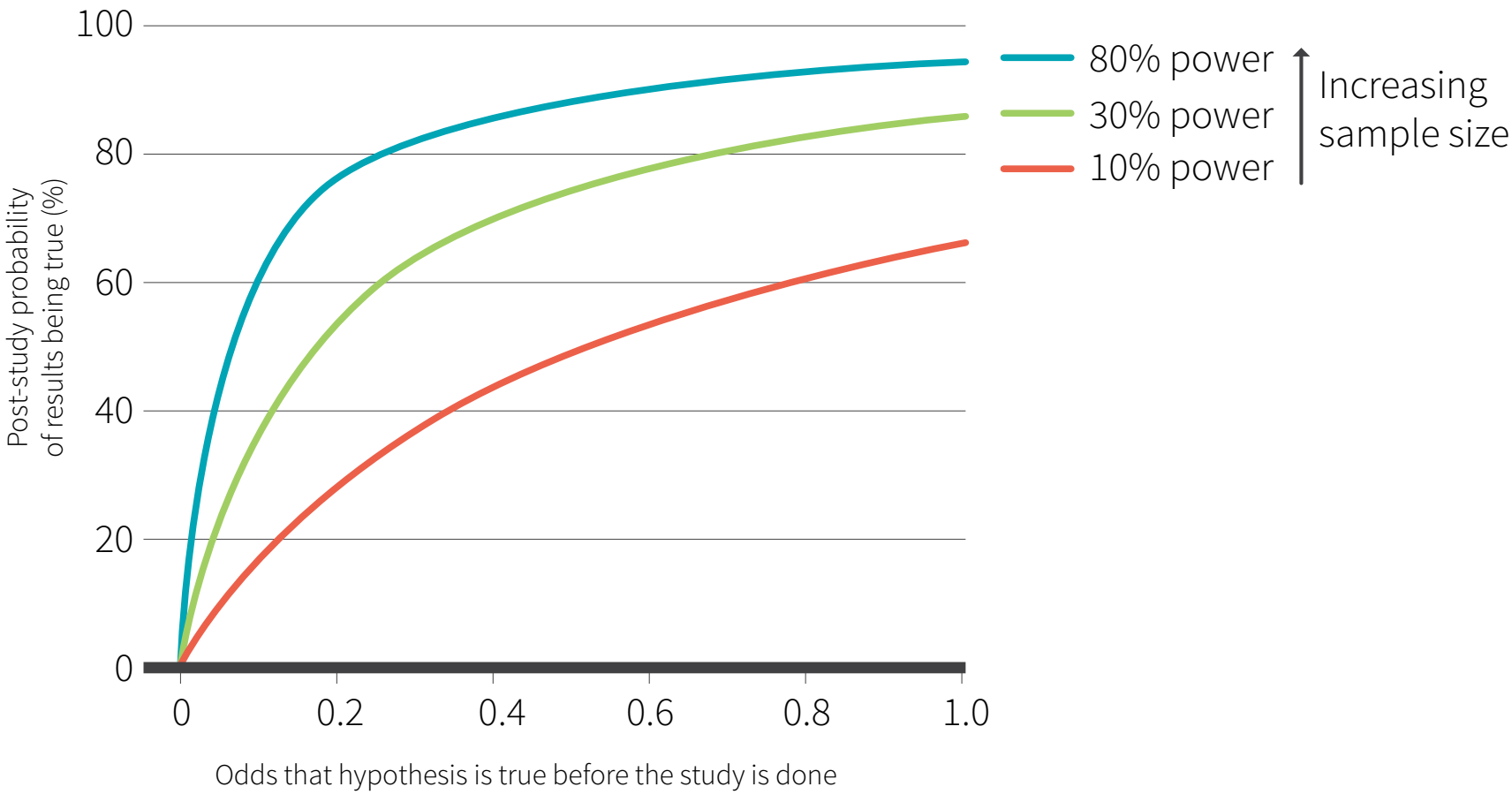
While this meta-analysis is suggestive, it is far from definitive for a few reasons. First, in all but one study included in the meta-analysis, the majority of participants were female. This means that the general results of this paper may not apply well to men. Curiously, the one study that did have a majority of men showed a stronger effect on weight loss. Also, the trials used in this study tended to have small sample sizes, which can lead to less reliable results (as shown in Figure 3). The trials also used a broad array of methods, making it hard to pin down which components of the interventions were effective in reducing weight. For these reasons, more research is needed to see if and how mindfulness-based interventions work for weight loss in the long run.

This study suggests mindfulness-based interventions (especially ACT) may assist in weight loss. However, these results may not apply as well to men, since most of the participants were women. Due to the small sample sizes and diversity of mindfulness techniques used, more research is needed to see if mindfulness works for weight loss in the longer run, and which techniques are most effective.

The big picture

Previous systematic reviews of mindfulness' effect on weight loss have either found smaller effects than those found in this study or no clear effect at all on weight loss. But, as mentioned in the Introduction, those reviews had participants whose BMIs ranged from normal to obese. This meta-analysis only looked at studies whose participants had a BMI of greater than 25, which could explain the discrepancy.

Figure 3: The amount of evidence a study provides increases with its sample size



Adapted from: Button et al. Nat Rev Neurosci. 2013 May.

But mindfulness isn't the only way to lose weight that doesn't require a pill or surgery. One other contender is cognitive-behavioral therapy (CBT). CBT is a form of shorter-term therapy that teaches people to question and work with distorted, unrealistic, and harmful thinking (that's the cognitive part) and also change how they act in the world (behavior). It has been used for everything from anxiety to addiction and chronic pain. A meta-analysis on CBT for weight loss showed an average weight loss of 4.8 kilograms, which was on par with what was seen here. But this meta-analysis was only based on two studies. And the meta-analysis has been withdrawn since it's quite old, with a new one is being prepared.

Some non-medical interventions may even do better than what was seen here for mindfulness, namely diet and exercise. One meta-analysis found that behavioral interventions combined with a very low-calorie diet led to an average of 10.3 kilograms (22.7 pounds) lost after 12 months. However, over the longer term, weight was slowly gained back. At 24 months, the average weight lost since the beginning was 4.2 kilograms (9.3 pounds), and at up to 60 months, it was 3.4 kilograms (7.5 pounds). Adding exercise to dietary interventions makes the intervention even more effective; people who add exercise to a diet lose an additional 1.14 kilograms (2.51 pounds) on average versus dieting alone.

However, some interventions don't do as well, but may be still effective. For instance, motivational interviewing is a technique using a collaborative communication style in which a therapist helps a client explore and resolve ambivalence about behavior change in a non-confrontational way. A meta-analysis of motivational interviewing showed a more modest decrease in weight than seen here. People with a BMI of greater than 25 lost 1.47 kilograms on average.

How do other interventions stack up to mindfulness in terms of lasting power? Another meta-analysis looking at behavioral interventions alone also indicated that they seem to have lasting power once the training is over, but the effect seemed weaker than it was for mindfulness. One meta-analysis found an average weight loss of 1.6 kilograms (3.5 pounds) after a year of follow-up compared to the 9.9 kilograms (22 pounds) found for mindfulness. However, this meta-analysis included 45 trials involving close to 8,000 individuals with follow-up for a year, which makes it much more solid than what was found in the meta-analysis under review here. Recall that only three trials of this meta-analysis had fully-reported follow-up data, and that those trials had a follow-up time of six months at most.

Some other interventions may not carry the emotional benefits of mindfulness seen in this meta-analysis. Behavioral interventions alone for weight loss don't seem to lower depression symptoms in people either using the behavioral program alone or that program in combination with a very low calorie diet. Realistic goal-setting in people with obesity did not affect psychological outcomes like self-esteem, either. But when you add a cognitive (thinking) component to the behavioral intervention to create a cognitive-behavioral intervention, anxiety and depression is in fact improved.

The effect sizes seen here are larger than those found in previous systematic reviews of mindfulness' effect on weight loss, but that may be because previous reviews included people of normal weight. Mindfulness seems to help people lose as much weight as cognitive-behavioral therapy (CBT) does, but not as much as very-low-calorie diets combined with behavioral interventions. But both CBT and mindfulness tend to help with emotional issues that may accompany dieting and weight, where behavioral interventions may not have an effect.

Frequently asked questions

How is mindfulness supposed to help people lose weight?

In theory, mindfulness allows one to cultivate a different relationship with distress, discomfort, and urges. Instead of buying into these feelings automatically and mindlessly, one can observe them nonjudgmentally, allowing a space to choose what is in one's values. In other words, mindfulness allows for psychological flexibility. One's actions are ideally no longer directly and automatically tied to one's feelings and emotions. So, mindfulness is supposed to work by allowing for more freedom of choice.

For example, if someone automatically eats when stressed, one could instead be mindful of the stress. What is stress? How does it feel like in the body exactly? Where, exactly? Does it change over time? By becoming curious about what the phenomenon of what stress is, one gains some distance from it. And once that distance is gained, one can then ask: "Do I really want to eat now?" If so, they can. If not, they have then given themselves the space to choose not to.

What are some examples of mindfulness-based practices?

As mentioned in the Introduction, "mindfulness" doesn't have a single, agreed-upon definition, so there are a lot of mindfulness-based practices that exist. Below is a far-from-comprehensive sample.

One practice is breath meditation. One can sit down (although it can also be done in other postures), and either closes one's eyes or keeps one's eyes open with a soft focus. The attention can then be placed on the sensations of breathing wherever it's most prominent, from the rims of the nostrils to the belly. One can also gently count the breaths as they come in and out. When the mind wanders, which it inevitably does, one non-judgmentally and briefly notes that the mind was wandering (e.g. "hearing" if the distraction was a sound, "thinking" if it was a thought) and returns to breath sensations.

Another practice from Mindfulness-Based Stress reduction is mindful raisin eating. This practice involves slowly eating a raisin, attempting to focus on each individual sensation of the process, from bringing the raisin to one's mouth, to the taste and texture while chewing. This exercise is meant to both introduce the concept of mindfulness to people as well as allow for practicing mindfulness skills that can be carried over to daily activities.

One final example is from ACT, which tends to involve non-meditative mindfulness techniques. In order to gain mindful space from thoughts, one can add "I'm having the thought that…" to any thought one may have. For instance, if one thinks to themselves "I'm a loser," the practice is to amend the thought, instead saying "I'm having the thought that I'm a loser." The goal of this practice is to establish mindfulness of the thought as just a thought, thereby gaining some distance from it.

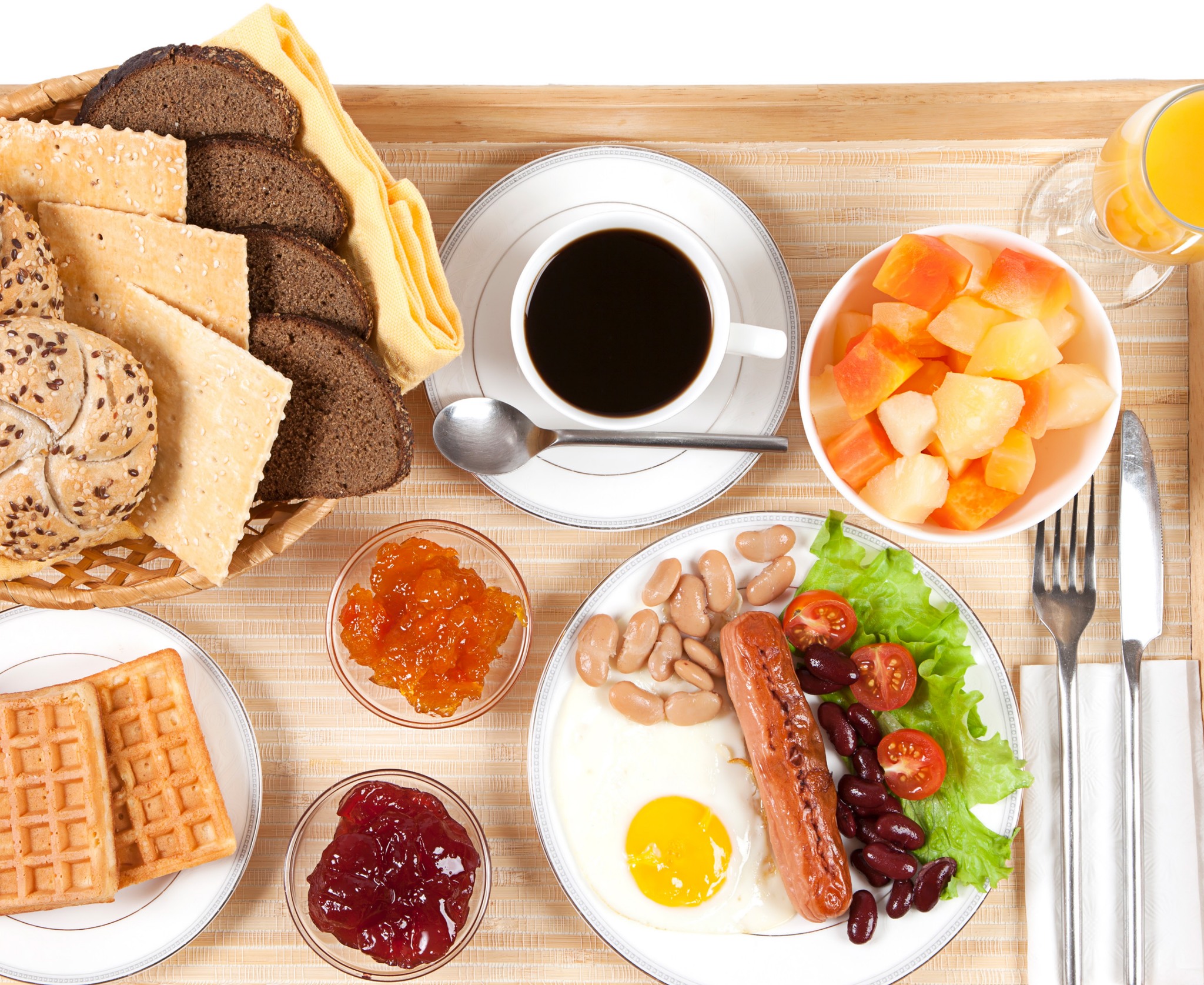
What should I know?

This systematic review and meta-analysis found that mindfulness-based training leads to weight loss and improves some aspects of mental well-being in people with overweight or obesity. However, the studies included here were small, mostly involved women, and used a wide variety of mindfulness-based techniques. Further research with larger, more diverse samples is necessary in order to confirm mindfulness' usefulness in the broader population. More research is also needed to elucidate which techniques may be most effective and how they may work. ◆

Do you accept the results of this paper? Are you committed to good discussion? Mindfully ACT up in the ERD Private Forum on Facebook!

Does forcing breakfast provide any benefits?

A randomized controlled trial to study the effects of breakfast on energy intake, physical activity, and body fat in women who are non-habitual breakfast eaters.



Introduction

Many people are familiar with the idea that "breakfast is the most important meal of the day." However, there is much debate in the scientific community about how beneficial breakfast consumption is to energy balance and weight maintenance. While breakfast itself is not the sole factor contributing to weight maintenance, its omission or consumption does promote a series of physiological responses that can affect bodyweight.

To date, the research investigating the effect of breakfast on weight is conflicting. Some studies have shown associations or demonstrated that eating breakfast promotes increased satiety and physical activity, decreased bodyweight and BMI, and improved regulation of hunger hormones. Others have demonstrated that eating breakfast has insignificant and potentially negative effects on total daily energy intake. Factors like macronutrient composition, caloric intake, and hormonal responses likely contribute to the inconsistent relationships observed between energy balance and breakfast. Thus, it is likely that the inconsistent findings reported in the breakfast literature stem from widespread differences in study designs and participant demographics.

It's almost ironic that there is so much hype around the idea that, "breakfast jump starts the metabolism"; given that scientific evidence does not support this idea in both lean and obese individuals. Of course, due to the debatable role of breakfast consumption in the regulation of bodyweight, and anecdotal support that eating the meal is great for reducing appetite and improving body composition, it's not hard to imagine how breakfast-skippers might consider adding breakfast to their daily routine.

Unfortunately for breakfast skippers, no studies were published prior to 2017 on the topic of how breakfast affects the weight of habitual breakfast skippers. That all changed recently though. In the study being reviewed, researchers examined for the first time the effect of breakfast consumption on the energy intake of habitual breakfast-skipping women and the effect of that additional meal on their physical activity, bodyweight, and body fat.

Breakfast has long been associated with healthy weight maintenance due to positive associations with energy balance, satiety, and physical activity. However, scientific evidence regarding these claims has been conflicting. The researchers conducting this study set out to determine how the addition of breakfast in habitual breakfast-skipping women affects energy balance.

Who and what was studied?

This randomized, controlled, parallel-arm trial examined how the addition of daily breakfast to the diet of

> "[...] inconsistent findings reported in the breakfast literature stem from widespread differences in study designs and participant demographics."

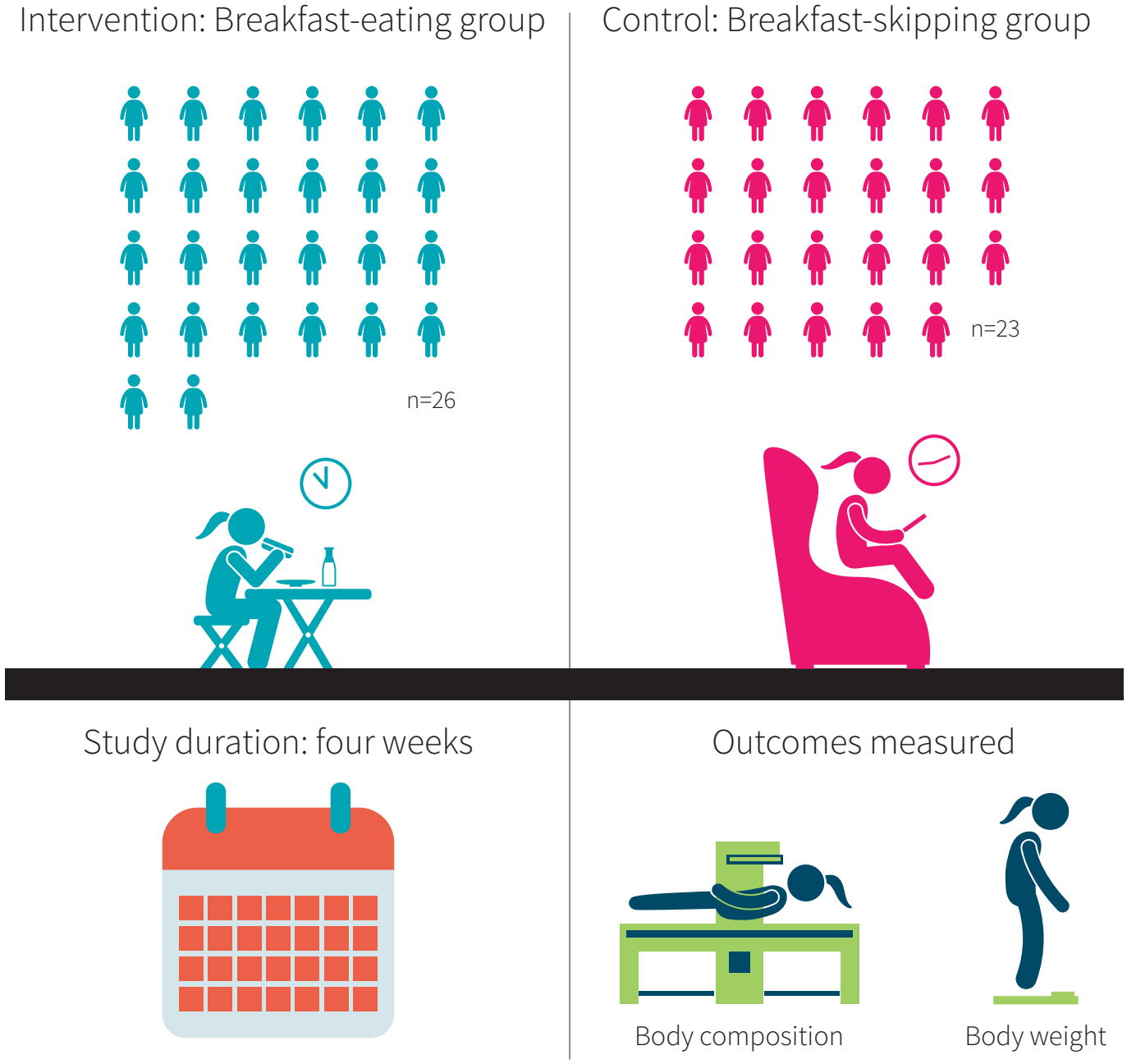
premenopausal women breakfast skippers affected their energy intake, physical activity, bodyweight, and body fat over the course of four weeks. The general study characteristics are shown in Figure 1.

These women were between the ages of 18-55, ate breakfast fewer than two days a week, slept for more than six hours a night, and were consistently early risers. All participants selected into the study were at a stable weight for over three months and were characterized as apparently healthy according to their responses to a health history questionnaire. The study had several exclusion criteria, such as excluding those who consumed breakfast more than twice a week. A total of 49 women were studied, with 26 completing the breakfast eating intervention and 23 completing the control intervention.

Women in the breakfast-eating group ate breakfast before 8:30 a.m. The meal contained at least 15 percent of their daily calories and was consumed no more than 90 minutes after waking up. There were no eating or snacking limitations imposed on the group following the breakfast meal. The non-breakfast eating controls differed only in that they withheld from food and alcoholic beverage consumption until after 11:30 a.m. All women studied were asked to wake up by at least 8:00 a.m.

To test their hypothesis that the addition of breakfast would affect non-habitual breakfast eaters' weight, the researchers gathered basic measurements, like bodyweight, height, and BMI. Dual energy x-ray absorptiometry (DXA) measurements were also obtained to assess participants' body composition

Figure 1: Study Methodology



(body fat percentage, fat free mass, fat mass) at baseline and at the end of the four-week intervention. Additionally, energy and macronutrient intake was assessed using the National Cancer Institute's automated self-administered 24-hour dietary recall (ASA24). Hunger levels were also measured prior to each meal during the last week of the study using the visual analog scale (VAS). Throughout the study, participants recorded daily sleep and food logs during their first meal of each day. These logs were reviewed at weekly appointments with research assistants. To determine whether or not the addition of breakfast affected physical activity levels in non-habitual breakfast eaters, physical activity was measured using hip accelerometers for four days at baseline and throughout the duration of the 28-day intervention.

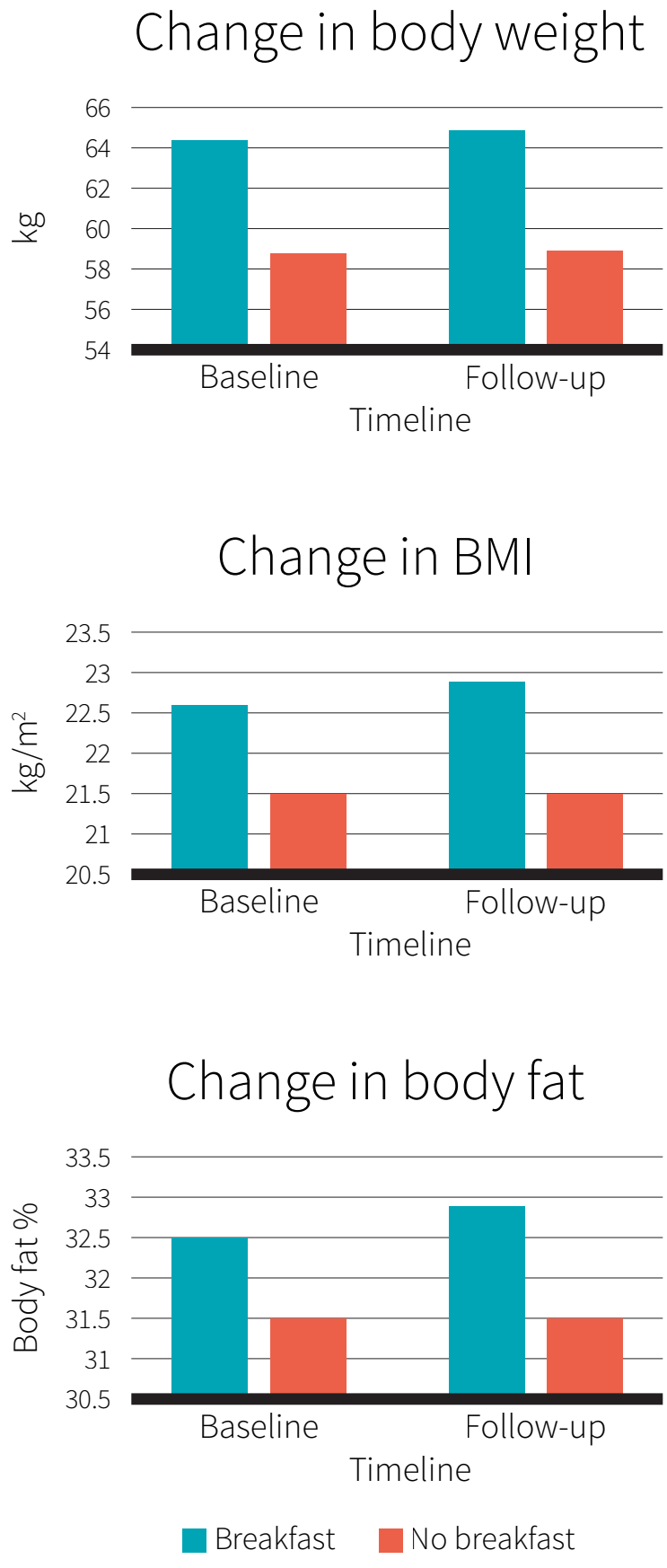
Premenopausal women who normally skipped breakfast were randomized into either an experimental group that consumed breakfast daily or a control group that abstained from eating breakfast for a total of 28 days, in order to understand how breakfast affects energy balance. BMI, lean mass, fat mass, and body fat percentage were used to determine changes in body composition.

What were the findings?

Some of the main study findings are shown in Figure 2. By the end of the intervention, there was a significant increase in self reported daily caloric intake (266 kcals) and in daily carbohydrate consumption (43 grams) in the breakfast eaters over baseline, which also statistically differed from the control group, which experienced no changes in either measurement. The women who ate breakfast also self-reported as feeling significantly higher energy levels.

There was no significant difference between the breakfast-eating group and no-breakfast controls in energy

Figure 2: Study Outcomes



intake at lunch, dinner and night time. Additionally, there were no differences between the groups' light, moderate, vigorous, or total physical activity levels. The reported hunger, thirst, and fullness levels between the groups were also unchanged. The addition of breakfast also resulted in the breakfast intervention group having a significant increase in bodyweight (0.7 kg) and BMI (22.6 to 22.9) The control group's BMI and weight remained stable throughout the study and was significantly lower

than the breakfast eaters' by the end of the intervention. A non-significant trend towards increased body fat (approximately 32.5% to 32.9%) was observed in the breakfast group at the end of the study. Neither group observed a change in lean mass by the end of the study.

The addition of breakfast to the diet of habitual breakfast skippers resulted in significant increases in energy and carbohydrate intake, as well as increases in bodyweight. Physical activity and satiety was not impacted by the addition of breakfast over the course of the four-week intervention.

What does the study really tell us?

The results of this study supported part of the researchers' initial hypothesis that requiring breakfast skippers to eat breakfast results in increases in weight, BMI, and caloric intake. However, their findings did not support the part of their hypothesis that stated the addition of breakfast would increase daily activity. Furthermore, their results demonstrated that the addition of breakfast did not result in reduced caloric intake at other meals or enhanced feelings of satiety. Overall, these findings support the popularized notion that forcing people to eat when they are not hungry is not beneficial to maintaining a healthy weight or body composition. That being said, certain aspects of this study warrant additional perspective.

For example, the finding that the addition of breakfast had no effect on satiety seems somewhat counterintuitive considering that the breakfast eaters were asked to consume 15% or more of their daily calories during their breakfast meal. In this study, no information was supplied relating to the source of the carbohydrates consumed. Different types of carbohydrates have different effects on body composition and satiety. More specifically, complex carbohydrate, high fiber, high protein breakfasts have been associated with increased satiety. Considering that carbohydrates were the only macronutrient whose intake was increased in the breakfast eaters, this would have been interesting information to report. It could have been that breakfast eaters were unsatisfied following breakfast, which could have been a reason they failed to reduce caloric intake at later meals. However, as the researchers mentioned, they chose to not control for, or investigate the source of the participants' macronutrients since they only aimed to understand if "breakfast is beneficial to health."

Also, the addition of breakfast had no apparent effect on physical activity levels. The participants, although within normal weight ranges, were not engaging in frequent vigorous activity. Habitual breakfast eaters have been shown to be more likely to exercise, making it difficult to imagine that habitual breakfast skippers would just pick up exercising or increase their physical activity simply due to their temporary requirement to begin eating breakfast. While this may be something that could have occurred with a longer intervention, there are too many confounding variables (such as adding exercise sessions to existing daily schedules) to know if this would be the case.

Overall, the design of the study makes it difficult to conclude whether the addition of breakfast, or just the addition of a meal normally skipped, was the cause of the participants' weight gain and increases in energy intake. Considering that the breakfast group did not experience increased feelings of fullness, reduced energy intake in subsequent meals, or increased physical activity, it's not hard to imagine why weight gain was observed in the breakfast group. The question of whether or not the study's outcomes were the result of an additional meal, or specifically breakfast, could be addressed in future studies by observing if the addition of lunch to habitual lunch skippers would be sufficient to induce the same kind of results.

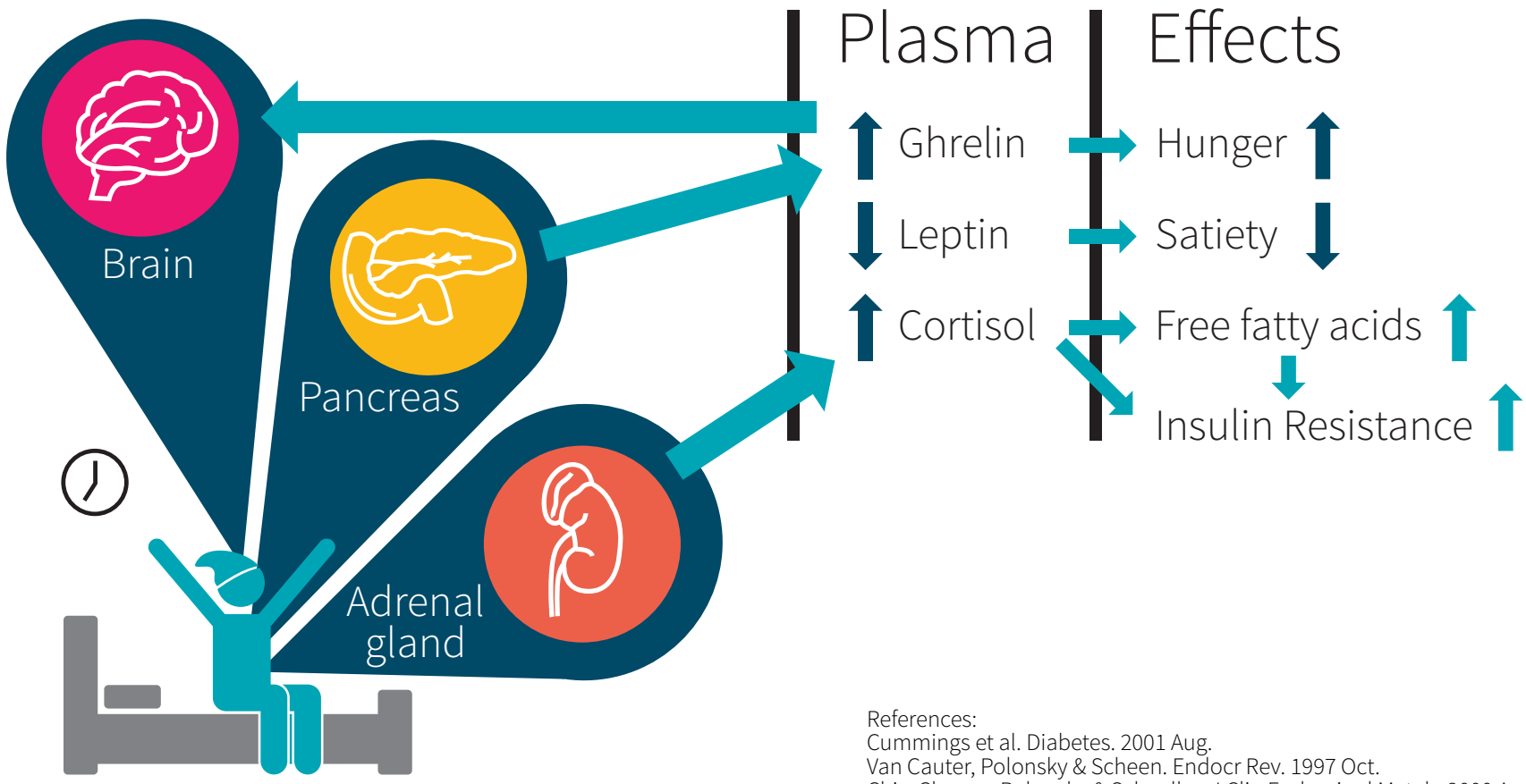
While this study demonstrated that the addition of breakfast to the dietary intake of habitual breakfast skippers is sufficient to increase daily caloric intake and weight gain over the course of four weeks, it is difficult to understand if these effects on energy balance resulted from the addition of an extra meal or from the addition of breakfast specifically.

The big picture

According to the researchers, this was the first study to look exclusively at the effect of how adding breakfast influences energy balance in habitual breakfast-skipping women. Although the findings from this study support the somewhat logical conclusion that eating when you are not hungry is not beneficial, this study opposes previous work demonstrating that breakfast promotes weight management by decreasing energy intake. In that randomized crossover trial, unlike the study being reviewed, the premenopausal women subjects were habitual breakfast eaters. This suggests that the breakfast habits of the participants being examined can greatly impact study results. Future studies are needed using habitual breakfast eaters and skippers to better understand how and why previous breakfast status determines the effect of breakfast on body composition.

Breakfast study results could vary depending on the macronutrient composition and caloric density of the meal, which can greatly influence the levels of specific hunger hormones and satiety prior to any observed changes in body composition or health. A series of specific hormonal and physiological effects are turned on in response to breakfast consumption, as depicted in Figure 3. At the time when the alarm clock first goes off, plasma cortisol and ghrelin levels peak. Whereas elevated ghrelin levels somewhat drive the act of "breaking the fast," elevated cortisol levels can both increase circulating free fatty acid (FFA) levels and oppose insulin to induce a state of inhibited peripheral glucose utilization. When the first meal is consumed before the start of daily activities and within two hours of waking, a series of physiological responses are triggered in response to meal-induced increases in plasma glucose levels.

Figure 3: Hormonal and physiological effects in the morning



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Previously, researchers had found that women in caloric deficits consuming breakfast had greater increases in total weight loss, a finding in opposition of those reported in the reviewed study. However, it's hard to know if the difference stems from being in a caloric deficit or differences in habitual breakfast skipping behavior. It's likely that the benefit of consuming breakfast is influenced by the energy balance status of an individual, their previous breakfast eating habits, and their particular hormonal and metabolic responses to the addition of breakfast.

The contradictory findings of different studies suggests that studies investigating physiological and metabolic responses are needed. It will be important to explore if forced breakfast consumption has a similar effect on women maintaining a caloric deficit, as well as to explore that link while simultaneously collecting biochemical and metabolic measurements. The findings from this study substantiate the claim that forcing people to eat when they would rather not has negative effects on body composition and energy balance.

Frequently asked questions

What are the physiological effects of skipping breakfast?

When the body wakes up in the morning, it is in a somewhat fasted state where circulating free fatty acids and elevated cortisol levels create a transient state of insulin resistance. In individuals consuming their calories after breakfast, fasting plasma glucose levels have been shown to be elevated, compared to breakfast eaters. Additionally, in response to the acute state of fasting while sleeping, leptin, the hormone that inhibits hunger and opposes ghrelin, is decreased. This allows for prolonged increases in the hunger hormone ghrelin and decreases in glucagon-like peptide-1 (GLP-1), creating an imbalance in satiety hormones that promotes increases in hunger.

What are components of breakfast that have influence over weight regulation?

Factors like caloric load, caloric energy density, caloric volume, and macronutrient composition have all been implicated in the association between bodyweight and breakfast. Specifically, the consumption of cereal grains and fibrous foods has been associated with healthy bodyweights. The addition of protein to breakfast is also associated with feelings of fullness. While calorie consumption at breakfast has been linked to lower daily calorie intake, the consumption of less energy dense, more voluminous foods (calories per unit weight of food) has also been shown to decrease caloric intake at subsequent meals, suggesting that meals with low caloric density, but high in protein and fiber, may be beneficial to weight maintenance.

Since the study under review did not focus on educating participants on strategies to prepare breakfast meals that would promote healthy weight maintenance, it is hard to conclude if breakfast failed to improve health in the participants because the researchers did not educate the participants on the importance of breakfast components implicated in weight regulation.

Why did the authors bother looking at forcing non-habitual breakfast eaters to eat breakfast?

Prior to this work, previous work had demonstrated that the detrimental effects of skipping breakfast on metabolic health were limited to habitual breakfast eaters.

What should I know?

Adding breakfast to the diet of women who habitually skip this meal was sufficient to increase bodyweight, daily energy intake, and carbohydrate consumption over the course of four weeks.

Since no information was provided on the subjects' breakfast meal composition, it is unclear if the addition of breakfast would have had similar effects if it had

been composed of satiety-inducing foods high in fiber or protein.

The addition of breakfast had no significant effect on reducing caloric intake at subsequent meals or increasing physical activity levels. Whether this effect is specific to forcing breakfast skippers to eat breakfast, or universal to habitual meal skippers, remains unclear and requires further investigation. ◆

To eat or not to eat (breakfast), that is the question. The answer seems to be that you don't have to eat it if you don't want to, and skipping it isn't likely to hurt your waistline. Discuss this study at the ERD Facebook forum.

Magnesium for depression

Effect of magnesium supplementation on depression status in depressed patients with magnesium deficiency: A randomized, double-blind, placebo-controlled trial

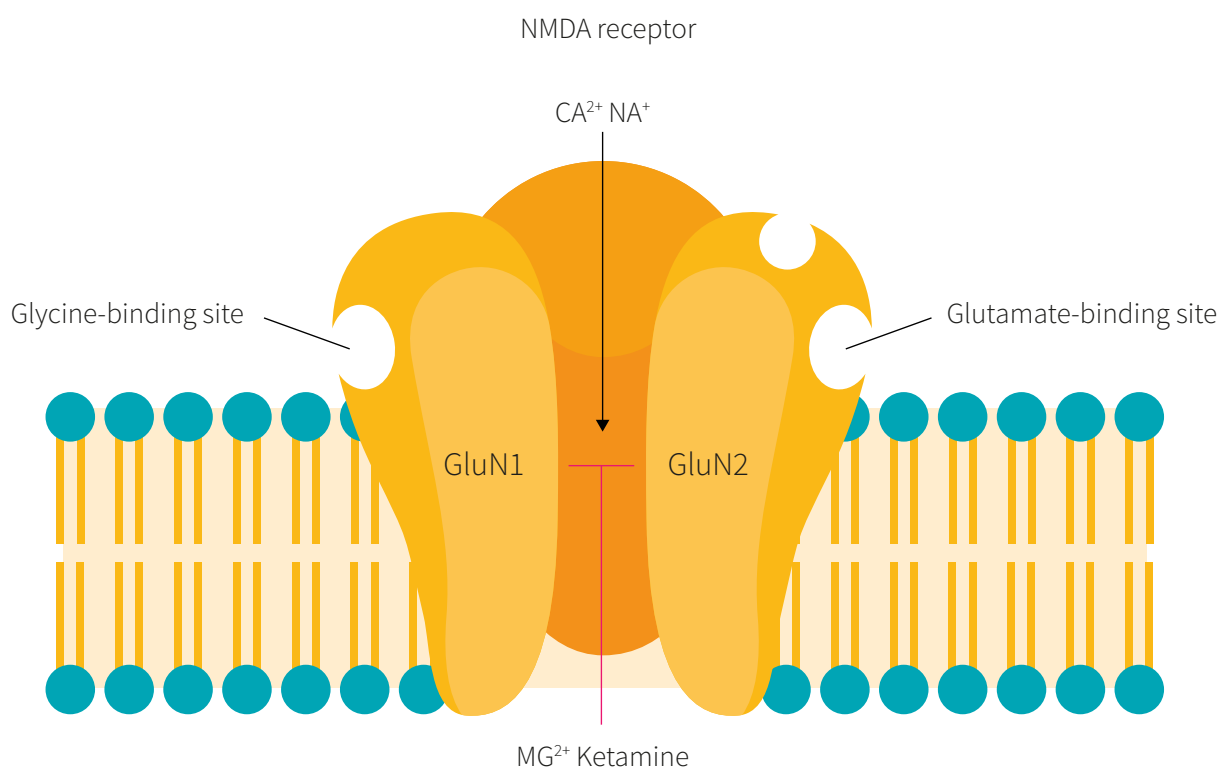
Introduction

Major depression is a common mood disorder affecting people all over the world. It's one of the leading causes of disability worldwide, and a significant burden on those who it affects. It's more than feeling down due to sad life events. Everybody gets the blues, but it becomes a medical issue when it exceeds normal grief and sorrow, with depressive episodes persisting for longer, being more intense, and oftentimes recurring more frequently than they normally would, suggesting an underlying vulnerability. Depression isn't merely a single emotional state, but is multifaceted with varying severity of symptoms depending on the individual, including feelings of worthlessness, low energy, lack of pleasure, insomnia, and changes in appetite.

Depression hurts, and that alone would be bad enough, but it may also increase the risk of various life-threatening diseases, making it medically concerning in several ways. It's typically managed with pharmaceutical antidepressants, psychotherapy, or both, with varying degrees of success depending on the individual. Pharmaceutical treatments can ease depression for many people, but not everyone can receive their full benefit. Some people don't respond to standard antidepressants, having treatment-resistant depression, and may require a long period of experimentation with various medications to find the right one, if they do at all. The difference between medication and placebo in the general population of patients with depression doesn't tend to be large, except in severe cases, suggesting a need for better treatment options.

Research into treatment-resistant depression using a novel class of drugs has yielded insights into its pathophysiology. The use of drugs that target NMDA receptors in the brain may offer an alternative approach to depression treatment. NMDA receptors (pictured in Figure 1) are ion channel proteins that sit on the edge of synapses. When bound by glutamate and glycine, these receptors play an important role in neural plasticity, allowing for the passage of ions, namely sodium and calcium, which leads to synaptic transmission. However, they can become dysfunctional. Studies suggest that abnormal NMDA function plays a part in the pathogenesis of depression, and NMDA antagonists have positive and potent effects on the symptoms of depression. Ketamine is the most widely known drug that specifically targets NMDA receptors, and has been observed

Figure 1: Magnesium and ketamine are both NMDA ion channel blockers



Reference: Ghasemi et al. Neurosci Biobehav Rev. 2014 Sept

to lead to a chain of events that are neuroprotective and enable plasticity, areas that may be relevant to depression.

Magnesium plays a role in blocking NMDA receptor ion channels under normal physiological conditions and it shares a number of similarities with ketamine in its effects on NMDA receptors. A low serum level of magnesium has also been correlated with depression. While not a knock-out case for the relevance of dietary magnesium, as there are differences between ketamine and magnesium, and a low intake of magnesium could go hand-in-hand with a worse overall diet and lifestyle, various researchers have become interested in a possible link. One small trial suggests that it performs roughly as well as the medication imipramine, but more trials are needed to test its efficacy and give us an idea of its effectiveness compared with a placebo. The study under review seeks to remedy that.

Evolving research into depression treatment suggests NMDA receptor antagonists to be a promising tool to treat depression and reverse some of the processes involved in it. Magnesium plays an important role in NMDA regulation and low magnesium levels could be contributing to depression in some people, leading researchers to investigate the possible connection.

Who and what was studied?

The study was a randomized, double-blind, placebo-controlled trial to assess the efficacy of magnesium supplementation in reducing the symptoms of depression, with Beck II Depression Inventory score being the primary outcome.

In the first phase, 650 potential participants were evaluated for Beck II scores and serum magnesium levels. Participants were included if they had scored 11 or higher in the Beck II Depression Inventory, meaning that they had at least a mild mood disturbance deemed to be more severe than the usual ups and downs of life. Participants were also included only if they had serum magnesium levels lower than 1.8 mg/dl in men or 1.9 mg/dl in women, and were between the ages of 20 and 60, making the implications of the study specific to people who have low serum magnesium. This yielded sixty individuals who were then randomly assigned to take either two tablets of 250 milligrams of magnesium oxide for a total dose of 500 milligrams per day, or placebo tablets, over the course of two months, after which Beck II and serum magnesium were evaluated again.

Dietary magnesium, macronutrient, and total energy intake were also assessed at baseline and at the end of the two months using a 24-hour dietary recall questionnaire; body mass index was assessed simultaneously.

Beck II depression inventory

The inventory is a simple 21 question multiple choice survey used to assess the severity of depression. Each question has four possible answers, each one corresponding to the different levels of severity in an area of life that could be impacted by depression. A score of 0 is assigned to the option that indicates that nothing's wrong, and a score of 3 is assigned to the option that indicates the greatest distress, with 1 and 2 for the options in between. The scores from all 21 questions are tallied up and the final score is interpreted as a representation of depression status, with 0-10 being normal, 11-16 being a mild mood disturbance, 17-20 being borderline clinical depression, 21-30 being moderate depression, 31-40 being severe depression, and higher than 40 being extreme depression. The maximum possible score is 63.

To ensure a more accurate assessment of genuine clinical depression, potential participants were excluded from the trial if they were suffering from life-threatening illnesses, were pregnant, had recently experienced adverse life events, such as a death in the family, loss of job, divorce, or had been taking various psychotropic medications over the past three months. Participants were also excluded if they had been taking a multimineral or multivitamin supplement.

Depressed people with low serum magnesium levels were given 500 milligrams of magnesium per day or a placebo for two months. Change in Beck II Depression Inventory score was the primary endpoint. Serum magnesium, diet and BMI were also measured at baseline and at the end of the study.

What were the findings?

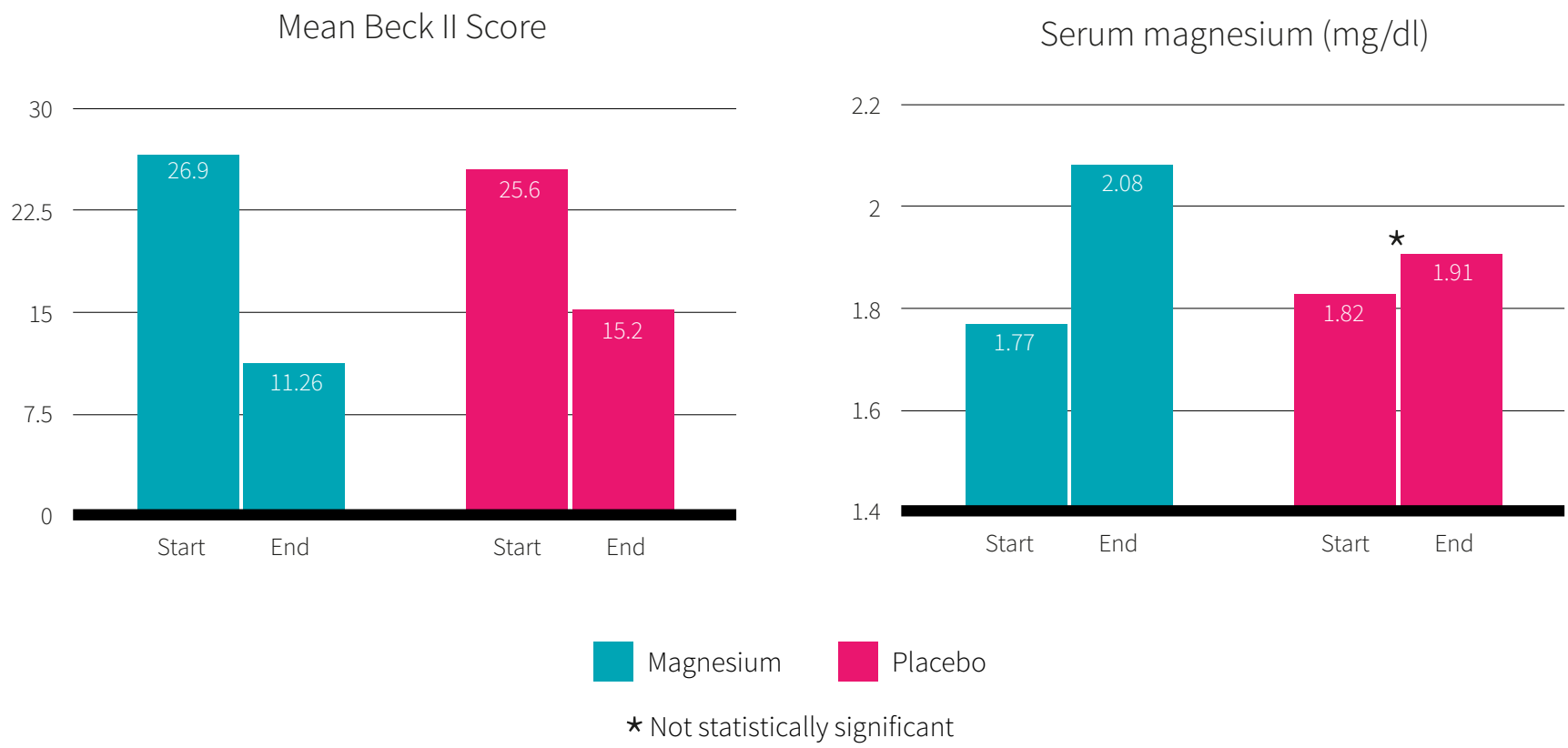
As seen in Figure 2, both the magnesium and placebo groups experienced significant reductions in mean Beck II scores, with the magnesium group experiencing a significantly greater reduction.

The placebo effect in this study was strong (with a change that was roughly two-thirds the change for magnesium), although this relationship is right in line with observations from clinical trials using antidepressant medication.

Serum magnesium concentration increased significantly in the magnesium group, from 1.77 mg/dl at baseline to 2.08 at the end of the study, whereas the placebo group saw a smaller increase from 1.82 to 1.91, which was not significant. All of the participants began with what the researchers deemed to be a serum level indicating magnesium deficiency, and by the end of the study levels were normal for 88.5% in the magnesium group and 48.1% of the placebo group. The only significant difference in measures of dietary intake or BMI was a modest reduction in carbohydrate intake in the placebo group.

A total of seven participants dropped out of the study, four from the magnesium group and three from the placebo group, with diarrhea being the only adverse effect possibly tied to a dropout in two participants in the magnesium group and one participant in the placebo group. This left 26 participants in the magnesium group and 27

Figure 2: Mean Beck II and serum magnesium at baseline and end



in the placebo group, a size calculated by the researchers to have sufficient power for the primary outcome.

Both groups experienced a reduction in their depressive symptoms, with the magnesium group experiencing a greater reduction. Magnesium levels rose in both groups, but to a much greater extent in the magnesium group.

What does this study really tell us?

The difference in the change on the Beck II test between the two groups, 5.25, isn't trivial for a single supplement; this would be enough to take many of the participants from being "moderately depressed" to being out of the clinical depression range as defined by the Beck II inventory. The difference between groups represents roughly 20% of the baseline Beck II score of the participants, who were "moderately depressed" on average.

The authors mentioned the short duration of the study as a possible limitation. The trial lasted for 8 weeks, but in interventions to treat depression, it's possible that more subjects will see a response to an intervention with a longer duration. Studies lasting for 8 or 12 weeks tend to see a greater response rate than studies lasting for 6 weeks, but the difference in response rate in studies longer than 8 weeks is unclear. It's possible that some subjects could require longer than 8 weeks to see a response, and a trial lasting for longer could be superior. Specifically in the case of magnesium, an essential nutrient that has many uses in the body, low status may require many months to overcome with supplementation for some individuals. Roughly 11.5% of the magnesium group still didn't have normal magnesium levels at the end of the trial, with trial length being one of the possible reasons, and dose and form of the supplement being another.

It's uncontroversial that a severe magnesium deficiency has neurological implications, and that magnesium supplementation may also have a role in remedying sleep disturbances, but the degree to which serum magnesium levels are reflective of concentrations in the central nervous system is suspect. This could possibly limit the ability of researchers to accurately assess who could benefit the most from a magnesium intervention. The authors acknowledged this and operated on the premise that the impact of magnesium on depressive symptoms would be most relevant to people with low serum magnesium levels, which has some support from epidemiological findings, but research on the relationship between serum magnesium and its implications for the central nervous system suggests that one isn't always informative about the other. Magnesium in serum isn't reflective of magnesium in mononuclear cells, and various animal experiments suggest that it isn't necessarily reflective of the status in organs. One study in which researchers induced magnesium deficiency in rats failed to find an impact on levels in the brain, and another study in which researchers increased serum levels in rats with supplementation didn't find much of a change in brain levels. Cerebrospinal fluid magnesium levels could be relevant to brain function, but thus far haven't been found to be correlated with depression risk. From the beginning of the study it was clear that the results weren't going to be particularly relevant to people with higher magnesium levels, but having low serum magnesium levels after a standard blood test may not indicate that the levels in the central nervous system are low in every case.

The magnesium levels of the participants were lower than average, but can go quite a bit lower in some cases where health conditions can compromise magnesium status. If the increase in magnesium levels in this study is relevant, then it might be even more critical in people with far lower levels, such as the participants in the first trial who had a mean serum level of only 1.4mg/dl.

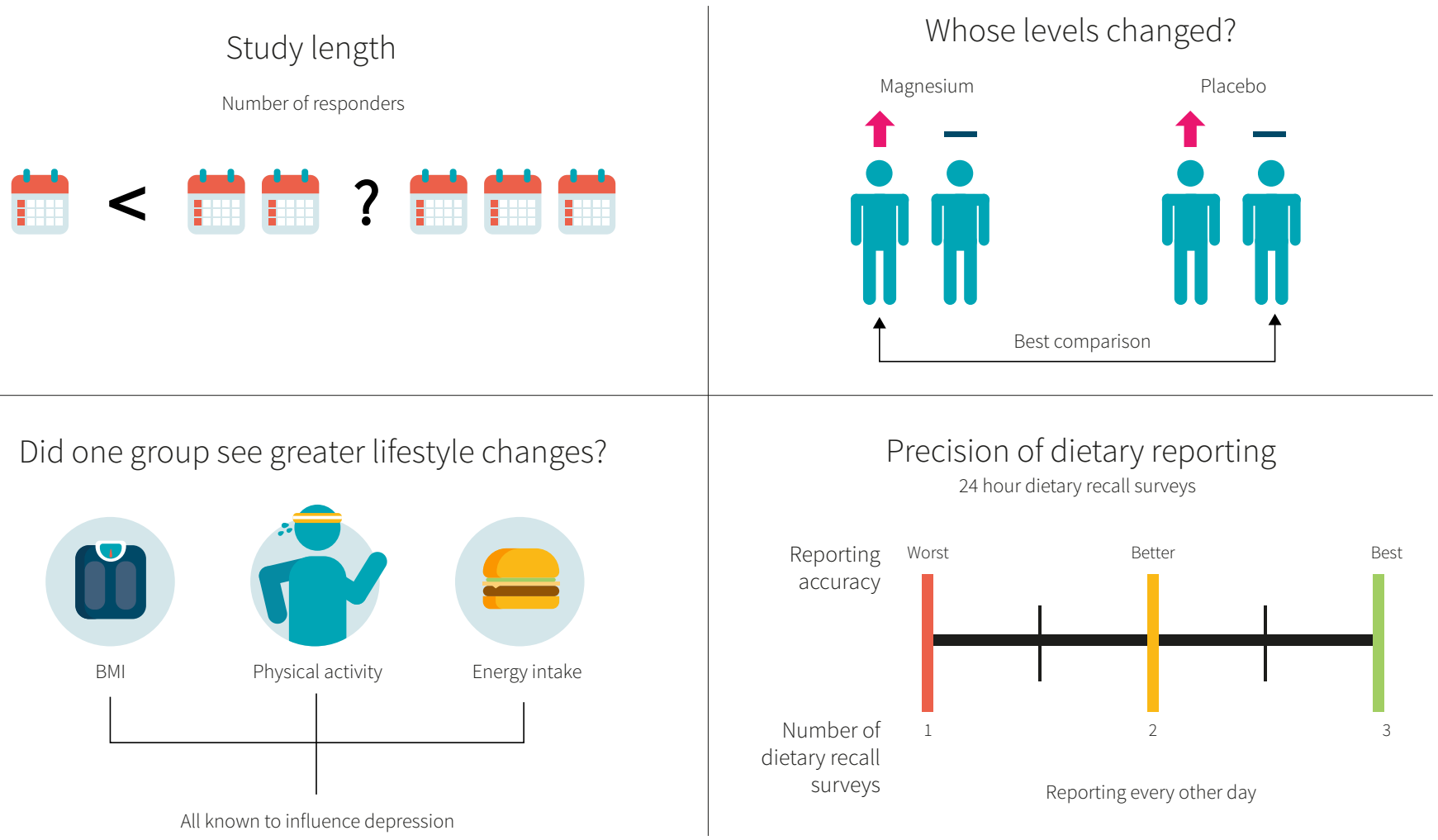
Dietary and BMI changes mostly didn't reach statistical significance, and the method of evaluating dietary changes was likely insufficient. The optimal number of 24-hour dietary recall surveys to measure energy intake is larger than performed in this study, even in a shorter length of time, and even then there's potential for inaccuracy. In studies on depression, it can be helpful to accurately record the changes in not only diet and body fat, but physical activity as well. Changes in physical activity, energy intake, or weight loss could have an effect on depression scores, and tracking these things can afford greater confidence that the changes in depression scores are due to the intervention. The authors acknowledged this by attempting to record dietary and BMI changes, but studies that are designed to be able to do this more effectively would be informative. Figure 3 summarizes some of the study design factors that could help future trials build on the current results.

Magnesium appeared superior to placebo, but greater confidence in its effects could come from larger and longer trials with more sensitive measures of total body magnesium status.

The big picture

NMDA receptor regulation is an exciting prospect for treating depression, and magnesium isn't the only nutrient that could be involved. A number of trials suggest that zinc can reduce depressive symptoms, and research also suggests that it plays a role in the regulation of NMDA receptors. Lithium, one of the original antidepressant medications, may also exert some of its effects via reduction of glutamate excitotoxicity. The truly big picture could have to do with a variety of elements and other nutrients that work together to correct dysfunc-

Figure 3: Best practices for future trials. What to look for?



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Fabricatore et al. Int J Obes (Lond). 2011 Feb
Yunsheng et al. Ann Epidemiol. 2009 Aug

tional synaptic transmission in depression, and studies that examine possible synergies between these nutrients could be a useful direction for depression research.

A number of depression medications lead to concurrent increases in intracellular magnesium concentrations in the brain, and it has been observed in one study that higher serum magnesium levels at baseline are associated with better responses to antidepressant medications, suggesting a possible role of magnesium as an adjunct in the conventional treatment of depression in people with low magnesium levels.

Maintaining adequate magnesium levels is important for whole body health and could tie into long-term depression risk and symptoms in indirect ways. Increasing magnesium status may improve exercise performance, which could facilitate the antidepressive effects of exercise, allowing people to work out more vigorously. Sleep disorders are extremely common in depression, and insomnia is a risk-factor for developing depression in the future or relapsing after treatment. Magnesium could lead to quality of life improvements and reduce the burden of insomnia in depression.

Magnesium supplementation is effective in improving magnesium status, but magnesium is an essential nutrient found in a wide variety of foods, namely fruits and vegetables, which are correlated with a lower risk for depression. Some of the association may be explained by magnesium, but there are likely other nutrients in whole food that also have an effect on depression risk. Risk for depression is correlated with elevated inflammatory markers, and studies investigating antidepressive effects of anti-cytokine medications suggest that avoiding excessive inflammatory signaling could reduce depressive symptoms. A healthy and nutritious diet could not only supply sufficient magnesium, but could also reduce the risk for depression or depressive symptoms in other ways.

Magnesium may have a part to play in easing the burden of depression, either alone, in combination with other nutrients, as an adjunct for medications, or by facilitating changes in lifestyle that could reduce symptoms and prevent relapse. Future research can elaborate on its usefulness in each context.

Frequently asked questions

Who is at an increased risk of low magnesium status?

People with a very low intake, of course, but that's not particularly common. Low magnesium status is more likely to be caused by medical conditions or ingestion of medication and other substances that cause magnesium wasting. People at a higher risk are those with type 1 or 2 diabetes, alcoholism, and gastrointestinal diseases such as ulcerative colitis, celiac disease, and Crohn's disease.

Why did the researchers use the magnesium oxide form?

This is the most common form found in stores. So even though it has very low absorption compared to other forms, the results of this trial are easily applicable to the general public.

What should I know?

The first randomized, double-blind, placebo-controlled trial for magnesium supplementation in depression suggested modest superiority of magnesium over placebo when comparing changes in symptoms according to the Beck II inventory. The trial is more applicable to people with low serum magnesium levels, and the benefits given normal levels are unclear. ◆

Magnesium isn't a magic bullet for depression, and magic bullets don't typically exist for this complex condition. But magnesium doesn't have major side effects, and is easily available. Discuss nutrition and depression over at the ERD Facebook forum.

Can fasting for five days once per month improve your health?

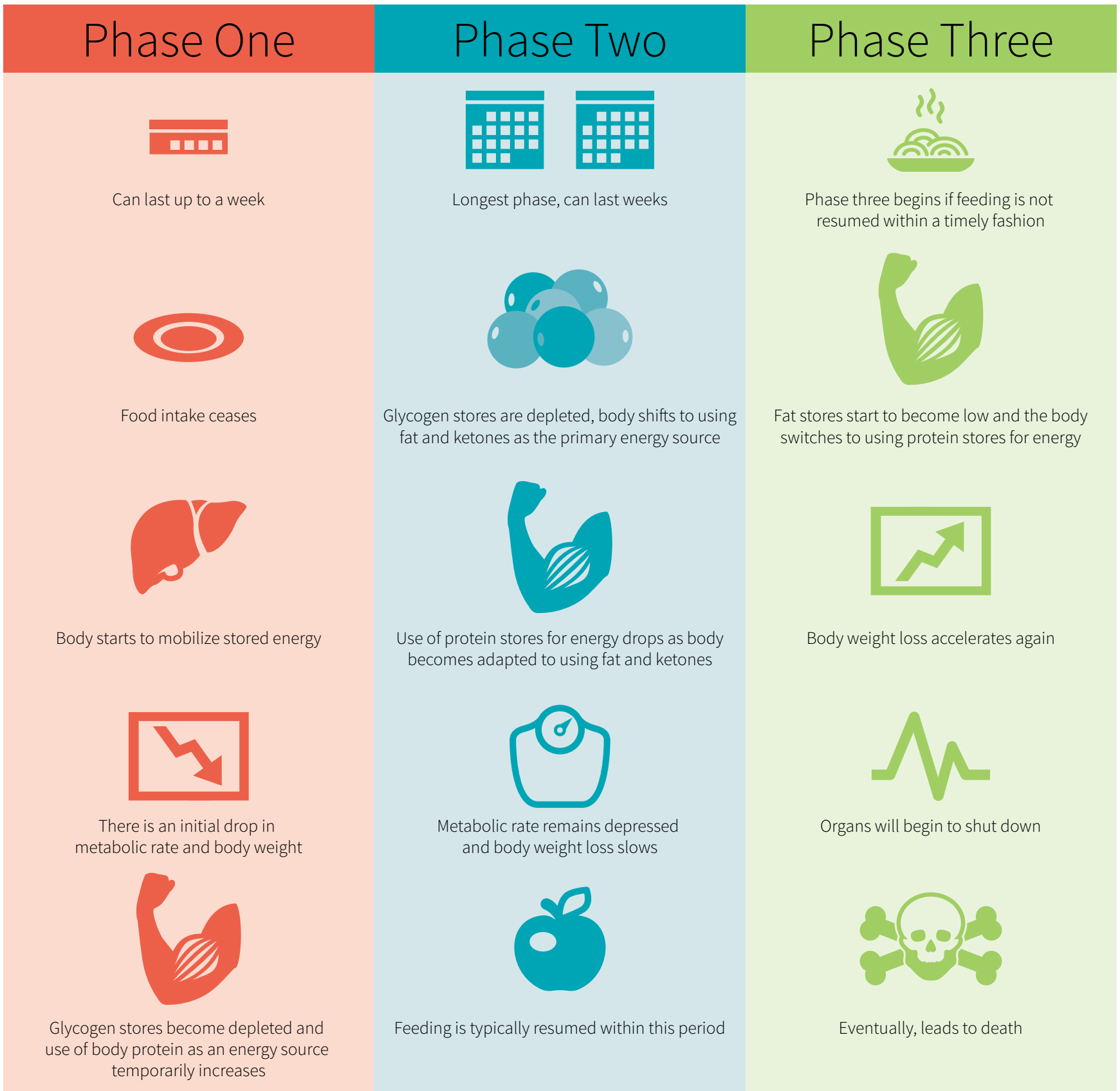
Fasting-mimicking diet and markers/risk factors for aging, diabetes, cancer, and cardiovascular disease

Introduction

Our bodies are well equipped to go for long periods of time without food. Generally, a bout of feeding and digestion is followed by an episode of digestive quiescence (i.e., fasting). In the modern day, feeding is rather frequent and fasting tends to be limited to our sleep, no more than 8-12 hours for most people. However, extended episodes of fasting are characterized by an extensive repertoire of physiological changes that promote the use of stored energy to prolong survival. Importantly, fasting is distinct from starvation, which is the ultimate endpoint at which survival is compromised due to the loss of organ function.

Extended bouts of fasting can be categorized into three chronological phases (depicted in Figure 1), with the duration of each phase depending on various lifestyle

Figure 1: Phases of fasting



Source: Secor and Carey. Compr Physiol. 2016 Mar 15.

and environmental factors. Phase I is relatively short (a couple days at most) and encompasses the transition from digestion and absorption of nutrients to digestive inactivity and the mobilization of stored energy as a fuel source. Glycogen stores are being depleted and the use of bodily protein as a substrate to create glucose has increased. Phase II is the longest phase where the body begins to rely more heavily on fatty acids and ketone bodies as an energy source, thus limiting its need for glucose and therefore minimizing the breakdown of bodily protein to make glucose. Phase III is the critical period of fasting during which fat stores have been depleted and the breakdown of bodily protein accelerates, eventually leading to organ failure and death (i.e., starvation).

As the body literally feeds on itself, numerous physiological adaptations occur to reduce energy requirements, including those central for growth and reproduction, with the focus shifting towards repair and maintenance. Notably, there is a suppression of the the growth hormone/insulin-like growth factor-1 (IGF-1) axis and mTOR-S6K pathway. Many of the interventions that extend lifespan in animals have the effect of reducing mTOR signaling, and using drugs to inhibit mTOR in mice without any other intervention increases lifespan by more than 20%.

A renewed interest in longevity has spurred the creation of many types of fasting regimens. Some of the most well known are variations of intermittent fasting, or consuming little to no calories for 12 to 24 hours on a regular basis. Intermittent fasting has been investigated in controlled trials for weight loss and reducing the risk of metabolic diseases such as type 2 diabetes, especially in comparison to daily energy restriction. However, the length of fasting may not be long enough to elicit the physiological changes related to life extension.

Of course, going for days without food is impractical for many in the modern world, not to mention probably very difficult. As such, fasting mimicking diets (FMDs) have recently emerged as a potential diet regimen that allows for eating while eliciting similar metabolic effects as complete abstinence from food. The expert consensus, based primarily on animal studies, is that FMDs are one of the more promising strategies for promoting longevity due to their ability to suppress the growth hormone/IGF-I axis and mTOR-S6K pathway.

To this end, a group of researchers published data in 2015 about a very low calorie and low protein FMD that caused physiological changes in mice that were similar to those caused by complete fasting. This publication also contained data on a pilot trial in 38 humans showing that the FMD was safe and feasible. The study under review is a follow-up randomized controlled trial of 100 participants evaluating the effects of the FMD on biomarkers and risk factors for metabolic syndrome and longevity.

Numerous physiological changes occur in response to fasting that have been shown in animals to extend lifespan. Accordingly, various fasting regimens have been developed and tested to promote longevity. One of these regimens is a fasting mimicking diet, which allows for food intake while still leading to similar physiological effects as complete fasting. The current study sought to test its effects on biomarkers and risk factors for metabolic syndrome and longevity in humans.

Who and what was studied?

This was a randomized controlled trial involving 100 generally healthy adults without major medical conditions or chronic diseases. Using BMI, 37% of the participants were normal weight, 39% were overweight, and 24% had obesity. The average age was 42 years, but a high level of variance and inclusion criteria allowed for anyone between 18 and 70 years old to participate.

Participants underwent a three-month, parallel-group intervention in which they were randomized to a con-

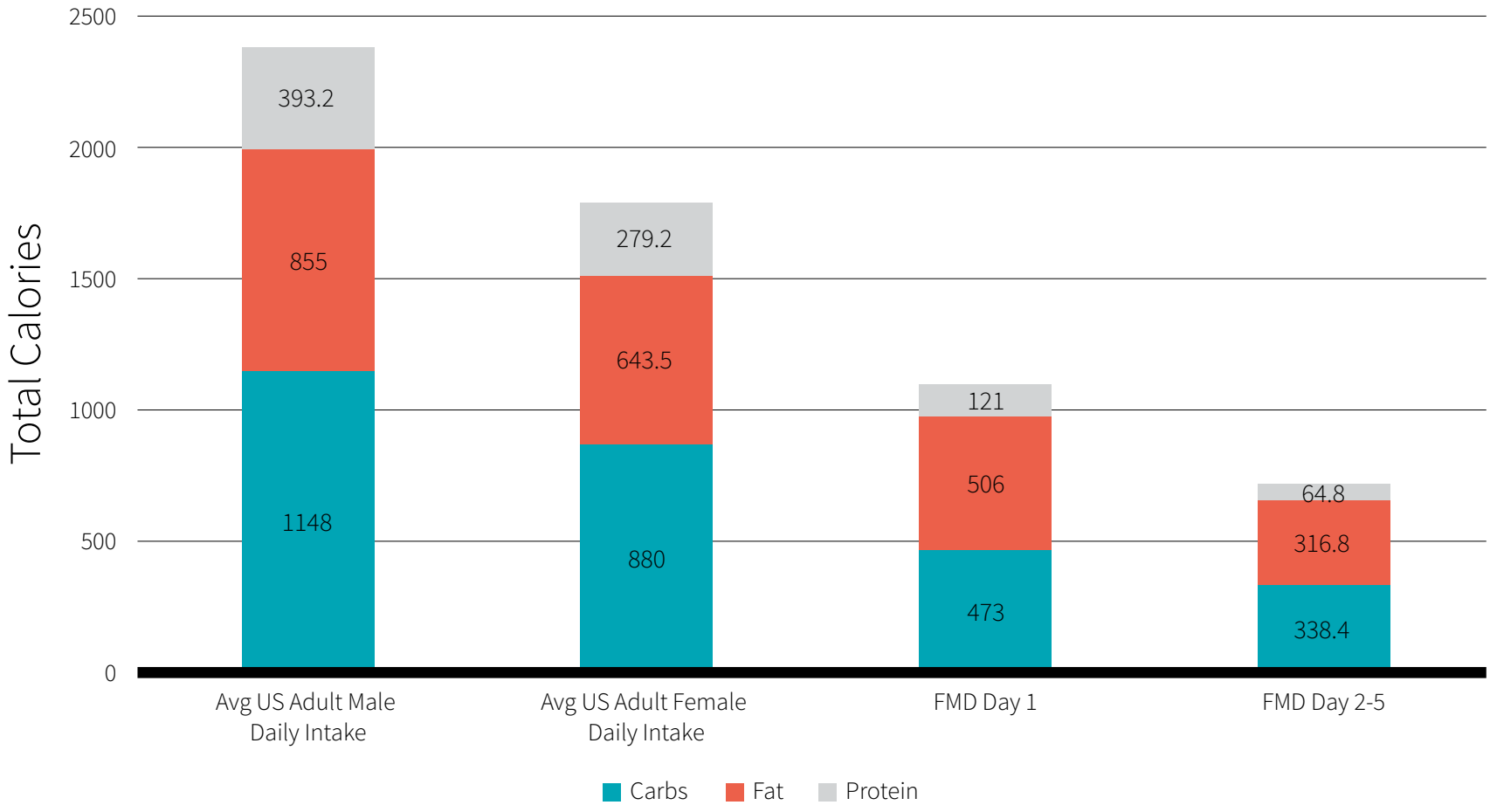
trol group or a FMD group. The control group was instructed to not change their usual eating habits. The FMD group was also instructed to not change their usual eating habits except to consume a FMD for five consecutive days once per month (three times in total throughout the three-month intervention).

The FMD was a plant-based diet based on proprietary formulations (the lead researcher has a patent on this diet) of soups, energy bars, energy drinks, chips, tea, and a multivitamin. As shown in Figure 2, the first day of the FMD provided roughly 1100 kcal (11% protein, 46% fat, and 43% carbohydrate) and the remaining days provided about 720 kcal (9% protein, 44% fat, 47% carbohydrate). All food was provided to the participants during this time and each item was individually boxed so that the participants could choose when to eat their food.

The outcomes measured in this study were changes in metabolic risk factors and biomarkers associated with longevity, including fasting glucose, blood pressure, blood lipids, C-reactive protein, IGF-1, and body composition (DXA scan). Assessments were conducted before and about one week after the interventions. Additionally, a third examination was made in the FMD group immediately following the completion of the first five-day FMD cycle to explore the acute effects of the diet. All outcomes were assessed with an intention-to-treat analysis and were corrected for multiple comparisons.

A group of 100 generally healthy adults took part in a three-month randomized controlled trial evaluating the impact of consuming a very low-calorie, low-protein, plant-based FMD for five consecutive days once per month while otherwise maintaining regular eating habits. Changes in body composition, metabolic risk factors, and biomarkers associated with longevity were compared between the FMD group and the control group that maintained their usual eating habits throughout the three months.

Figure 2: FMD diet versus average US adult daily intake



Source: *What We Eat in America*, NHANES 2013-2014

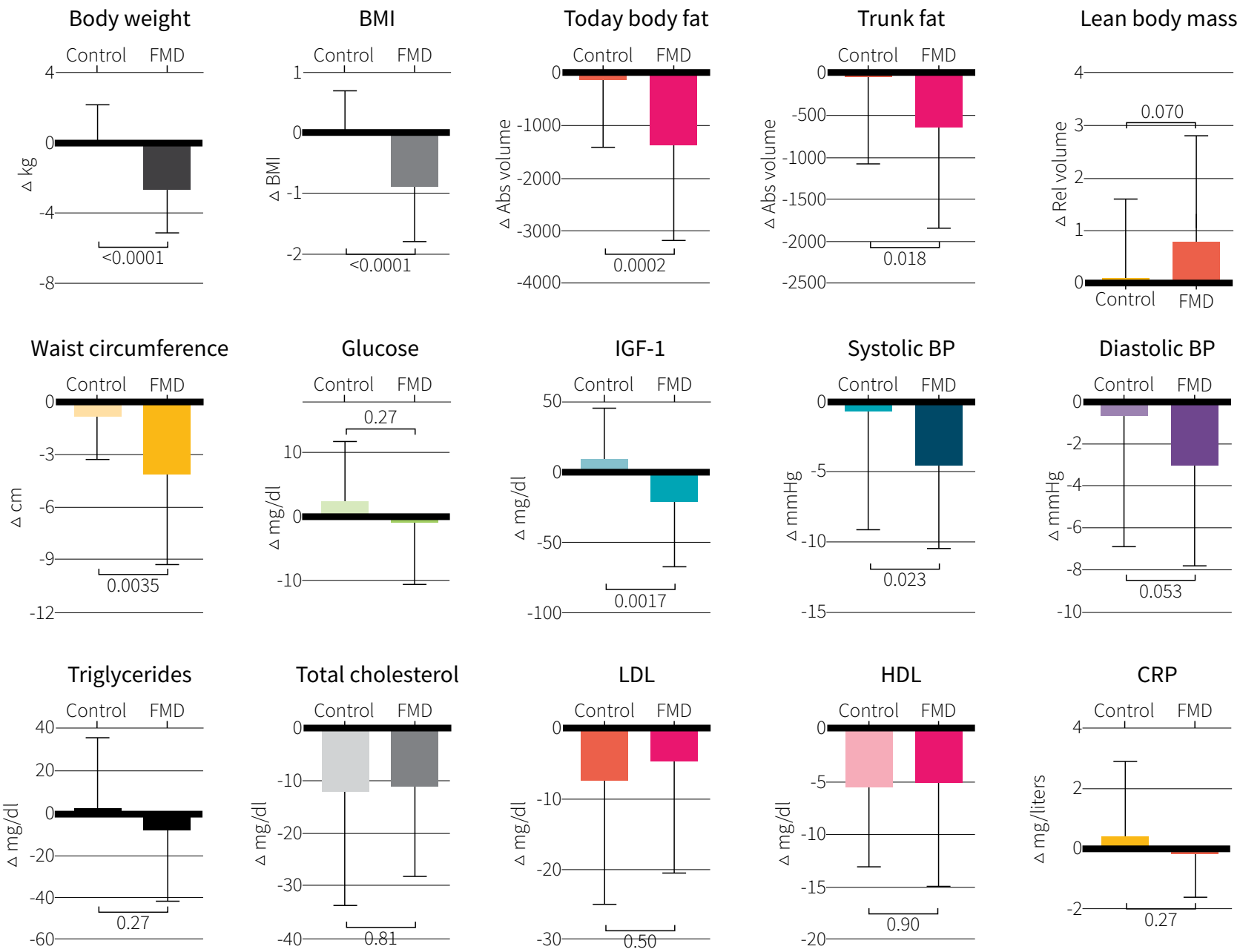
What were the findings?

The main study results are shown in Figure 3. Compared to the control group, the FMD group experienced significant reductions in body weight (2.6 kilograms; approximately 6.0 pounds), BMI (0.9 units), total body fat (1.3 kilograms; approximately 3.0 pounds), trunk-specific fat mass (0.6 kilograms; 1.3 pounds), waist circumference (3.3 centimeters), and IGF-1 (30.4 ng/mL). The FMD group also showed non-significant reductions in lean body mass (1.1 kilograms; approximately 2.4 pounds; p=0.07) and diastolic blood pressure (2.4 mmHg; p=0.053) compared to the control group. However, there were no differences between groups for fasting glucose, triglycerides, total cholesterol, LDL-cholesterol, HDL-cholesterol, or C-reactive protein.

To explore the acute effects of the FMD, participants had an exploratory assessment conducted immediately following the completion of the first FMD cycle. Significant reductions were observed for bodyweight, BMI, lean body mass, waist circumference, fasting glucose, diastolic blood pressure, and IGF-1, while significant increases were seen for LDL-cholesterol and beta-hydroxybutyrate (ketone). Other outcomes were not significantly altered, although there was a trend for body fat and systolic blood pressure to go down.

In a post hoc analysis comparing healthy to at-risk participants, it was observed that healthy people benefited less from the FMD intervention than less healthy people. Specifically, people who were obese at baseline lost more weight than people who were not obese and peo-

Figure 3: Changes in metabolic variables from baseline



ple with elevated blood pressure, glucose, triglycerides, total cholesterol, LDL-cholesterol, C-reactive protein, or IGF-1 saw greater reductions than their healthy-range counterparts. Notably, the healthy folk saw no significant change in fasting glucose, triglycerides, LDL-c, HDL-c, or C-reactive protein, suggesting limited health effects in this population.

Finally, some of the participants returned three months after the intervention's completion to see if any of the effects of the FMD persisted. Compared to before the intervention began (i.e., six months ago), body weight, BMI, lean body mass, waist circumference, fasting glucose (among at-risk only), blood pressure, and IGF-1 (at-risk only) remained significantly lower, albeit not as low as after the intervention itself.

The FMD intervention was well-tolerated by most of the participants. No serious adverse events were reported and no negative effects of the FMD on liver or kidney function were observed. However, nearly half of the participants complained of mild fatigue, about one-quarter complained of mild weakness and headaches, and at least 10% complained of mild dry mouth, memory impairment, and muscle pain. Overall, significantly more participants in the FMD group dropped out of the study compared to the control group (25 vs. 10 %).

The FMD intervention resulted in significant reductions in bodyweight, body fat, waist circumference, and IGF-1 compared to the control group, as well as nearly significant reductions in lean body mass and diastolic blood pressure. However, no differences were observed for other metabolic risk factors. Some of these effects appear to persist for several months after stopping the intervention and the magnitude of change appears to be larger in less healthy people, but follow-up research is needed to test these observations directly.

What does the study really tell us?

The study under review suggests that spending five days eating a FMD once per month is safe and effective at reducing body weight, body fat, waist circumference, and IGF-1. However, the implications of these findings regarding longevity remain to be determined. Moreover, most metabolic risk markers were unchanged and lean body mass trended towards reduction, both of which raise uncertainty about the pragmatic health benefits of the FMD.

But, importantly, the FMD was compared to a control group who were not assigned any intervention at all. Thus, all the effects that were seen could very well be simply attributed to weight loss. After all, it is difficult to separate the effects of energy restriction from weight loss since the two go hand-in-hand. The lack of weight loss and change in IGF-1 in the control group lends support to this idea. So, this study did show that the FMD helped to lose weight, but it's quite possible that all the effects seen were due to weight loss, and not to FMD specifically. On the other hand, several studies have reported significant weight loss without a concomitant change in IGF-1 concentrations. One study even reported a significant increase in IGF-1 with weight loss. Regardless, further investigation is necessary to compare the tolerability and health effects of the FMD to other forms of fasting and energy restriction. For example, how would the FMD intervention used in the study at hand compare to daily time restricted feeding during which all food was consumed within an eight-hour window?

Chronic energy restriction is well established in animal models (both rodents and nonhuman primates) to extend lifespan, reduce oxidative stress, and promote cellular repair processes by reducing serum levels of IGF-1 and inhibiting mTOR, a major pathway for growth and reproduction. However, there is little to no evidence about how energy restriction would impact the

lifespan of longer-lived species like humans. Moreover, maintaining chronic energy restriction for years and decades may be difficult. Accordingly, interest in fasting and FMDs has grown as a potential solution that allows for similar physiological changes as chronic energy restriction without the chronic restriction component.

Notably, severe restriction of dietary protein (or specific amino acids) can also extend the lifespan of animals to a similar extent as chronic energy restriction. The study at hand used a FMD that was very low in protein, supplying about 20 grams of protein per day, as well as very low in calories. This appeared to lead to some changes that mimic energy or protein restriction, such as the reduction in IGF-1, but the implications of this finding for longevity are unknown. Also, was the reduction in IGF-1 owed primarily to the FMD's low protein or energy content? Future research will be needed to identify the components of the FMD that resulted in the observed effects of the study at hand.

Assuming the FMD would extend lifespan, it must be questioned whether this additional life could be lived healthfully. The FMD group experienced a significant reduction in their lean body mass (40% of total weight loss), which is paramount to health. Skeletal muscle plays an important role in the prevention of many metabolic disorders such as obesity, type 2 diabetes, and osteoporosis, and the loss of muscle mass and function with aging, called sarcopenia, is a widespread health concern with devastating consequences on quality of life and survival. The loss of muscle mass is a key contributor to frailty, an increased likelihood of falling, and an inability to perform basic activities of daily living.

There are many ways to help offset the loss of muscle mass with aging and dieting, including resistance training and eating a diet sufficient in dietary protein. Future research will need to investigate how the FMD impacts health when combined with resistance training. Similarly, it remains to be determined how a FMD diet that uses a different combination of macronutrients affects health- and longevity-related outcomes. At least one study in bodybuilders has shown that IGF-1 declines during contest preparation despite a high protein intake, alluding to potential benefits for lifespan while potentially maintaining lean body mass. This suggests that the energy restriction component of the FMD is at least partially responsible for the reduction in IGF-1.

Several limitations of the study under review must be acknowledged. The dropout rate was high for the FMD group, but the study used an intention to treat analysis. While this provides a pragmatic set of results by ultimately including all people who began the intervention, it doesn't represent the effect of the intervention per se, which would require only looking at adherent participants (per protocol analysis). Similarly, the diversity of participants regarding health status may have resulted in too great variation for significant effects to be noted, which was suggested by the post hoc analysis. Follow-up research will be needed to determine the effects of the FMD on more focused groups of participants, especially those with metabolic diseases. The current study was also short, lasting three months. Whether the intervention would be maintainable and what effects it would have on health over a longer time remain to be determined.

Consuming a FMD for five consecutive days once per month is safe and effective for reducing body fat and IGF-1, but it also reduces lean body mass and leaves most metabolic risk factors unchanged. Accordingly, the long-term health effects are debatable, especially since sarcopenia is a widespread health concern. Future research is necessary to test different types of FMDs in different populations.

The big picture

A major goal of research on aging has been to find ways to reduce morbidity and delay mortality. Although

great strides have been made over the last several decades, clear-cut answers continue to elude us. Many researchers have turned to the Blue Zones for answers, which include societies where people routinely live to be older than 80-100 years (Sardinia in Italy, Okinawa in Japan, Loma Linda in California, and Nicoya Peninsula in Costa Rica, among others).

Surveys of the Blue Zone residents report some common lifestyle characteristics, like family coherence, avoidance of smoking, a plant-based diet, moderate and daily physical activity, and social engagement throughout the community. This is in stark contrast to the chronically stressed, sedentary, and socially isolated Westerner who eats a nutritionally void and calorically dense diet based on processed grains, meats, and oils. While it is tempting to draw conclusions about diet from Blue Zone societies, it is impossible given the numerous other lifestyle factors so vastly different from the modern Western world.

Nonetheless, dietary trials aimed at mimicking the longevity effects observed in animals have been conducted. The CALERIE trial placed adults on a 25% calorie-restricted diet for two years and found numerous changes in body composition and metabolic factors, including reduced fat mass and lean body mass, inflammation, triglycerides, cholesterol, blood pressure, and insulin resistance. Similar observations were made during another two-year trial following people trapped in a BioSphere. But, these studies tell us nothing about lifespan.

The absence of adequate information on the effects of energy restriction in humans reflects the difficulties involved in conducting long-term energy-restriction studies, including ethical and methodologic considerations. It simply isn't feasible to control certain aspects of people's lives for decades. As such, there may never be a completely satisfactory answer regarding the effects of any diet, be it energy restriction or an FMD, on human life span.

Observational data on longevity is confounded with numerous lifestyle habits that may influence any dietary associations, and long-term clinical trials are not feasible with an outcome such as lifespan. There is the possibility that the effect of diet on lifespan may never have a satisfactory answer.

Frequently asked questions

How applicable are longevity studies in mice to humans?

The cells of mice and humans use similar molecular mechanisms to regulate growth, replication, differentiation, and death, which is one reason why mouse models are used to study human diseases and ageing processes. However, another reason that mice are used, especially for research into ageing, is because their average lifespan is about 24 months, far shorter than the 80-year average of humans. Overall, one human year is equivalent to nine mouse days.

One reason for this difference in lifespan is owed to differences in metabolism that present a major barrier in longevity research. For example, reactive oxygen species (ROS) are a byproduct of energy metabolism that are believed to regulate lifespan, and reduced ROS production occurs with energy restriction that extends lifespan. It has been suggested that organisms with a high mass-specific metabolic rate will typically be characterized by high levels of ROS production and a low capacity to maintain ROS levels within certain limits. Therefore, these organisms will be more responsive to any intervention that reduces ROS production.

Mice have an energy expenditure rate per unit of body mass that is seven times greater than humans. As such, they are expected to be far more responsive to the longevity effects of energy restriction and other interventions that reduce ROS production when compared to humans, who are less prone to the effects of variations in ROS production, at least when it comes

to longevity. So mice studies may not apply well to humans. However, returning to the point made in the Big Picture section, there is no way of knowing for sure because studies evaluating lifelong energy restriction in humans are all but impossible to conduct.

There also appears to be substantial variability between strains of mice, suggesting that the effects of calorie restriction on lifespan are not simple nor straight-forward. One study placed 41 strains of mice on the same "longevity" diet and showed that it actually shortened life in more strains than it lengthened, with the magnitude of change ranging from a loss of 700 days to a gain of 400 days.

What about nonhuman primate research into longevity? Certainly, monkeys and apes are more closely related to humans than mice. Since nonhuman primates can be studied under highly controlled experimental conditions, they make for a great stepping stone away from other animals and towards human research. However, one of the longest studies to date suggests that there are important qualifiers to reap the life-extending benefits of food deprivation. The researchers placed monkeys on unrefined, whole-food diets for 26 years with or without 30% energy restriction, beginning in youth or in middle-age. Neither energy-restricted group experienced an increase in average or maximal lifespan compared to the controls without energy restriction. Granted, metabolic health was improved significantly with energy restriction, just not longevity.

What should I know?

Prolonged fasting causes physiological changes that extend lifespan in animals. However, abstaining from food for days at a time may be impractical or inconvenient for many people in the modern world. A fasting mimicking diet is one that allows for food intake while still permitting similar physiological changes as complete fasting.

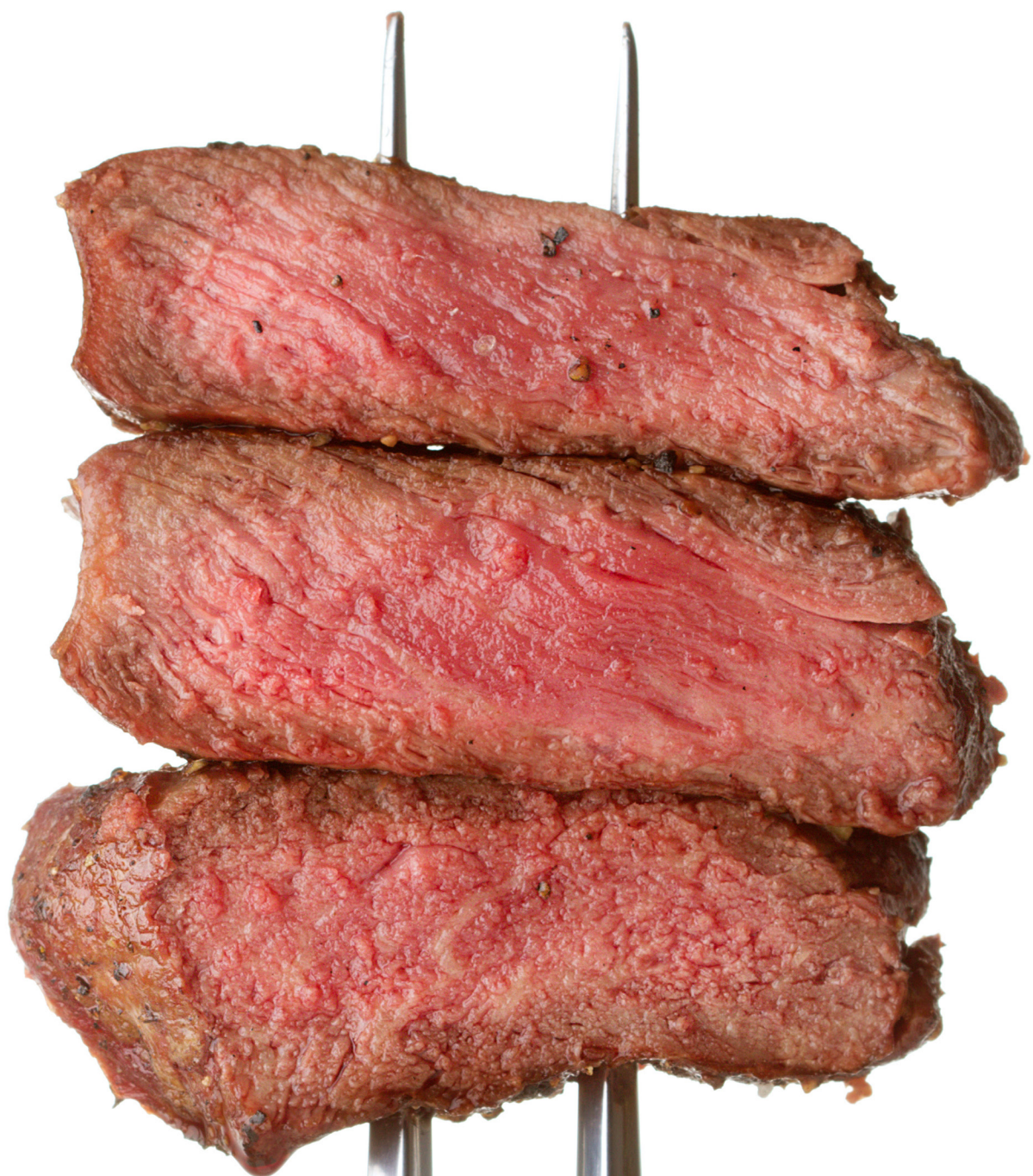
The study under review tested the health effects of consuming a fasting mimicking diet for five consecutive days once per month for three months. Although bodyweight and IGF-1 were significantly reduced, suggesting a potential benefit for longevity, most metabolic markers were unchanged. These outcomes were in comparison to not doing anything, which raises questions about the usefulness of this type of intervention. Additionally, the dropout rate was high, suggesting that the fasting mimicking diet is not easy to adhere to. Future research is necessary to test different types of fasting mimicking diets in different populations, especially with regard to the protein content of the diet and the health status of the participants. Additionally, the fasting mimicking diet will need to be compared to other forms of fasting and regular energy restriction. ◆

Fasting, intermittent fasting, and fasting-mimicking. Each holds promise, but we don't yet know how these diets would perform in the general population. Discuss these issues at the ERD Facebook forum.

> "One study placed 41 strains of mice on the same "longevity" diet and showed that it actually shortened life in more strains than it lengthened,"

Red meat and heart disease: what do controlled trials tell us?

Total red meat intake of ≥0.5 servings/d does not negatively influence cardiovascular disease risk factors: a systemically searched meta-analysis of randomized controlled trials



Introduction

Red meat consumption has become quite a contentious issue in the past few decades. The prevailing view in the public health community is that red meat is unhealthy, but this conclusion is based heavily on contradictory observational evidence. For example, several studies have found a relationship between red meat consumption and cardiovascular disease morbidity and mortality, while others have not and argue that these associations were owed to problems with data collection and how red meat is classified (such as grouping unprocessed and and processed red meats together).

Regardless, observational evidence does not allow for establishing causality. At the same time, performing randomized controlled trials that evaluate long-term health outcomes such as dying from a heart attack are difficult and expensive to conduct. Accordingly, researchers instead look at known cardiovascular disease risk factors, such as a person's blood lipids or blood pressure, which change on a relatively short timescale. If red meat does increase the risk of cardiovascular disease, then there is a good chance that it does so through these well-established cardiovascular disease risk factors.

A previous meta-analysis of eight studies suggested that beef consumption did not significantly alter the blood lipid profile of healthy adults when compared with poultry or fish. However, this doesn't tell us the effect of adding red meat into the diet per se, and does not include all types of red meat, only beef. The study under review is a meta-analysis of randomized controlled trials investigating the impact of red meat consumption on blood lipids and blood pressure, two well-established cardiovascular disease risk factors.

Observational evidence reports an inconsistent link between red meat consumption and cardiovascular disease. However, no study has yet to systematically review controlled trials looking at red meat and cardiovascular disease risk factors. The study under review is a meta-analysis of randomized controlled trials investigating the impact of red meat consumption on blood lipids and blood pressure.

Who and what was studied?

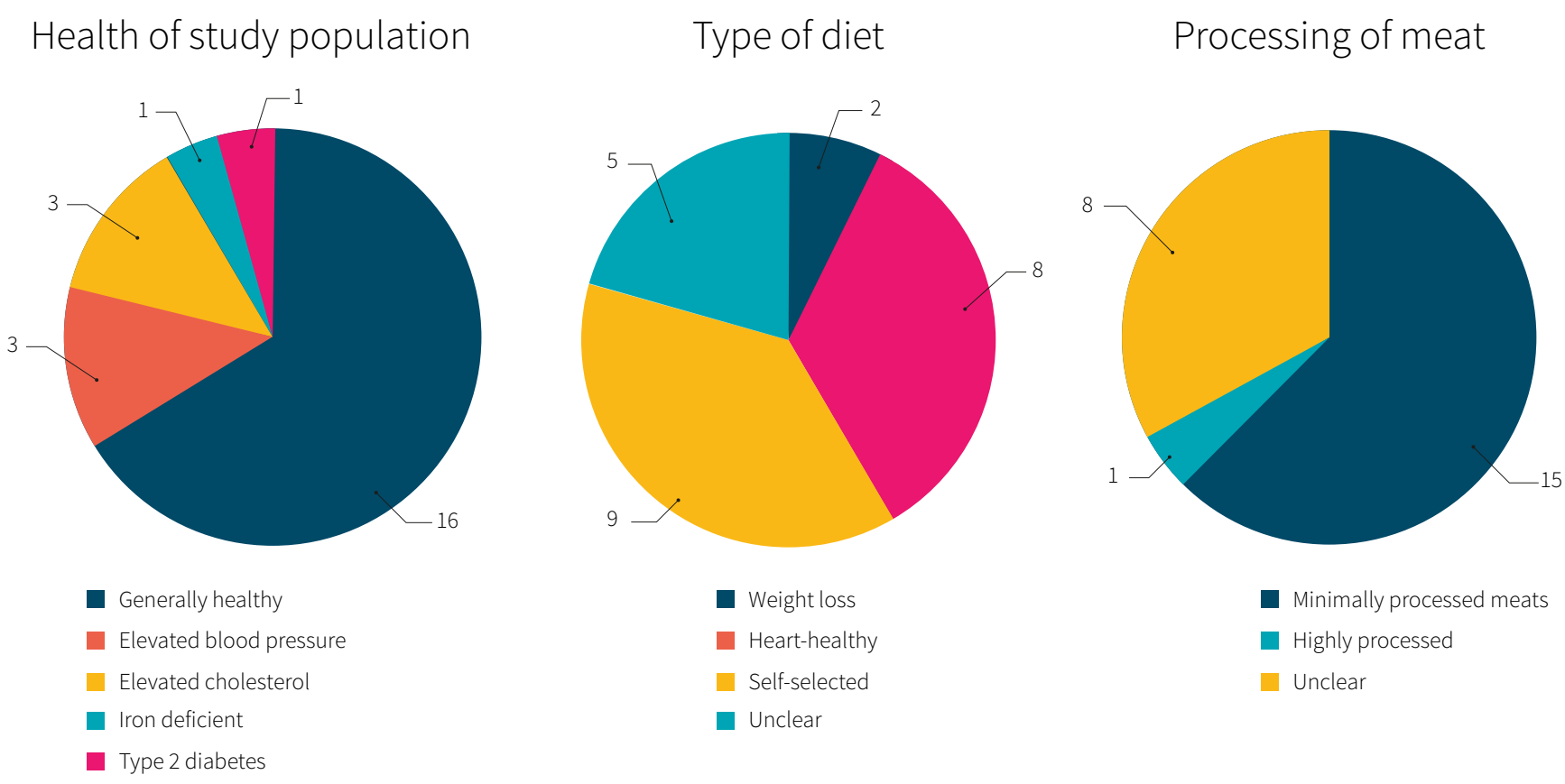
This meta-analysis is based on 24 randomized controlled trials in adults, comparing intervention groups that consumed more than 0.5 servings of red meat per day to control groups consuming less than 0.5 servings per day. The authors used the Dietary Guidelines for Americans definition of red meat: "all forms of beef,

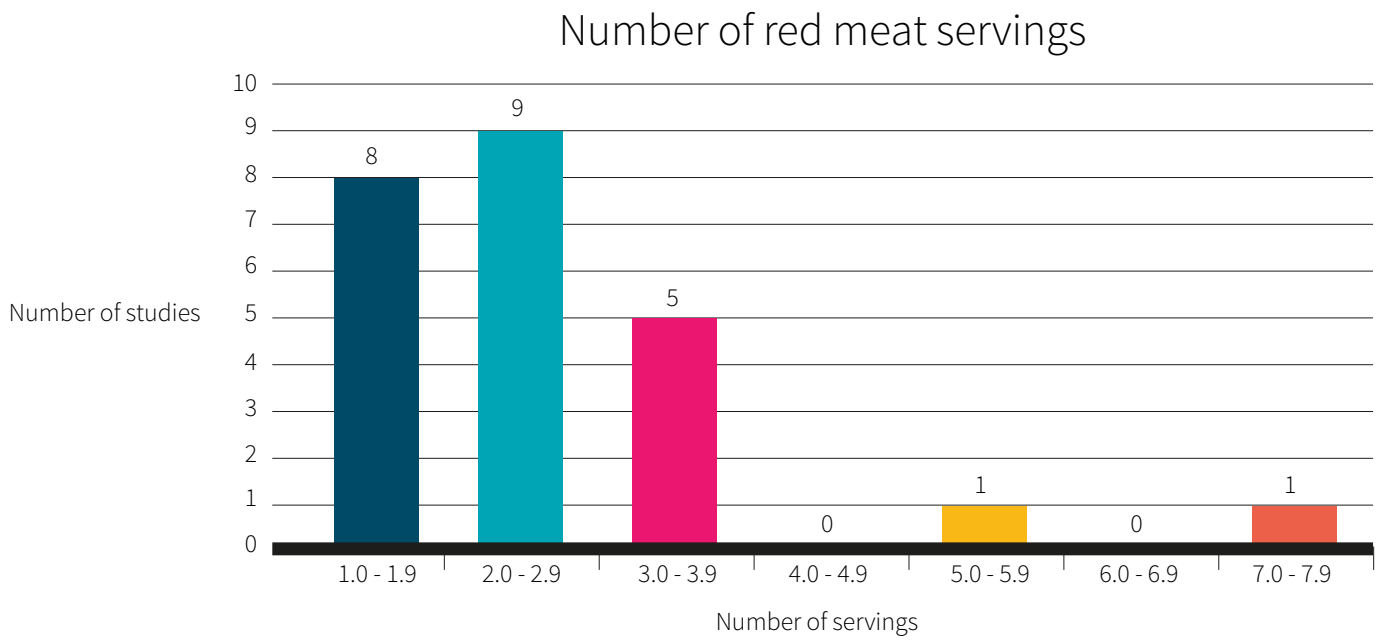
> "[...] performing randomized controlled trials that evaluate long-term health outcomes such as dying from a heart attack are difficult and expensive to conduct."

pork, lamb, veal, goat, and non-bird games (e.g. venison, bison, elk)," and considered one serving to be 2.5 ounces (70 grams), which is the middle ground of the American Heart Association's two to three ounce serving size for cooked meat.

Figure 1 shows characteristics of the 24 included studies. The average red meat intake in the high-meat groups ranged from 1.0 to 7.1 servings per day (2.5-17.75 ounces or 68-500 grams) and averaged two servings per day (5.0 ounces or 140 grams). By contrast, the control group averaged zero servings of red meat per day, with a range of up to 0.4 servings (1.0 ounce or 30 grams). About one-third of the studies performed their intervention in the context of a "heart-healthy" diet, while 37% allowed for the participants to choose their diet, and the remainder were unclear. About 62% of the studies used minimally processed red meats exclusively, while one study used processed meats and the remainder did not specify. Intervention lengths ranged from two to 32 weeks.

Figure 1: Characteristics of 24 included studies





The primary outcomes were the difference between the high- and low-meat groups regarding changes in total cholesterol, LDL-cholesterol, HDL-cholesterol, the total to HDL cholesterol ratio, triglycerides, systolic blood pressure, and diastolic blood pressure. Several sensitivity analyses were conducted, including the removal of each individual study one-by-one to make sure none were single-handedly influencing the outcome of the meta-analyses, as well as the removal of study clusters containing design features that had the potential to confound the results. Finally, post-hoc analyses were performed with meat intake divided into quartiles (0-0.9, 1.0-1.9, 2.0-2.9, and more than 3.0 servings per day).

This was a meta-analysis of 24 randomized controlled trials in adults comparing a high-meat diet group (1.0-7.1 servings per day; average of 2.0 servings) to a low-meat diet group (0-0.4 servings per day; average of zero servings) regarding changes in total cholesterol, LDL-cholesterol, HDL-cholesterol, the total to HDL cholesterol ratio, triglycerides, systolic blood pressure, and diastolic blood pressure.

What were the findings?

There was no significant difference between groups for any outcome variable. Significant heterogeneity was present for each outcome except for systolic and diastolic blood pressure. However, results weren't affected when performing sensitivity analyses removing individual studies and removing study clusters that used weight loss diets, heart-healthy diets, diseased populations, processed meat or unspecified processing, or diets differing in total protein intake. Also, comparing quartiles of red meat intake showed no difference between the control group and any intake level of red meat for any outcome except that HDL-c was significantly higher in the high-meat group when eating more than 3.0 servings per day.

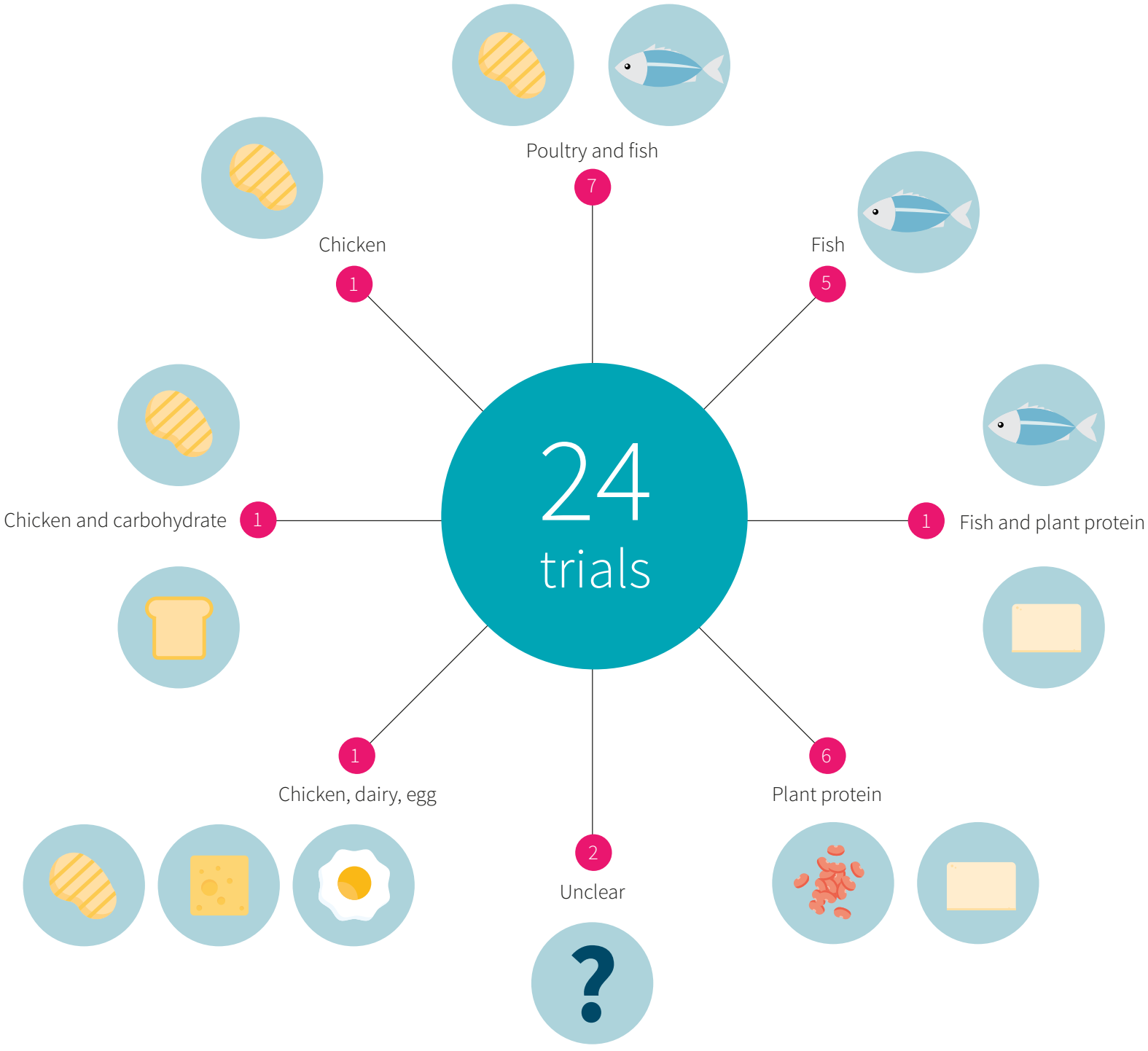
What does the study really tell us?

Compared with eating less than an ounce of red meat per day, consuming more does not appear to have a significant influence on blood cholesterol, triglycerides, or blood pressure. Importantly, this study is not saying that eating red meat is heart healthy – only that it does not appear to influence commonly measured cardiovascular disease risk factors. There are many other risk factors that this study did not look at, such as lipoprotein concentrations and particle size or inflammatory markers.

The results of this meta-analysis appear to be robust and have high external validity to the general population, considering that the included studies used a variety of background diets, types of meat, and diversity of participants. Moreover, sensitivity analyses removing these variables did not materially change the results, suggesting that red meat has a benign effect on blood lipids and blood pressure regardless of what else is being eaten and the person eating it. Similarly, the post-hoc analysis found largely null findings when comparing even the highest red meat consumers to the lowest consumers, again supporting the validity of these findings when looking at a wide range of people with varying meat intake.

As shown in Figure 2, the control diets also varied greatly in their comparator. For instance, although some control diets did compare red meat to no meat or a vegan source of protein such as soy or tofu, others compared red meat to fatty fish, lean seafood, and poultry. This adds heterogeneity to the meta-analysis, but also provides a broader overview of the impact of red meat consumption when simply added to the regular diet or substituted for other meats or vegan protein sources. Unfortunately, no sensitivity analysis was performed based on the type of diet eaten in the control group, so we can't say how red meat fares against other types of meat or vegan proteins specifically. Still, a previous meta-analysis of RCTs comparing beef to poultry and fish found no significant

Figure 2: Replacement foods in control groups



difference for blood lipids, suggesting that these commonly eaten meats are comparable.

No analysis for publication bias was reported, and study quality was not systematically evaluated. This raises questions about the degree of confidence we may be able to place in the findings, since a meta-analysis is only as good as those studies which it evaluates. Also, we should be aware that two of the three authors received financial support from the American Egg Board and one of these two also received support from several meat-related companies, including the Beef Checkoff. However, the lead author had no conflicts of interest and was the only one to analyze the data.

Eating red meat does not appear to impact some common cardiovascular disease risk factors, and this conclusion appears to be relevant to the general population with a wide range of red meat intakes. However, this does not necessarily mean that red meat is heart healthy, as other cardiovascular risk markers were not evaluated and there is more to heart health than a handful of blood lipids and blood pressure.

The big picture

Nutritional science is rarely black and white. As is likely the case with most foods, whether eating red meat ben-

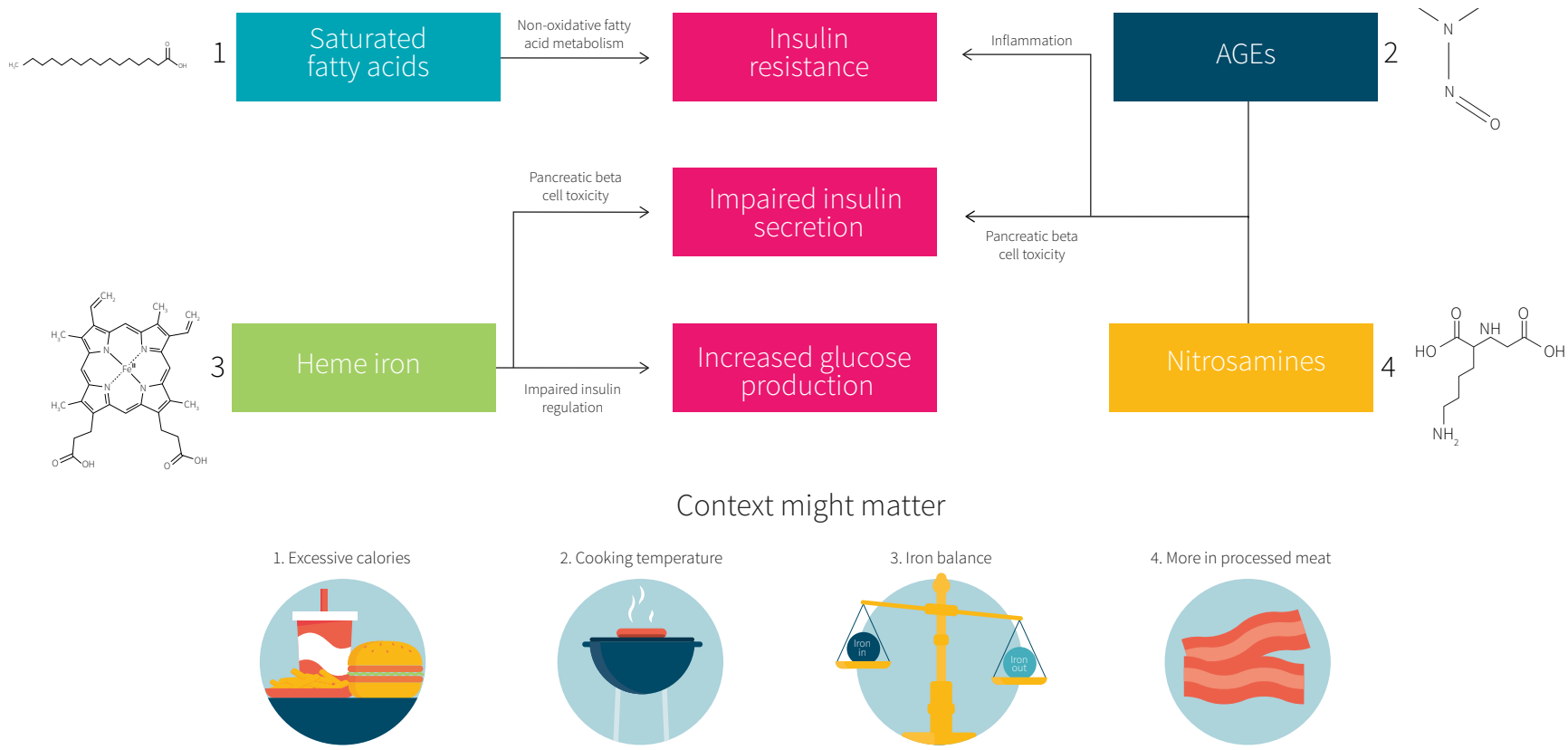
efits, harms, or has no notable effect on health depends on context. For example, red meat is one of the richest dietary sources of iron and would be healthful for someone with anemia and harmful for someone with hemochromatosis (too much iron). Similarly, there is evidence that supplementing the diet of impoverished children with ground beef increases physical activity, cognitive performance, initiative and leadership behaviors, and lean body mass, possibly through providing several key nutrients that are intrinsic to red meat (high-quality and bioavailable protein, zinc, iron, and vitamin B12).

In the elderly, for whom sarcopenia is a growing concern, eating lean red meat in combination with a four-month resistance training program was shown to be more effective than eating pasta and rice at increasing strength and lean body mass. It also led to a greater reduction in IL-6, a well-established marker of inflammation, without differentially affecting blood lipids or blood pressure. The authors of this study are currently working on another controlled trial to investigate how supplementing the diet of elderly folk with lean red meat impacts cognitive performance in addition to muscle mass and function.

But while red meat may have benefits in the elderly and people at risk for malnutrition, there is also evidence that red meat may exacerbate metabolic diseases. From a mechanistic standpoint (as seen in Figure 3), eating red meat has the potential to contribute to insulin resistance by increasing intake of heme iron, advanced glycation endproducts (AGEs), nitrosamines, polycyclic aromatic hydrocarbons (PAHs), and heterocyclic amines (HCAs). ERD #24, Volume 1, *The high cost of high heat cooking*, discussed a randomized controlled trial showing that merely changing the way in which you cook food can reduce insulin resistance and other markers of inflammation and oxidative stress, possibly through reducing exposure to AGEs, PAHs, and HCAs.

It's important to note, however, that the participants of the above intervention did not change the amount of meat they ate, only the way in which it was cooked,

Figure 3: Possible roles of red meat in Type II diabetes



Reference : Kim et al. Metabolism. 2015 Jul

which comes back to the importance of context in nutritional science. Red meat is likely to be more harmful when prepared in certain ways compared to others. It would be quite the stretch to state that a charbroiled burger patty, bacon, sausage, or pepperoni are the same as a medium-rare sirloin steak or stewed ground beef.

A related example of context comes from ERD #12, Volume 1, *Throwdown: plant vs animal protein for metabolic syndrome*, in which we discussed a trial showing that eating up to three servings of lean beef per day within an otherwise DASH-compliant diet led to similar metabolic health improvements as the traditional version that limits red meat to less than 0.5 servings per day. We therefore have evidence suggesting that the overarching dietary pattern may mediate red meat's health effects.

Context is one reason why observational evidence is conflicting in the case of cardiovascular disease. Not only must we consider the difference between processed and minimally processed red meats, but also possible subcategories and preparation methods. Also, what are the lifestyle traits of people who tend to eat these types of foods? Observational evidence is at risk for confounding since good or bad habits tend to group together. The person who opts for a lean steak is probably more likely to also exercise regularly and maintain a healthy weight compared to someone whose red meat consumption is limited to fast food hamburgers, even though both could be considered minimally processed red meats.

Context matters. The healthfulness of red meat depends not only on the needs of the individual but also on the type of red meat, the way it is prepared, and the overall dietary pattern in which it is consumed. Observational studies have difficulties accounting for these nuances, which helps explain their inconsistent findings on the relationship between red meat consumption and health outcomes.

Frequently asked questions

How can I limit the potential harmful effects of eating red meat?

There are several ways to minimize the potentially detrimental aspects of red meat consumption, beginning with the type of meat you choose to eat. A large body of mechanistic, observational, and experimental evidence supports the notion that processed meats such as bacon, sausage, pepperoni, luncheon meats, and hot dogs increase the risk for developing various diseases due to a combination of factors involved in created the processed meat (high-fat, high-salt, added nitrites/nitrates, and harsh cooking methods). Accordingly, opt for minimally processed red meats when possible.

Cooking method is another important consideration. Harsher cooking methods such as frying, broiling, grilling, and roasting consistently led to higher levels of toxic compounds (AGEs, PAHs, and HCAs) than gentler cooking methods such as boiling, poaching, stewing, and steaming.

Finally, take note of your overall diet and lifestyle. Eating healthy and exercising regularly can greatly increase your body's ability to "buffer" any potentially harmful compounds that come with eating red meat. For example, exercise increases the rate of red blood cell turnover, which increases the body's need for and utilization of iron. As such, active people may be able to handle more red meat from an iron standpoint, whereas the iron content can contribute to oxidative stress in people who are sedentary.

What should I know?

Observational data evaluating the relationship between red meat consumption and cardiovascular disease is conflicting. The study under review was a meta-analysis of 24 randomized controlled trials testing the effect of meat consumption on cardiovascular disease risk markers, including cholesterol, triglycerides, and blood

pressure. Eating any amount of meat, as compared to eating less than 0.5 serving (1.25 ounces or 35 grams) had no significant effect on any outcome. Further research is necessary to understand red meat's effect on other cardiovascular risk markers, such as insulin resistance and inflammation. However, evidence to date suggests that the healthfulness of red meat depends not only on the needs of the individual but also on the type of red meat, way it is prepared, and overall dietary pattern in which it is consumed. ◆

Do you have strong opinions on red meat? Then keep those to yourself, but do discuss facts over at the ERD Facebook forum.

Can chondroitin save knee cartilage?

Chondroitin sulfate efficacy versus celecoxib on knee osteoarthritis structural changes using magnetic resonance imaging: a 2-year multicentre exploratory study

Introduction

Osteoarthritis of the knee is a painful condition that affects a lot of people. Almost 4% of the global population has it. Guidelines from the American College of Rheumatology recommend managing the associated pain in part by starting with acetaminophen and escalating to non-steroidal anti-inflammatory drugs (NSAIDs) if the former is ineffective. However, these drugs have several safety concerns. Acetaminophen's liver toxicity is well known, and there are also concerns that it may negatively affect the gastrointestinal tract and kidneys. NSAIDs also have a host of safety concerns. In addition, these treatments are unlikely to affect the progress of osteoarthritis of the knee.

Chondroitin sulfate, an important component of cartilage that provides much of its resistance to compression, may be able to overcome these problems. Orally supplementing with chondroitin is relatively safe and has also shown promise for improving pain and function in knee osteoarthritis. There is also a host of mechanistic evidence that suggests it could slow the progress of osteoarthritis. However, chondroitin's efficacy is not a settled matter. Some of the researchers who participated in the study under review suggested that the question of efficacy may be, in part, due to poor quality control. Some formulations of chondroitin sulfate could have dosing variations, contaminants, or composition differences. Using pharmaceutical-grade chondroitin, whose purity and dose is vetted, may provide a better test of its effectiveness. Combining this treatment with an objective measure of its effect on the joint, such as MRI, would be even better.

The study under review did both. Its goal was to explore whether pharmaceutical-grade chondroitin sulfate could slow the progression of knee osteoarthritis.

There are safety concerns about current pharmacological treatments for knee osteoarthritis. In addition, these treatments may not actually slow the progression of the disease. Chondroitin sulfate is relatively safe, but its track record for efficacy is mixed, which could be due to variable composition and purity.

Who and what was studied?

This was a double-blind, randomized trial recruiting 194 men and women with symptomatic osteoarthritis of the knee diagnosed according to American College of Rheumatology guidelines. The participants also had signs of synovitis (warmth or swelling around the knee, indicating inflammation of specialized connective tissue that lines the inner surface of the capsule surrounding the knee joint, called the synovium). All participants also rated pain while walking as at least 4 out of 10 on a visual analog scale. Additionally, their arthritis was rated

"Using pharmaceutical-grade chondroitin, whose purity and dose is vetted, may provide a better test of its effectiveness."

grade 2 or 3 using Kellgren-Lawrence scoring, meaning that their joint space was narrowed and there were some bone spurs evident on x-rays, indicating joint damage. Overall, the people in this study had moderate osteoarthritis: they felt it, and there was a decent amount of joint damage, but it could be worse. On average, the participants were 61 years old and had a BMI of a little over 30. People with severe leg alignment issues or those whose osteoarthritis was caused by another disease were not included in the study.

Participants were then randomized to take either 1200 milligrams of pharmaceutical-grade chondroitin sulfate or 200 milligrams of celecoxib every morning for 24 months. The authors state that this dose of chondroitin sulfate is the largest and most commonly used dose when used alone. Celecoxib is a newer anti-inflammatory drug that is effective for relieving pain and improving function in osteoarthritis. While it still has gastrointestinal side effects like other NSAIDs, its risk is relatively lower. Participants in the study were not allowed to take any other NSAIDs during the study, but could take up to three grams of acetaminophen per day if needed, except 48 hours before study assessments to reduce confounding. Compliance with the treatment was also monitored, and participants were removed from the study if they weren't mostly compliant. There was no placebo group.

The pre-specified primary outcome was cartilage volume loss in the lateral (outside of the leg) compartment, which was measured via MRI at 12 and 24 months. This was chosen as the primary outcome because similar changes in the lateral compartment were observed in a previous pilot study and similar clinical trials. During the MRI scan, secondary outcomes included cartilage changes in the medial (inner) side of the knee and changes in the synovium. Other non-structural secondary outcomes were also measured every three to four months during a visit. These included knee pain assessed by a visual analog scale, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores, consumption of pain medications, and adverse effects.

The authors did not perform a power analysis to determine the chances of failing to identify any differences between the two treatments, if they existed, because they considered this an exploratory study. The researchers also did not correct for multiple comparisons for the same reason.

Meet the COXs

Non-steroidal anti-inflammatory drugs (NSAIDs) all work through a similar mechanism: they block an enzyme called cyclooxygenase (COX). But there's a twist - this enzyme comes in two major forms: COX-1 and COX-2. COX-1 is involved in the production of prostaglandins, which perform many functions in the body, including maintaining good kidney function and producing the protective layer of the gastrointestinal (GI) tract. COX-2, on the other hand, produces molecules responsible for pain and inflammation, so that's the one to target if you want to reduce these effects. Most NSAIDs nonselectively target both COXs, which explains their infamous GI side-effects. However, the NSAID celecoxib binds more to COX-2 than COX-1, so it can target pain and inflammation with fewer side effects, at least in theory. In reality, the advantages of celecoxib are not so clear-cut. A recent review found that the relative harm and benefit of celecoxib for people with osteoarthritis are hard to assess, partially because of the general scarcity and possible bias of evidence due to industry involvement.

Close to 200 people with moderate knee osteoarthritis were given either 1200 milligrams of pharmaceutical-grade chondroitin sulfate or 200 milligrams of celecoxib daily for 24 months. MRIs of the knee were taken at 12 and 24 months, with pain, functional measurements, and adverse effects measured more frequently. The primary outcome was change in cartilage thickness in the lateral knee compartment. All other measurements were considered secondary.

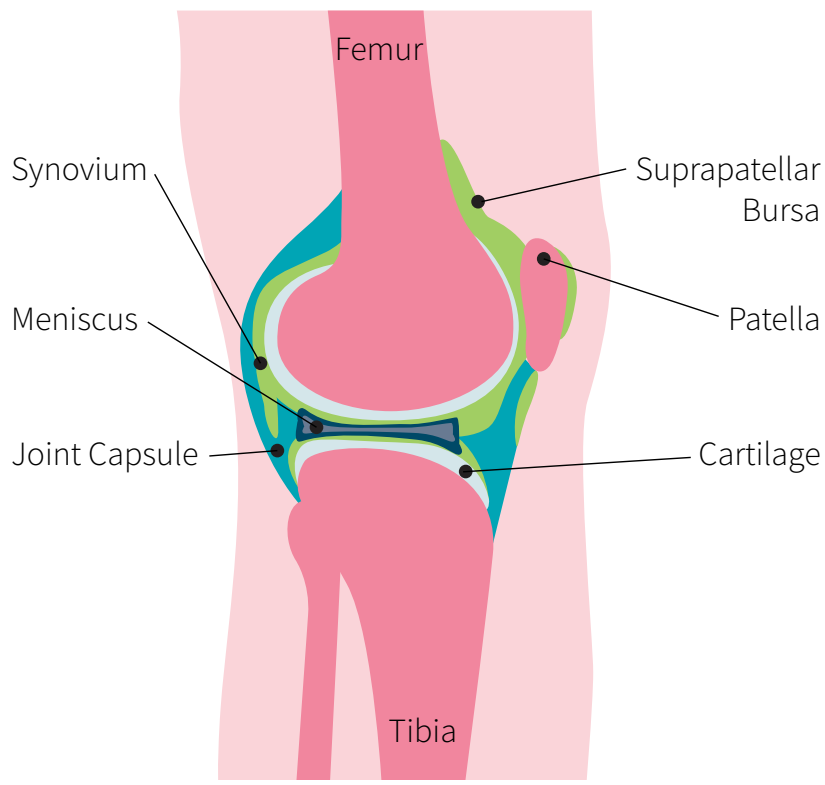
What were the findings?

The celecoxib and chondroitin arms both lost around a third of their participants during the course of the trial. The biggest reason cited was adverse effects in both groups. The majority of these effects, however, were not attributable to the treatments, and most weren't serious. Surprisingly, gastrointestinal problems and cardiovascular events didn't seem to differ between the two groups. The only major difference was back pain: 17% of those who left the study and were taking chondroitin cited back pain as their primary reason for dropping out, compared to only 5% of those on celecoxib. The researchers attributed one serious adverse event (iron-deficiency anemia) to chondroitin, and two (pneumonia and blockage of a blood vessel in the lungs) were attributed to celecoxib. The reasoning behind these attributions was not spelled out by the authors. However, past research hasn't found an effect of chondroitin on iron absorption; chondroitin does bind iron but is usually absorbed. In fact, chondroitin-iron complexes have been used for the treatment of iron-deficiency anemia. On the other hand, pneumonia has been seen to co-occur with celecoxib use, although causality isn't clear.

The results for efficacy were mixed. Cartilage loss in the lateral knee compartment, which was the primary outcome, did not differ between groups. Celecoxib and chondroitin performed statistically similarly, with both groups losing just over 4% of their cartilage in the lateral compartment over 24 months.

Secondary structural outcomes fared a little better, but were still mixed. Cartilage loss in the medial knee compartment was attenuated in the chondroitin group. The chondroitin group lost 6.3% over 24 months, compared to an 8.1% loss in the celecoxib group. The difference was statistically significant. The overall mean synovial thickness did not differ between treatments. However, the researchers did find a trend for significance for the medial suprapatellar bursa. The suprapatellar bursa, which can be seen in Figure 1, is a fluid-filled sac that sits above the kneecap and helps reduce friction. The medial portion of it sits closer to the inner thigh. In this portion of the bursa, there was a trend ($p = 0.076$) toward a reduced increase in thickness in the chondroitin group, compared to the celecoxib group. Furthermore, this finding was correlated with decreased cartilage volume loss in the medial knee compartment. In other words, participants who had a smaller increase in synovial thickness in the medial suprapatellar bursa also experienced a slowdown in cartilage loss.

Figure 1: Some knee anatomy relevant to this study (Knee viewed from the side)



No other structural differences were seen between the two treatments.

Both groups experienced subjective improvements of a similar degree. Pain decreased by about 40% for both groups. Function and quality of life measurements improved to a similar extent in both groups as well.

The primary outcome of cartilage loss in the lateral knee compartment did not differ between groups. Both lost about 4% of their cartilage in that area over the course of the study. However, people in the chondroitin group lost significantly less cartilage in the medial knee compartment, and synovial thickness, a marker of chronic inflammation and arthritis, in one part of the knee may have increased less in the chondroitin group as well. There were no differences between groups in subjective functional and pain outcomes.

What does the study really tell us?

This study hints at two aspects of chondroitin's effects on knee osteoarthritis: its possible efficacy and some putative aspects of its mechanism.

Overall, this study found little difference between celecoxib and chondroitin. Subjective pain and function tests improved to a similar extent in both groups. Most of the structural effects were also similar; for the most part, things got a little worse in terms of cartilage loss in both groups.

So, it seems that this study found that celecoxib is roughly on par with chondroitin. The question is: how well does celecoxib actually prevent the progression of osteoarthritis? If it's effective at preventing progression, then being on par would be pretty good. There is quite a bit of mechanistic evidence from *in vitro* studies that suggests celecoxib could indeed prevent its progression.

Unfortunately, celecoxib has not fared as well in human trials. One 12-month open-label study found that celecoxib didn't prevent cartilage loss compared to a historical cohort. A more rigorous double-blinded clinical trial found that celecoxib was no different from placebo (nor was glucosamine plus chondroitin for that matter). However, this trial was hampered a bit by an inadequate sample size and joint space narrowing that was much lower than expected, even in the placebo group. This means there is room for further research in this area.

However, none of this bodes particularly well for chondroitin's performance in the current study under review.

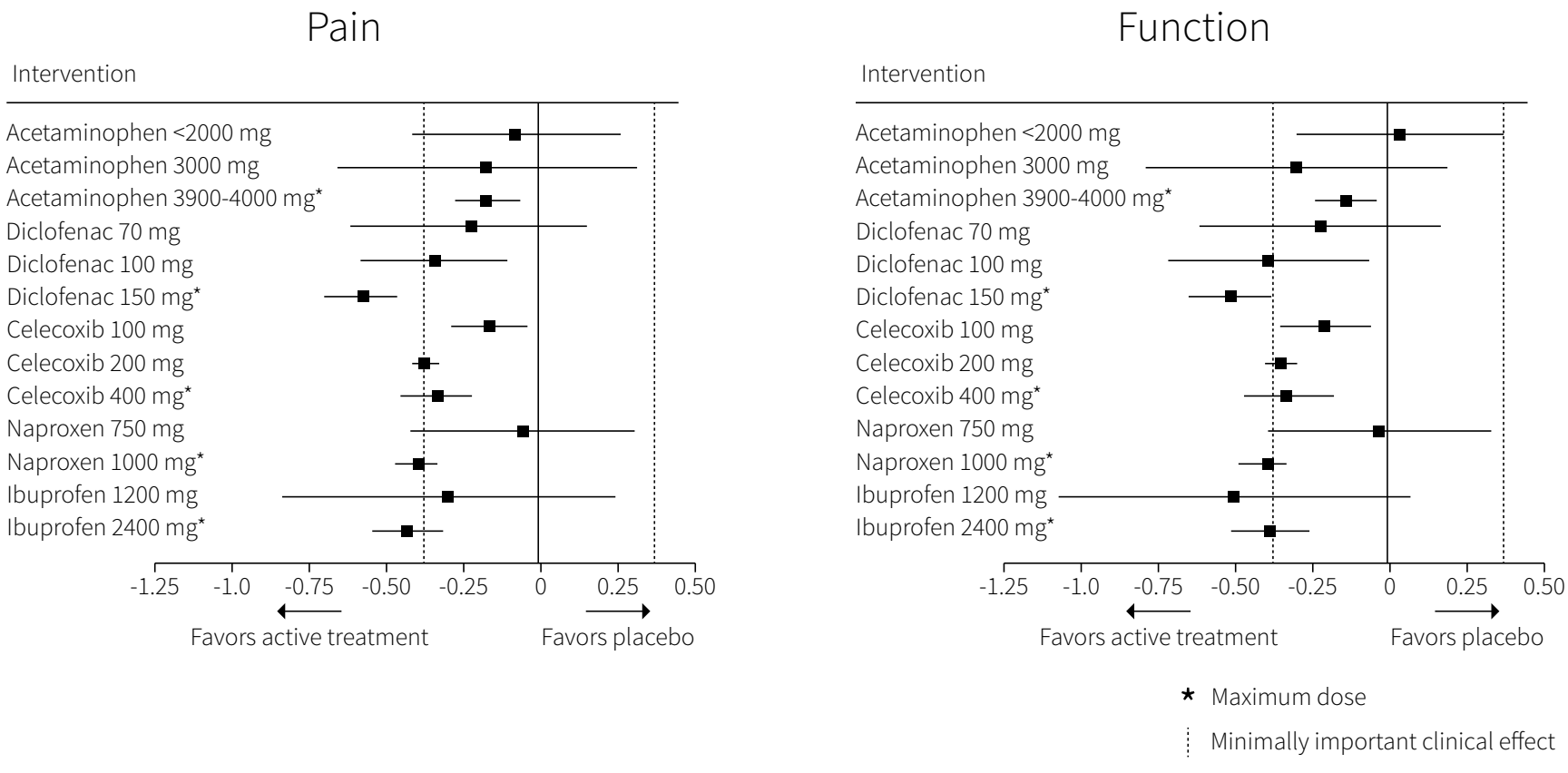
> "If chondroitin is on par with celecoxib, and celecoxib does little to prevent osteoarthritis progression, then it stands to reason that chondroitin didn't do too much, either."

If chondroitin is on par with celecoxib, and celecoxib does little to prevent osteoarthritis progression, then it stands to reason that chondroitin didn't do too much, either. Since this study did not have a placebo group, this conclusion can't be asserted with much certainty. On the other hand, being on par with celecoxib for pain and improved function is pretty decent, since celecoxib leads to moderate improvements in both of these areas, as seen in Figure 2. There are two problems with these outcomes, though. First, these outcomes for chondroitin were secondary outcomes, and so should be taken with a grain of salt, especially since the primary outcome did not differ between chondroitin and celecoxib. Second, pain and function in osteoarthritis are susceptible to the placebo effect, so even if these treatments did nothing physiologically, changes may still be seen.

While celecoxib and chondroitin were roughly on par in many of the outcomes, there were a few differences between the two. The major difference of note was less synovial thickening around the medial suprapatellar bursa in the chondroitin group. This finding was not quite statistically significant, though, and so should be taken with a grain of salt. But relative synovial thinness was associated with lower cartilage loss in the medial knee compartment. This may suggest that chondroitin may be targeting more than just cartilage, and is affecting other parts of the joint. It could also suggest that the larger doses of pharmaceutical-grade chondroitin are causing some anti-inflammatory effects of its own. This could be occurring through inhibition of NF-κB, which regulates a host of inflammatory responses, including regulating COX-2.

This study itself doesn't really reveal why this correlation occurred, though. However, it is notable that synovial thickening is associated with the severity and symptoms of osteoarthritis. Thus, improvements in synovial thickness may be associated with improvements in overall disease progression. The synovial findings here also slightly bolster the idea that drugs that could break the putative pro-arthritic cycle between the inflamed synovium and cartilage breakdown, seen below in Figure 3, could benefit osteoarthritis. However, keep in mind that synovial thickness was not different between groups overall; just in the

Figure 2: How celecoxib stacks up to other drugs for osteoarthritis



Adapted from: da Costa et al. Lancet. 2016 May.

medial suprapatellar bursa, and even then it only trended toward statistical significance. So this may also be a false positive, if it's a positive at all.

These findings may also be slightly slanted, since all participants in this study had clinical inflammation of the synovium. However, this doesn't limit the generalizability too much, since emerging evidence suggests a lot of people with osteoarthritis have synovial inflammation, even if it's subclinical in many.

What limits the findings more is the nature of this study itself. As stated in the study's title, it was exploratory in nature. That means that there were a lot of outcomes tested to uncover possible associations. As we've pointed out in ERD #18, Volume 1's *Don't drink and drive, unless it's grape juice*, this practice increases the risk of finding false positives. Measuring many outcomes may provide useful hypotheses for future studies, but doesn't conclusively say much about chondroitin's ability to slow osteoarthritis progression. Some of these findings may be true, but further research is needed to confirm it.

These future studies can benefit from the findings from the study at hand in a few ways. First, it strongly suggests that looking at cartilage changes in one compartment of the knee isn't reliable. Instead, future research should probably look at cartilage changes in the whole knee and use a larger sample size to increase the chances of seeing an effect. Also, this study suggests that looking at synovial changes would be a worthwhile secondary endpoint to also include in future studies of chondroitin or other osteoarthritis treatments. In addition, using a chondroitin supplement whose dose and content is verified would be useful due to the issues surrounding chondroitin quality mentioned in the introduction. Finally, it may also be useful to include a placebo in future research. The authors of the study under review mention that it may be unethical to use placebo in this case, since the study was long and some evidence exists suggesting that both celecoxib and chondroitin could help with osteoarthritis. However, this ethical concern could be addressed in a few ways, such as having an arm with an active treatment plus placebo vs. the same active treatment plus chondroitin. Coupled with a larger sample size, this type of study should be able to detect any possible effects of chondroitin while still addressing the study participants' needs.

This was an exploratory study that provides valuable information about how to design a more definitive clinical trial of chondroitin's effects on knee osteoarthritis. However, due to the absence of a placebo group, the lack of difference in the primary outcome, and the number of variables explored, this study alone does not provide much information concerning chondroitin's efficacy or ability to slow cartilage loss. Accordingly, the results here are mildly promising, especially concerning pain and knee function, but far from definitive.

The big picture

While this study's exploratory nature limits what it can say about chondroitin's possible ability to slow the progress of osteoarthritis, there is some other evidence on the topic.

Some of the evidence comes in the form of x-ray studies looking at chondroitin's effects on joint space narrowing in osteoarthritis. The most recent Cochrane systematic review on the topic showed a 60% improvement in the reduction of minimum joint space width over two years, with high quality evidence. The number needed to treat in order to benefit was calculated as seven, meaning that for every seven people treated with chondroitin, one would benefit clinically in this regard. The authors note that while this sounds promising, these results were only derived from two studies, so more evidence is needed. They also note that the relationship between reduction in minimum joint space

> “The most recent Cochrane systematic review on the topic showed a 60% improvement in the reduction of minimum joint space width over two years, with high quality evidence.”

width and clinical outcomes isn't clear, so whether these improvements would actually translate to anything clinically meaningful is uncertain.

Further doubt concerning chondroitin's efficacy in slowing down osteoarthritis has been cast by a more recent trial not included in the Cochrane review above, which looked at the effects on knee osteoarthritis of glucosamine, chondroitin, or their combination. This study found no clear effect of 800 milligrams of chondroitin daily over two years on joint space narrowing. However, the combination of glucosamine and chondroitin did show an effect of borderline statistical significance. The population for this study mostly had early-stage osteoarthritis, and the authors speculate that trials in more advanced osteoarthritis or of longer length could, in theory, show an effect.

While there's a bit of x-ray data looking at chondroitin's effect on osteoarthritic knees, there's less MRI data looking at cartilage loss. One pilot study exists, which was performed by some of the same researchers as the paper currently under review. This study randomized people with knee osteoarthritis to 800 milligrams of chondroitin or placebo daily for six months. The chondroitin group lost about 40% less knee cartilage over six months compared to the placebo group.

The big picture suggests chondroitin has some promise for slowing the progression of cartilage loss and joint space narrowing in knee osteoarthritis. However, the clinical relevance of these findings is not entirely clear. Also, the information that exists comes from only a handful of trials, leaving room for more evidence before a verdict is determined.

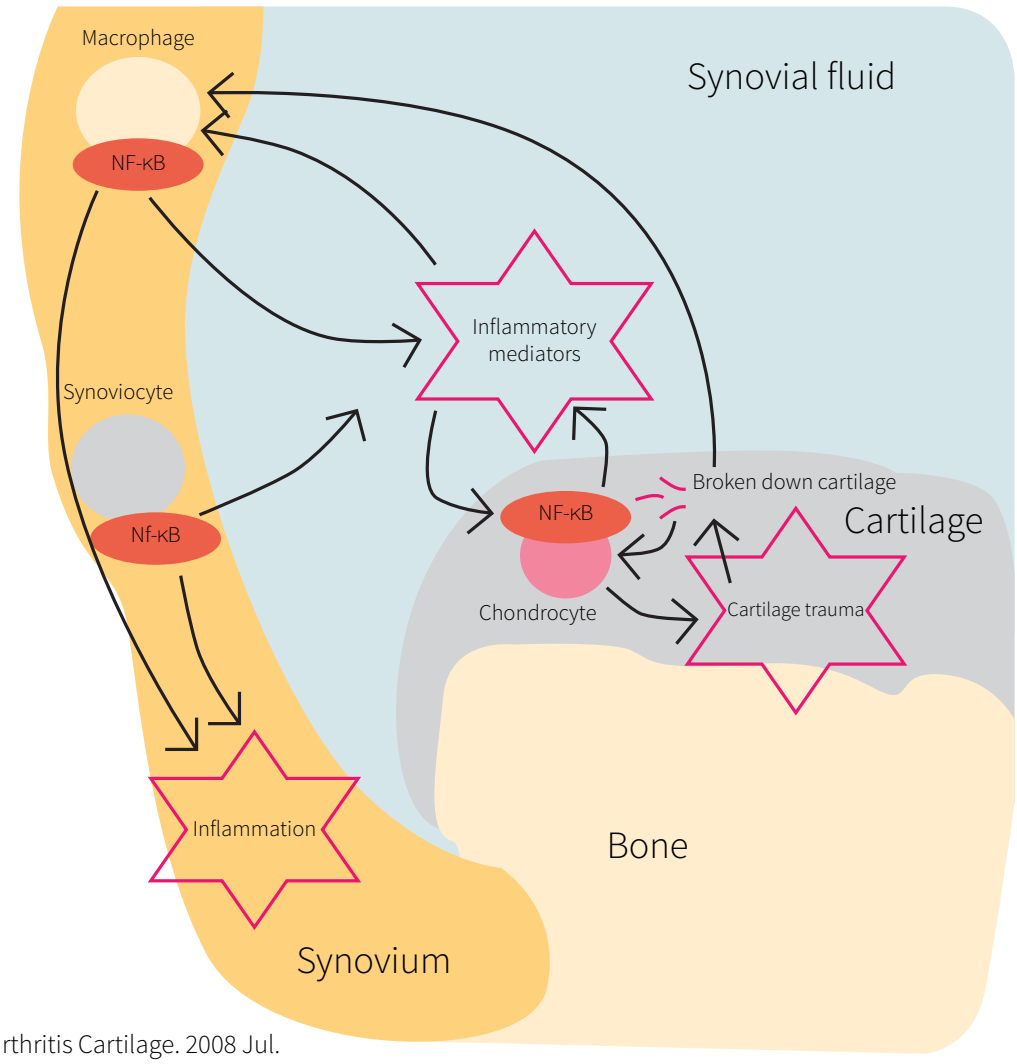
The current evidence, while mixed, suggests that chondroitin is able to slow, but not halt, joint space narrowing and cartilage loss in knee osteoarthritis. There is a need for additional research, though, given the mixed findings, the limited number of trials, the unknown clinical relevance of these findings, and differences in participants' osteoarthritis severity in the trials that do exist.

Frequently asked questions

How might chondroitin work to slow osteoarthritis?

The answer to this question is unknown, but there are a couple of hypotheses. Animal evidence suggests that chondroitin is able to restore the extracellular matrix of cartilage, which may slow or prevent its breakdown. This makes sense, since chondroitin is a key component of cartilage. Another possible theory involves sulfate. While this article has used the shortened term 'chon-

Figure 3: Putative inflammatory interplay between the synovium and cartilage



Adapted from:Iovu et al. Osteoarthritis Cartilage. 2008 Jul.

droitin', most chondroitin is taken as the sulfate salt: chondroitin sulfate. Since sulfur-containing amino acids are needed in the synthesis of the extracellular matrix of cartilage, some researchers have suggested that the sulfur in chondroitin sulfate may be contributing to its efficacy. Also, as mentioned briefly above, chondroitin sulfate may inhibit NF-κB, whose role can be seen in Figure 3. This could lead to broad anti-inflammatory effects that can slow synovitis and cartilage loss.

What about other evidence concerning chondroitin's effect on pain in knee osteoarthritis?

The Cochrane review mentioned above found that chondroitin produced a statistically and clinically relevant reduction in pain in one out of every five patients treated. However, they noted that the quality of the evidence was low, with a high risk of bias and lots of differences between the trials, so there's plenty of room for more evidence.

What should I know?

This exploratory study in people with knee osteoarthritis found no difference between 200 milligrams of celecoxib and 1200 milligrams of pharmaceutical-grade chondroitin sulfate daily in its primary outcome of cartilage volume loss in the lateral compartment of the knee. Both groups lost about 4% over two years. There were also no discernable differences in pain and functional scores between the groups. However, the chondroitin group did lose less cartilage in the medial compartment of the knee and possibly experienced less synovial thickening compared to the celecoxib control group. But, since these were secondary outcomes and because of the exploratory nature of this study, more evidence is needed to assess chondroitin's impact on knee osteoarthritis. ◆

Want to keep exploring this exploratory study? Head on over to the ERD Facebook group!

Can fasted exercise increase fat oxidation in women?

Exercise before breakfast increases 24-h fat oxidation in female subjects.

Introduction

It's pretty common to see "fat-burning zone" or "weight loss zone" plastered on cardio equipment. This fabled aerobic exercise intensity is supposed to be the best for melting the fat away. The thinking behind the fat-burning zone has a little bit of science to back it up. The relative contribution of fat versus glucose to fuel activity reaches its peak at moderate intensities of exercise - this is the fat-burning zone. Here, the body is using more fat relative to glucose in order to fuel the exercise.

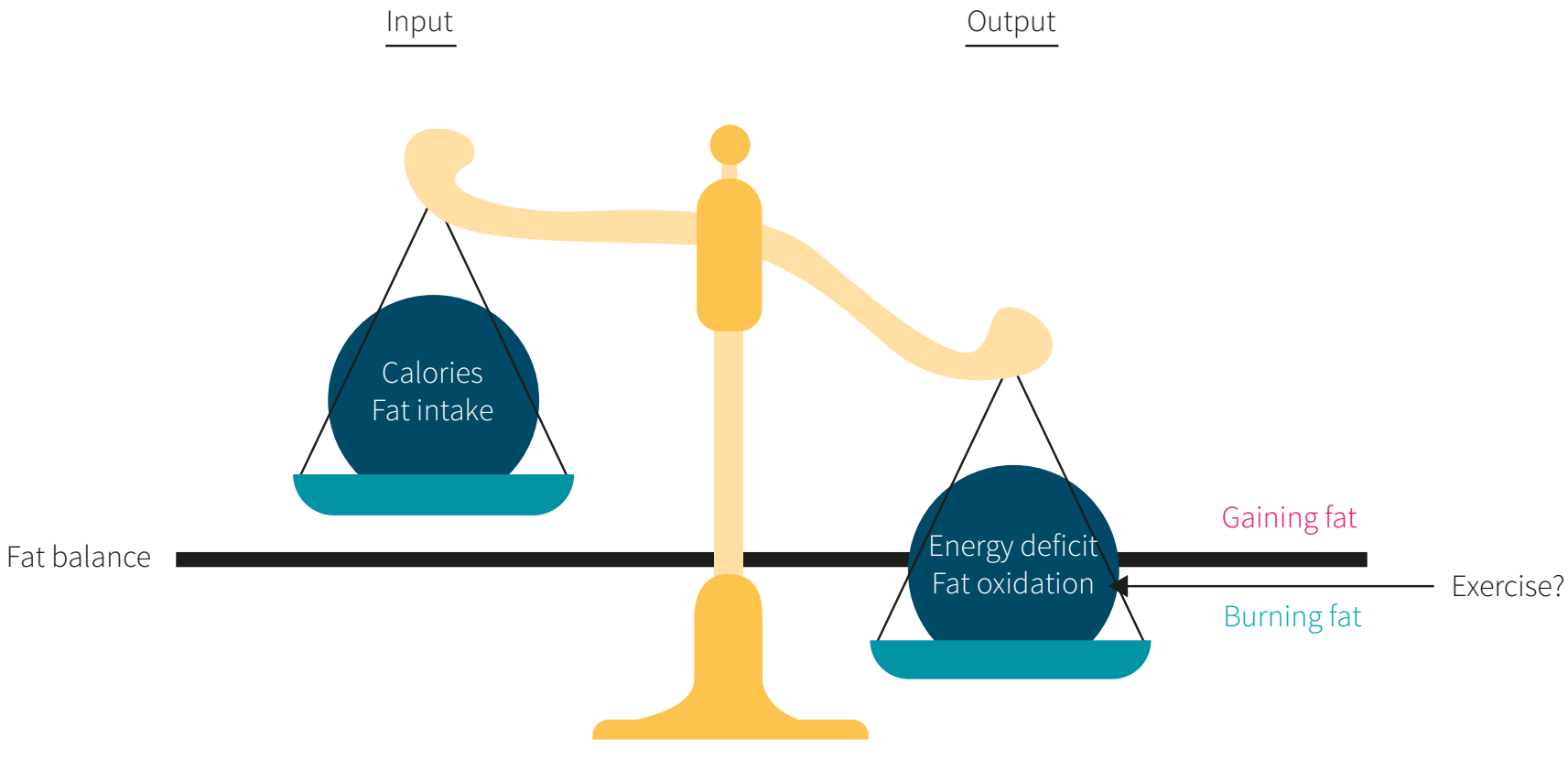
But fat burning *during* exercise doesn't tell the whole story. After all, it's not really the goal of people training in the "fat-burning zone" to switch up the ratio of fuel their muscles are using in the moment. Presumably, their goal is to lose fat mass. And here's where the science of the "fat-burning zone" starts to break down.

As shown in Figure 1, in order to lose body fat, the body has to be in a negative fat balance. One way to tip the fat balance scales could be to increase the fat oxidation rate. This concept has been tested, and at this point, the general consensus is that exercise does not affect 24-hour fat oxidation compared to sedentary controls, at least if energy balance is maintained (i.e., you eat just enough food to compensate for the greater energy expenditure from exercise). So, while the body uses more fat as fuel *during* moderate intensity exercise, over the course of a day, fat balance is the same as if the person just laid around all day. In other words, it looks like exercising does not magically make you lose fat. The key to fat loss is burning more energy than you consume.

The story doesn't end there, though. Recently, a series of studies have found that if moderate intensity exercise is done while fasted (i.e., before breakfast), 24-hour fat oxidation is indeed increased, even when energy balance is maintained. But there's a nuance here that limits generalizing these results: the studies were all done in men, which is a common problem in exercise science. This leaves open the question of whether these findings extend to women.

There are several physiological differences between the sexes, many of which are related to exercise and

Figure 1: Fat balance in a nutshell



Reference: Melanson et al. Exerc Sport Sci Rev. 2009 Apr.

fat metabolism. On average, women burn more fat than men during exercise, but less fat afterward. Men's and women's skeletal muscle also adapts differently to endurance training. Some of these differences involve how skeletal muscle utilizes fat as a fuel, and can be observed at the genetic level. So, it's far from clear that aerobic exercise in a fasting state could burn more fat for women. The study under review aimed to address this gap in the research.

Current consensus is that aerobic exercise in a fed state doesn't affect fat oxidation over a 24-hour time frame; fat balance is maintained, and so the "fat-burning zone" of cardio exercise doesn't live up to its name in practical terms. However, recent evidence has suggested that if exercise is done in a fasted state, fat burning increases. But this evidence has only been collected from studies involving men. Physiological differences raise the question of whether this effect would also be seen in women, and the study under review sought to answer it.

Who and what was studied?

Nine healthy women were enrolled in this randomized, controlled crossover study. They were all deemed to be moderately physically active (they exercised about 2.5 hours per week, on average). None of the women were taking any medication at the time of the study, including oral contraceptives. On average, their BMI was about 22 and they were around 24 years old.

The researchers determined the participants' baseline workload capacity by using a cycle ergometer to measure their maximal oxygen uptake capacity (VO_{2max}) and the amount of work on the bike that each participant could perform that corresponded to 50% of their VO_{2max}. The participants' average baseline VO_{2max} was almost 44 mL/kg/min, which puts them well above the 90th percentile for women their age.

The participants were then either randomly assigned to a sedentary or exercise condition. In the sedentary condition, the participants remained at rest for an entire day. In the exercise condition, participants pedaled on a cycle ergometer before breakfast for 60 minutes at 50% of their VO_{2max}, then remained sedentary for the rest of the day. Both conditions were performed in controlled conditions, ensured by a metabolic chamber, so macronutrient metabolism (how much fat, carbs, and protein was burned) could be measured using indirect calorimetry. In the chamber, participants were fed standardized meals containing 15% protein, 25% fat, and 60% carbs three times a day at regular times. Each meal contained about a third of the participants' calculated needs to maintain energy balance for the day, and the amount of calories each participant was fed depended on their baseline measurements and whether they were exercising or sedentary for the day. Non-exercise activity was taken into account using an activity monitor worn on the wrist.

From all that, net energy balance was calculated by subtracting energy intake (that was controlled through the meals) from total energy expenditure (which was estimated by indirect calorimetry).

After each participant completed the day-long experiment, they switched conditions. Those who were in the sedentary group exercised for an hour, and vice versa. Each experiment was done during the early follicular phase (during or right after menses) of the participants' menstrual cycles in order to control for hormonal contributions to metabolism. Additionally, each participant was asked to maintain their bodyweight between experiments to control for body composition differences. Also, the two experiments were done within a two-month time frame to minimize possible variability of results over time.

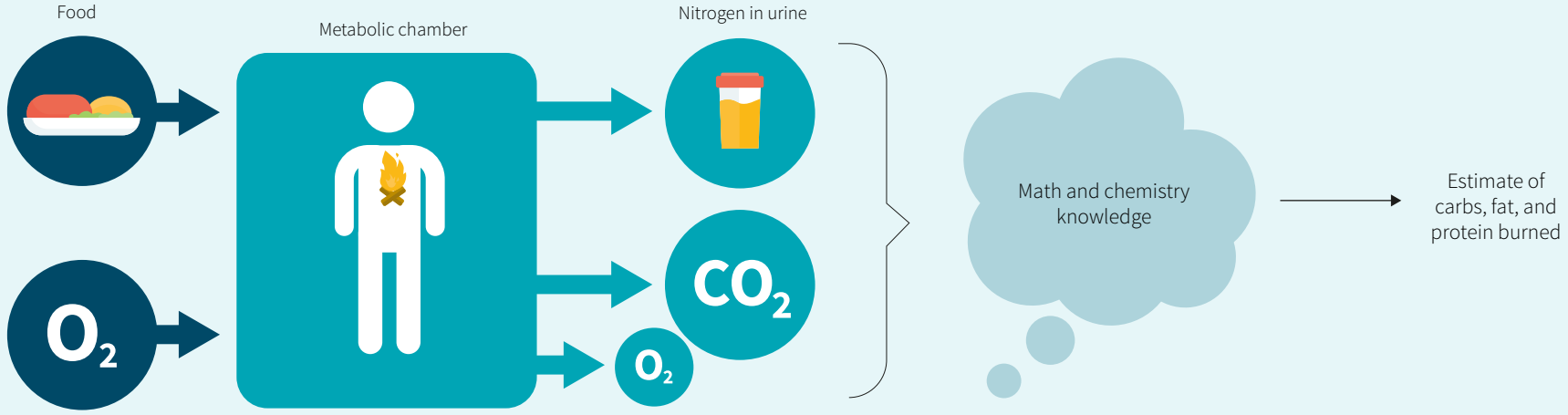
Indirect calorimetry and the magic of chemistry + math

Calorimetry literally means "the measurement of heat," so it may be surprising to learn that heat was not measured by the method of indirect calorimetry that was used in this study. Instead, three things were measured in this study: each participant's amount of oxygen consumed, carbon dioxide excreted, and the amount of nitrogen in urine over the course of 24 hours.

These three measurements, plus some math and basic knowledge of biochemistry, are enough to estimate the contribution of carbs, protein, and fat to the subjects' energy supply. This process is summarized in Figure 2. This is because basic chemistry dictates that burning these three macros in the presence of fixed amounts of oxygen yields fixed amounts of carbon dioxide and nitrogen. So, if you write out these chemical reactions, you have three equations and three unknowns that can be solved mathematically. Since urine nitrogen content comes mainly from metabolized protein and burning carbs and fat doesn't yield nitrogen, you can get a direct estimate of protein metabolism from urine nitrogen, and then calculate carb and fat metabolism using changes in carbon dioxide and oxygen in a sealed metabolic chamber.

With just three measurements and a little math and chemistry knowledge, researchers can estimate macronutrient metabolism indirectly.

Figure 2: Indirect calorimetry



The goal of this study was to determine how exercise before breakfast affects fat metabolism in women. Nine healthy, young women with normal BMI were assigned to two conditions in a metabolic chamber for a day: one where they did moderate aerobic exercise before breakfast for an hour and one where they were at rest. Their overall energy expenditure and their carb, fat, and protein metabolism was estimated.

What were the findings?

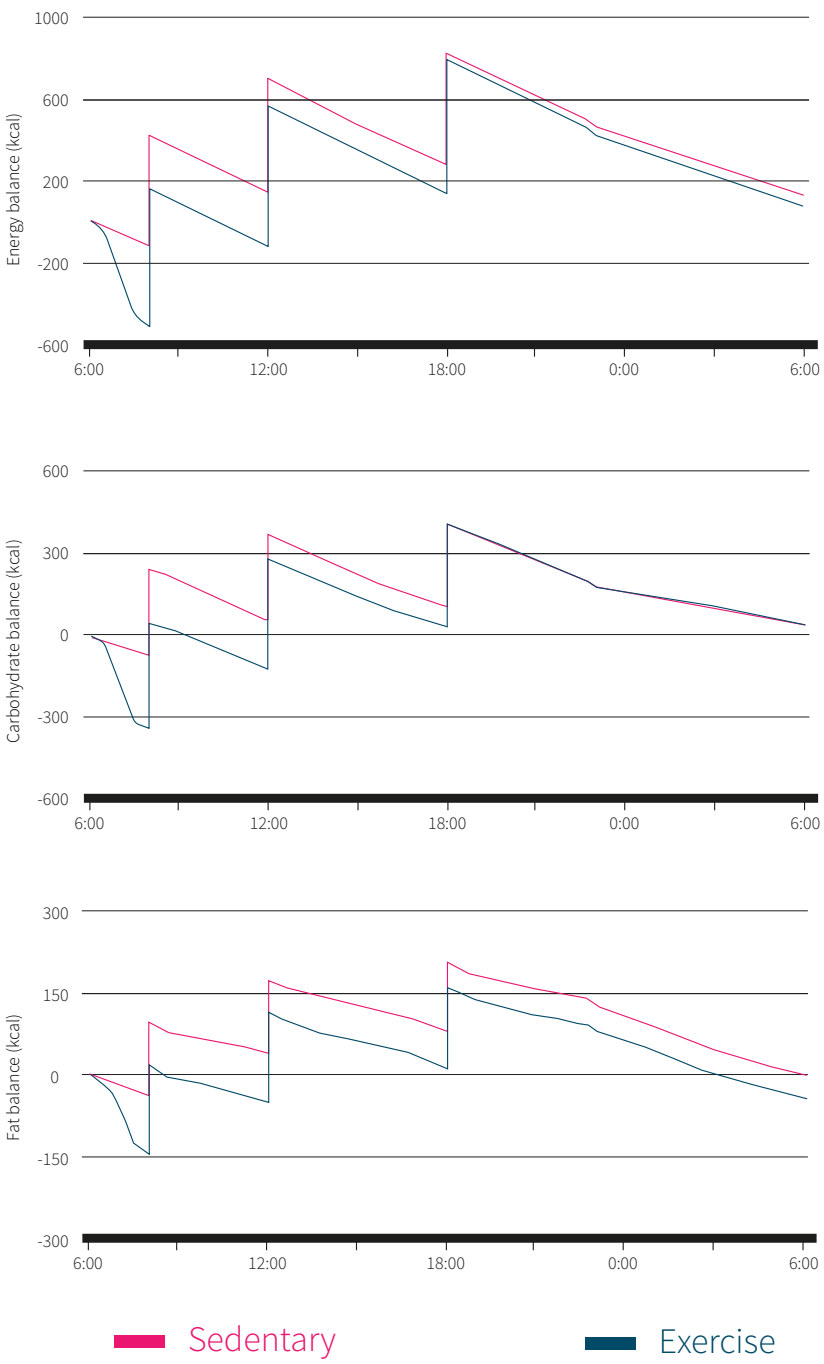
The exercise condition burned about 120 kilocalories more fat than the sedentary condition over 24 hours. Thus, fat oxidation increased over the course of the study. Also, about 235 kilocalories more carbohydrate were burned than the sedentary condition

The experiment was designed to keep total energy balance the same between participants and conditions by

providing extra calories as a proportion of the overall diet, as opposed to directly replacing the substrates oxidized during exercise. This seems to have succeeded, as no significant difference between the conditions was observed. Participants were also able to maintain body-weight over the course of the experiment.

The time courses for energy, carbohydrate, and fat balance can be seen in Figure 3. While transient differences between the sedentary and exercise conditions existed, the carbohydrate and total energy balance evened out between conditions toward the end of the study. However, a significant difference between the sedentary and exercise conditions remained for fat balance.

Figure 3: Energy, carb, and fat balance over 24 hours



Moderate intensity aerobic exercise before breakfast increased 24-hour fat oxidation in healthy, young, fit women relative to being sedentary.

What does the study really tell us?

When combined with other findings from previous studies, this study fills a gap in the research.

This gap arises from the previously described lack of effect of moderate exercise on fat oxidation in both men and women when overall energy balance is neutral. In other words, if you're eating as many calories as you're consuming every day and exercise in a non-fasted state, you won't burn more fat than if you just laid around.

But what about fasted exercise? This question was addressed by some of the same researchers as the current study under review, but only in men. They found that fat oxidation under energy-balanced conditions in lean, healthy men could be increased by moderate exercise, but only in a fasted state in the morning.

Together, these findings are quite interesting, but they do not answer the question of whether this fat-burning effect would also be found in healthy women of normal BMI. Due to the physiological differences between men and women mentioned in the Introduction, it cannot be assumed that these effects would carry over to women. And that's where the study under review comes in; it was designed and conducted to confirm that this fat-burning effect does indeed seem to apply to women.

One possible weakness of this study lies in the control group. The control in this study was women at rest, not women exercising in the fed state. Ideally, future research will compare fasted to fed conditions to tease out the effects of feeding state more clearly.

The larger problem lies not with the study itself, but misinterpreting it. This study tells us something about how the body uses fat relative to carbohydrates as a fuel 24 hours after fasted exercise while in energy balance. What it does not tell us much about is body fat loss while in energy balance. This study justifies more research looking into whether the fat-burning properties of chronic pre-breakfast exercise could lead to body fat loss in the long term for people who take in as many calories as they burn. However, it does not demonstrate body fat loss.

What would fat loss while in energy balance look like? If energy balance is maintained and fat is lost, weight wouldn't be lost. That means that either protein or carbohydrate storage would offset the fat loss. But the carbohydrate pool in the body is too small to make much of an impact weight-wise, leaving increased protein stores, possibly in the form of muscle, as the main contender in maintaining weight in the presence of fat loss. Some people with training experience may raise an eyebrow at the suggestion that moderate intensity aerobic exercise could be a muscle builder. But some evidence indeed exists that aerobic exercise can influence muscle mass and hypertrophy. While there's much reason to be skeptical, the study under review does warrant more research looking into the effects of repeated bouts of fasted versus non-fasted aerobic exercise on body composition in the longer term.

Previous research has found that moderate aerobic exercise in healthy men of normal BMI in energy balance increases fat oxidation if it's done before breakfast. The study under review adds to the research by showing that the same effect holds for women. More research is needed to see if these effects last for chronic pre-breakfast exercise and to elucidate possible long-term effects on body composition in the presence and absence of caloric deficits.

The big picture

While the researchers of the study under review were mostly correct that there has been little research done looking at the effects of aerobic exercise on fat burning in women, there has been some research that's at least somewhat relevant.

One such study looked at a population of young, recreationally active women fairly similar to those in the study under review. The participants consumed either water or a meal of rolled oats before exercising. The researchers did not use indirect calorimetry, but did measure blood lipids, and found that the meal suppressed plasma lipid levels, which is suggestive of using less fat for energy, although that's not certain since fat oxidation wasn't measured.

Another study, however, did use indirect calorimetry. This study also had a similar population to the study under review. In this study, fit, young women exercised 30, 60, or 90 minutes after consuming a test meal of chocolate chip breakfast bars and low-fat chocolate milk or consuming no meal at all. They then exercised on a treadmill for 30 minutes at around 60% of VO_{2max}. The study found that, during exercise, the women's total energy expenditure didn't vary between conditions. However, the women who had no breakfast burned about 20 kilocalories more in fat than women who had breakfast at any time. However, this study only performed calorimetry while the women exercised. The study under review, in contrast, extends this research by measuring macronutrient oxidation for a full 24 hours.

The two studies above were included in a recent meta-analysis examining the question of aerobic exercise's effects on fat burning. This study found that aerobic exercise in a fasted state burns about three grams more fat on average than exercise in the fed state. However, the population characteristics did slant heavily toward male and trained individuals. Subgroup

analysis found that most populations burned more fat when exercising while fasted, regardless of BMI, time spent exercising, sex, or training level. However, one pattern that stuck out in the analysis was training intensity: the authors did not see any difference in fat burning between the fasted and fed states when exercise intensity was at 70% of VO_{2max} or above. So, it seems that high intensity exercise while fasting may not burn a higher percentage of fat relative to carbs. Only moderate intensity aerobic exercise does the trick.

While the long-term effects of aerobic exercise while fasting and in energy balance have yet to be explored, exercise while in a caloric deficit has been. One study found that body fat was indeed lost in healthy, young women who exercised aerobically, but no difference was seen between exercising in the fasted versus fed state (for more information, see ERD Issue 3, "*Running on empty: can we chase the fat away?*"). High-intensity interval training in both the fasted and fed state also led to similar amounts of fat loss in women who were sedentary and overweight in another study. Caloric intake was not strictly controlled, though, so it's hard to tell if caloric deficit is what led to the fat loss. A third study compared the effects of exercise in the morning versus evening in women with overweight. The women who exercised in the morning lost weight and a statistical trend for body fat loss was seen, while evening exercise didn't affect weight or body fat. However, it is not clear if the women who exercised in the morning did so before or after breakfast. In addition, the morning exercisers also seemed to take in fewer calories as the study progressed, further confounding the effects of the exercise alone on fat loss.

The study under review agrees with previous research looking at fasted aerobic exercise in women, although that evidence is limited. Overall, it looks like fasted aerobic exercise of moderate, but not high, intensity can burn relatively more fat regardless of training status, BMI, or sex. Whether fasted exercise while in energy balance can translate to body fat loss remains to be determined, but some evidence to date concerning exercise in a caloric deficit indicates no difference in body fat loss between people exercising in the fasted or fed state.

Frequently asked questions

Why does aerobic exercise on an empty stomach burn relatively more fat than carbs while exercising?

The authors of the study hypothesize that it comes down to reduced glycogen stores. The body's pool of carbohydrates available for use is relatively small compared to its fat and protein pools. Accordingly, the

"[...] some evidence to date concerning exercise in a caloric deficit indicates no difference in body fat loss between people exercising in the fasted or fed state."

body's metabolic reaction to changes in the carbohydrate pool tends to be more sensitive. So, it's reasonable to suspect that in the morning before breakfast, carbohydrate pools stored as glycogen are relatively low, making the body turn to fats for its energy needs. Indeed, it's known that skeletal muscle and the liver both turn to fat when glycogen stores are low. It's possible that circadian rhythms could play a role in fat burning as well. However, research in men speaks against this hypothesis, since exercise in the morning and evening burned the same amount of fat after an identical meal. Also, eating carbs stimulates insulin release, which in turn suppresses fat oxidation.

Does the menstrual cycle affect fat burning?

It seems so. Recall that the study under review was done in the early follicular phase, right around or shortly after the time of menses. The authors did this since a lot of other research also focuses on women in this phase. However, some research suggests that more fat is burned during the mid-luteal phase (after ovulation) compared to the early follicular phase due to higher levels of sex steroid hormones. Furthermore, since glycogen utilization is influenced by the menstrual cycle as well, further research is needed to see how fasted aerobic exercise affects fat oxidation during the luteal phase.

Given what was said above, would oral contraceptives impact the fat-burning effects of aerobic exercise in the fasted state?

One study found little difference in fat oxidation between women taking oral contraceptives and those who weren't. If there was any difference at all, it's swamped by the effect of exercising in the fasted state. However, oral contraceptive use does seem to increase the intensity of exercise needed to reach maximal fat oxidation, although it is not clear if this effect was found in the fasted or fed state.

So far you've focused on aerobic exercise. What about resistance training?

This area is less well studied, but some evidence exists for both men and women. In men, neither aerobic nor resistance exercise increases 24-hour fat oxidation in the fed state. And in women, fat oxidation is increased by resistance exercise in the short term, but not over 24 hours. This looks like the pattern seen with aerobic exercise. However, more research is needed to see if fasted resistance training affects fat oxidation.

What should I know?

The consensus is that aerobic exercise leaves the body fat-neutral throughout the day, at least if the amount of calories coming in each day equals calories going out. However, recent evidence suggests that aerobic exercise in the fasted state can actually lead to the body increasing the percentage of fat used as fuel over the course of a day, even in energy-neutral diets. Much of this evidence comes from studies in men, though. Due to several physiological differences between men and women in terms of fat metabolism and exercise adaptation, it's not clear if exercise in the fasted state would also lead to higher fat oxidation in women on an energy-neutral diet.

The study under review examined this issue, and found that women indeed do burn more fat over the course of a day when undertaking moderate intensity, pre-breakfast aerobic exercise relative to being at rest. However, this does not necessarily translate to repeated bouts of cardio affecting body fat. More research is needed to see if this effect actually translates to changes in body composition in the longer term. Ideally, future research would directly compare the effects of exercise in the fasted and fed states. ◆

Head on over to the ERD Facebook forum for some moderate intensity discussion about this study!

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-analysis 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 bodyweight 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 μm2).

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.

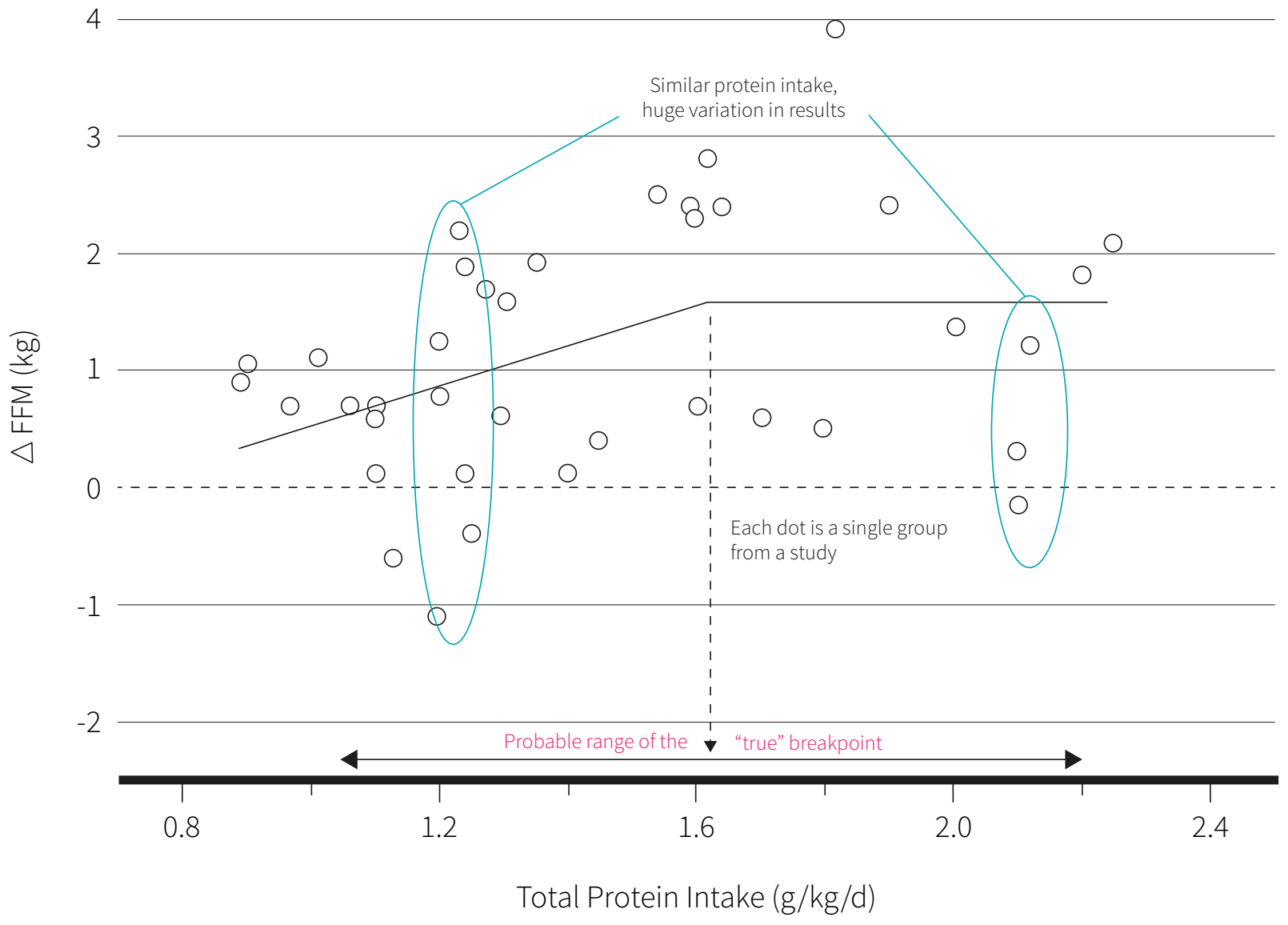
The increase in FFM was greater in trained (+1.05 kg) participants compared to untrained participants (+0.15 kg), which matches up nicely with the finding that changes in FFM were correlated with training status. Chronic resistance training appears to dampen growth-promoting signaling pathways in muscle 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 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 supplementation 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

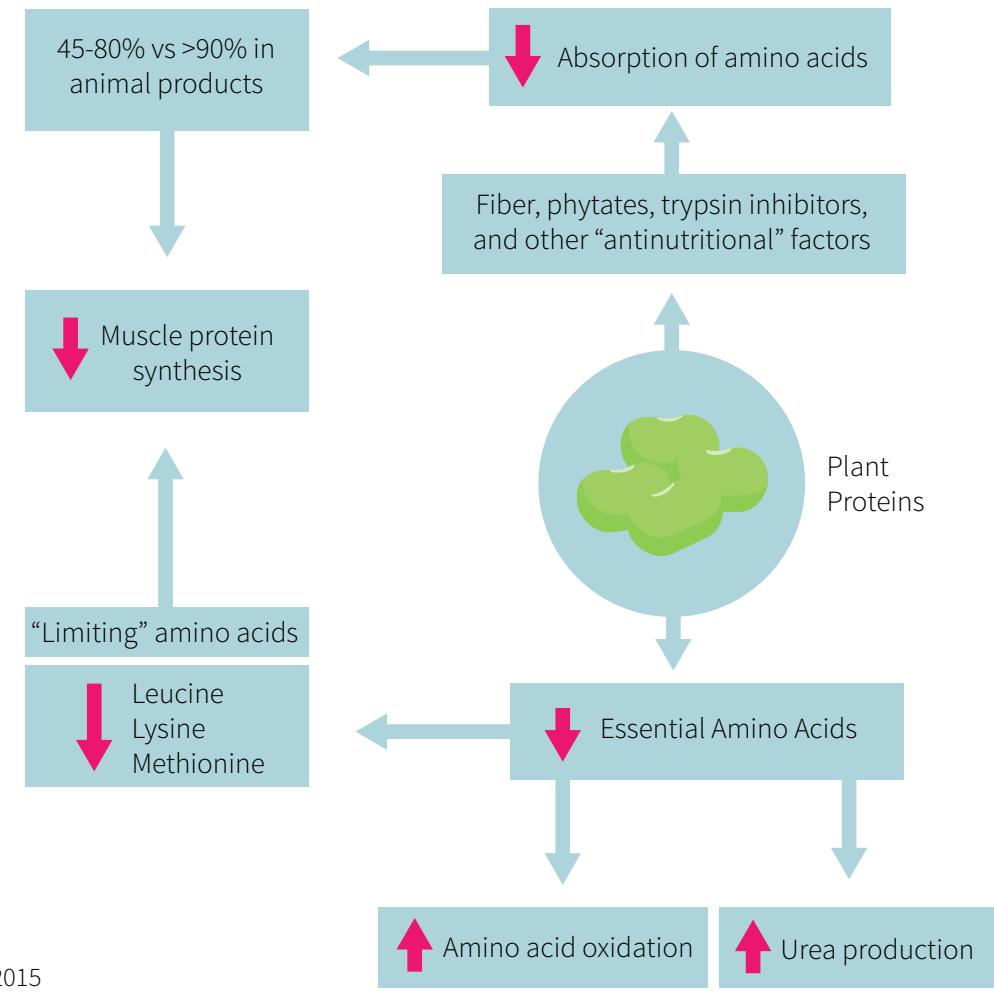
Does it matter what type of protein is used use?

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). ◆

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