ERD

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Research Digest

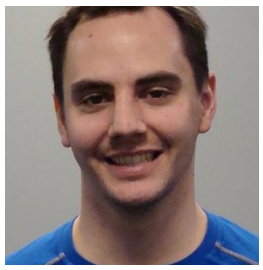
Dean Somerset ◆ 5 Year Anniversary Edition

From the Editor

First, we want to thank you for taking the time to check out the Examine.com Research Digest (ERD). We feel a connection to those who love to get their hands dirty, wading through interesting and complex topics in nutrition and supplementation.

Examine.com was founded five years ago to help cut through the massive amount of misinformation on the web and everywhere else. To make sure we stay unbiased, we have a strict policy of accepting no advertising, sponsorship, product samples, or pretty much anything else that could even slightly skew our research. There's a reason why over 50,000 people visit us ***every*** day.

As our reputation grew, health professionals started asking if they could get continuing education credits from reading our reviews. We responded with ERD, which covers new research in depth, using editors and reviewers from academic fields ranging from neuroscience to immunology. Each month, ERD looks at eight recent papers that are both interesting and practical, and presents them in an easy-to-read and graphically pleasing manner. We are now approved for CECs from NSCA, NASM, The Academy, and more.



Dean has always been a big supporter of ERD, so we made this special anniversary issue for his readers, containing five ERD articles he thought you would find interesting.

For 72 hours only, we are offering ERD at a sale price of **20% off**.

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Kamal Patel, *Editor-in-Chief*

> *Examine.com is always the first place I turn to for the best and most unbiased information on supplements, and I regularly refer my clients to their site to research further on supplements they may want to use. Their information is both comprehensive and user friendly, something that's a very hard blend to achieve, but makes for a very valuable resource.*
>
> *- Dean Somerset*

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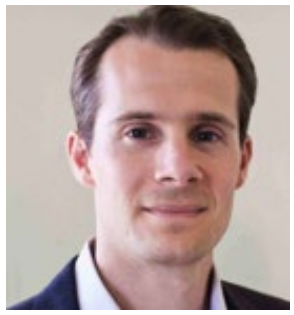

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The chocolate fountain of youth

Cocoa flavanol supplementation influences skin conditions of photo-aged women: A 24-week double-blind, randomized, controlled trial

Introduction

Antioxidants are a hot topic. We've previously discussed one type of antioxidant, flavonoids, in several ERD articles, including 'Blueberries every day keeps high blood pressure at bay' in ERD #6 and 'Don't forget the cocoa!' in ERD #2.

Flavonoids are typically divided into five different subgroups: anthocyanins (the "blue" in blueberries), anthoxanthins, flavanones, flavanonols, and flavans (which are of interest to chocolate lovers everywhere, and also this study). The flavans subgroup includes flavanols, which are the biggest source of flavonoids in cocoa— primarily catechin, epicatechin, and procyanidins.

Flava-what?

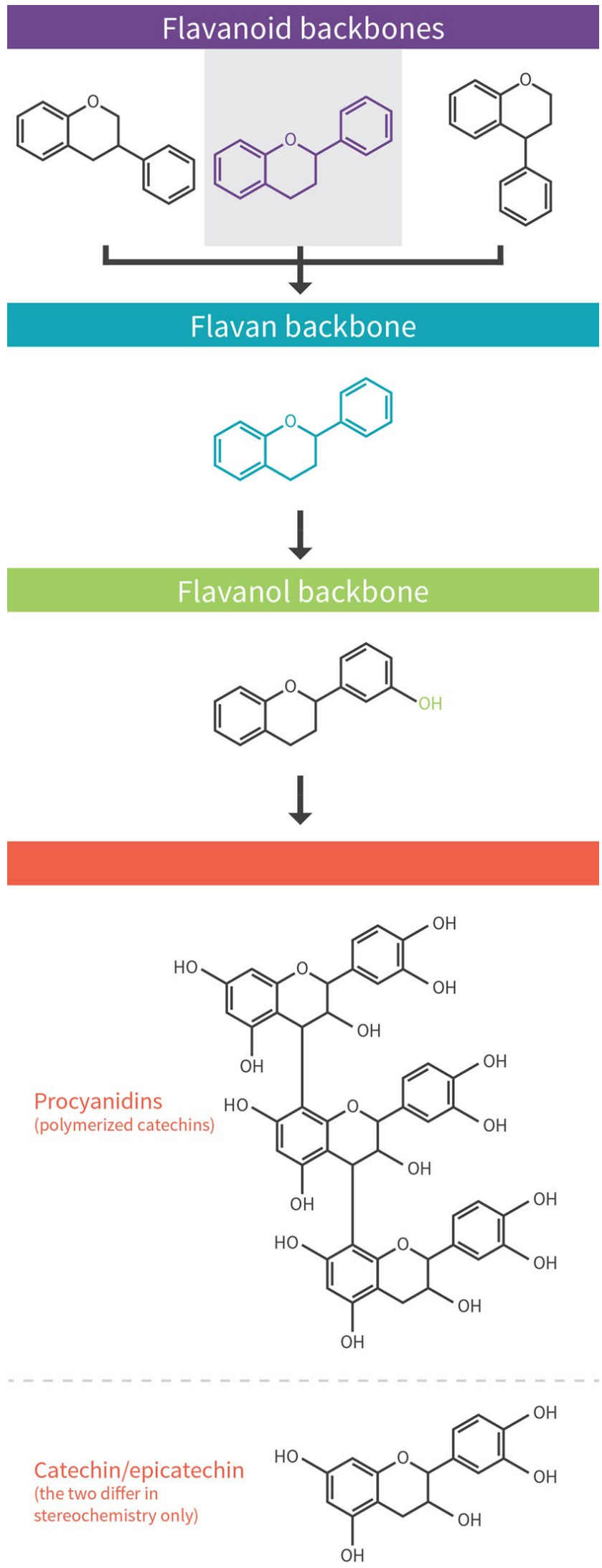
There are a lot of similar terms when it comes to flavonoids, so it's easy to get confused. We'll break it down real quick, and you can check out Figure 1 for depictions of these structures.

Flavonoids: the main class of biological molecules. These are all plant-based compounds, and all have the base structure of two phenol rings (six carbons each) plus a third connected ring that has an oxygen molecule in place of one of the carbon molecules. The arrangements of the rings and other attached molecules are what differentiate the subgroups and molecules within the subgroups.

Flavans: one of the five subgroups of flavonoids. Here, we're getting more specific about the base structure: all flavans have the second phenol ring attached one atom away from the oxygen molecule in the middle ring.

Flavanols: the specific type of flavans primarily found in cocoa. All of these molecules have an -OH (hydroxyl) group attached two atoms away from the oxygen molecule in the middle ring.

Figure 1: Flavanoids, flavans, and flavanols



The main flavanols in cocoa are catechin, epicatechin, and procyanidins. These molecules have antioxidant properties.

Antioxidants have been studied for a number of different beneficial outcomes, including improvements in the skin's appearance and protecting the skin from sun damage. Results of previous trials that evaluated flavanols in cocoa, however, have been mixed. Some studies have shown positive benefits of cocoa consumption on protection from sun damage and skin condition, while others have not.

This study aimed to overcome some of the limitations of previous studies by extending the length of the trial and being more selective in the study population. Prior studies only lasted six to twelve weeks, and included both men and women, as well as younger participants. The hope was that by reducing possible variability in the measurements, and allowing more time for changes to be observed, a clearer picture would emerge regarding the effects of cocoa on skin condition.

Previous studies investigating the effects of cocoa flavanols on the skin have shown mixed results. This study was designed with a longer trial duration and a less diverse study population to overcome some of the limitations of previous studies.

Who and what was studied?

Researchers recruited 62 healthy Korean women for this study. They were all between 43-86 years old (the average age was early 60s), and had visible facial wrinkles. None of the women had any cosmetic anti-aging procedure in the three months prior to the study, nor did any have diets that included "functional foods" particularly high in antioxidants in the month prior to the study.

"This study was designed with a longer trial duration and a less diverse study population to overcome some of the limitations of previous studies."

Half were randomly assigned to consume a powdered beverage containing 320 milligrams of cocoa flavanols from minimally processed cacao beans daily, and half were assigned to consume a nutritionally matched and artificially chocolate-flavored beverage powder with no cocoa flavanols.

The participants had noninvasive assessments of their facial skin done at the beginning of the study, at 12 weeks, and at 24 weeks into the study. A silicon mold was made based on a small section of facial skin, then the topography of the mold was measured for rough-

ness, which was expressed in various R values. As wrinkles in the face increase, the R values go up, and vice versa.

The elasticity of the skin was determined by applying suction to an area of skin and measuring the skin's resistance to the suction and its ability to return to its previous shape. Finally, skin hydration was measured using a small probe called a tewameter, which calculates the rate of water evaporation from the skin's surface. The study was double-blinded, so the researchers taking the measurements did not know which beverage each woman had been assigned to consume (and neither did the participants).

In addition to these noninvasive measurements, 10 participants from the cocoa group and nine from the placebo group agreed to undergo exposure to ultraviolet light. At baseline and at the end of 24 weeks, one-centimeter square areas of skin on the participant's buttock were exposed to increasing doses of UV-B, the short wave ultraviolet light primarily responsible for sunburns. The researchers assessed the irradiated areas of skin 24 hours after exposure to determine the minimum UV-B dose needed to produce a sunburn, known as the Minimal Erythema Dose (or MED, shown in Figure 2).

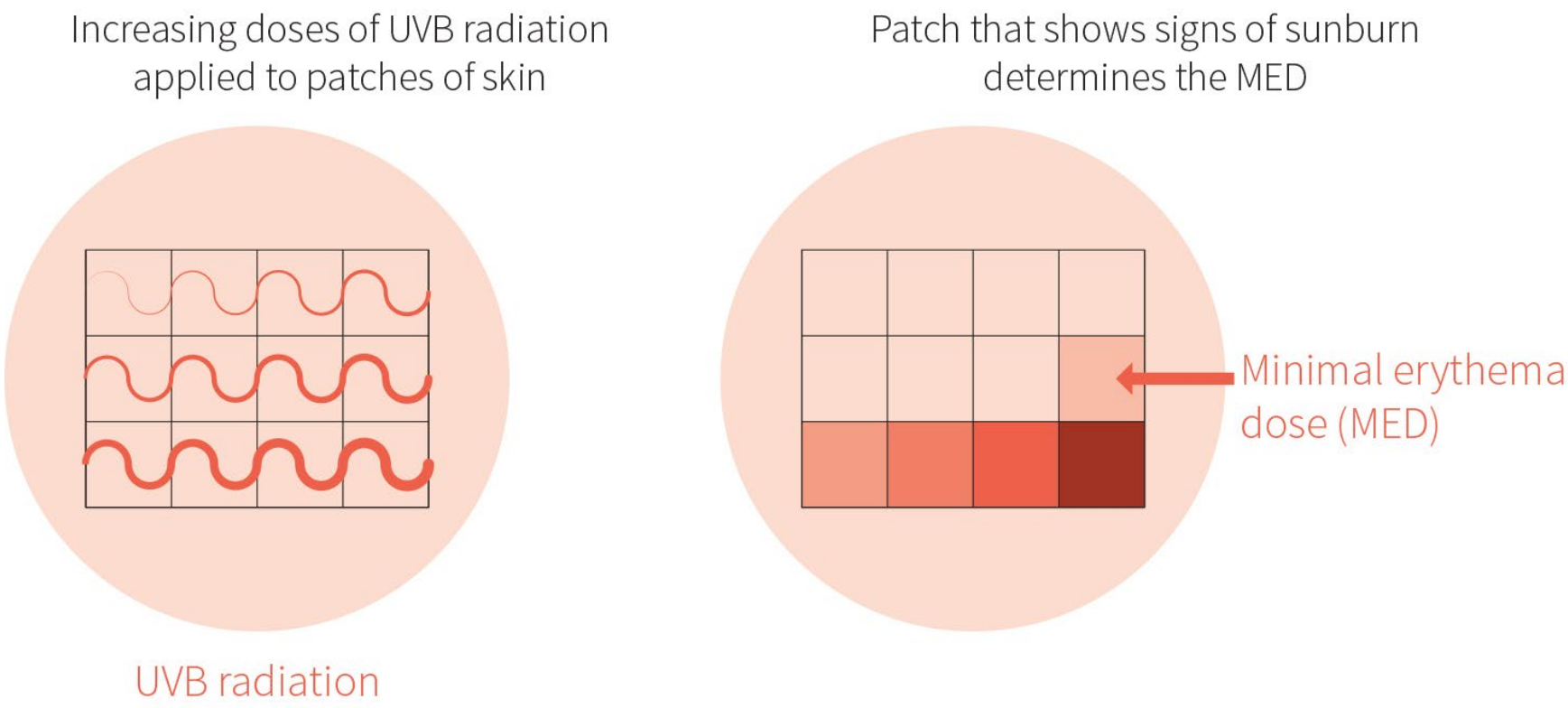
All participants had blood samples drawn at the beginning and end of the study to assess the safety of the cocoa supplement, and had their weight tracked at each visit. Researchers also assessed compliance at 12 and 24 weeks by checking the number of beverage packages remaining.

Middle-aged and elderly Korean women were given a daily beverage containing cocoa flavanols, or a placebo beverage, for 24 weeks. Measures of skin wrinkles, elasticity, and hydration were quantitatively measured, and tolerance to doses of ultraviolet irradiation were tested at the beginning and end of the study.

What were the findings?

The study's findings are summarized in Figure 3. After 12 weeks of consuming the cocoa supplement, there were no differences in any of the facial roughness or facial hydration measurements compared to the placebo group. One of the three elasticity measurements (gross

Figure 2: How minimal erythema dose (MED) was determined



elasticity) showed a statistically significant improvement in the cocoa supplement group, while the other two measurements (net elasticity and biological elasticity) were statistically unchanged. On the other hand, after 24 weeks, all three markers of skin elasticity showed statistically significant improvements, averaging about a 10% improvement in the measurements compared to the placebo group. Two markers of skin wrinkles, average roughness (Rz) and maximum roughness (Rm) also showed statistically significant improvements in the cocoa supplement group, showing an improvement of approximately 8-9% over placebo measurements.

For the smaller group that also received the UV-B exposure, cocoa supplementation also produced a statistically significant effect. While the MED of the placebo group was basically unchanged after 24 weeks, the cocoa group could tolerate a dose of UV-B irradiation that was, on average, 65 millijoules per square centimeter (mJ/cm2) higher before producing a sunburn.

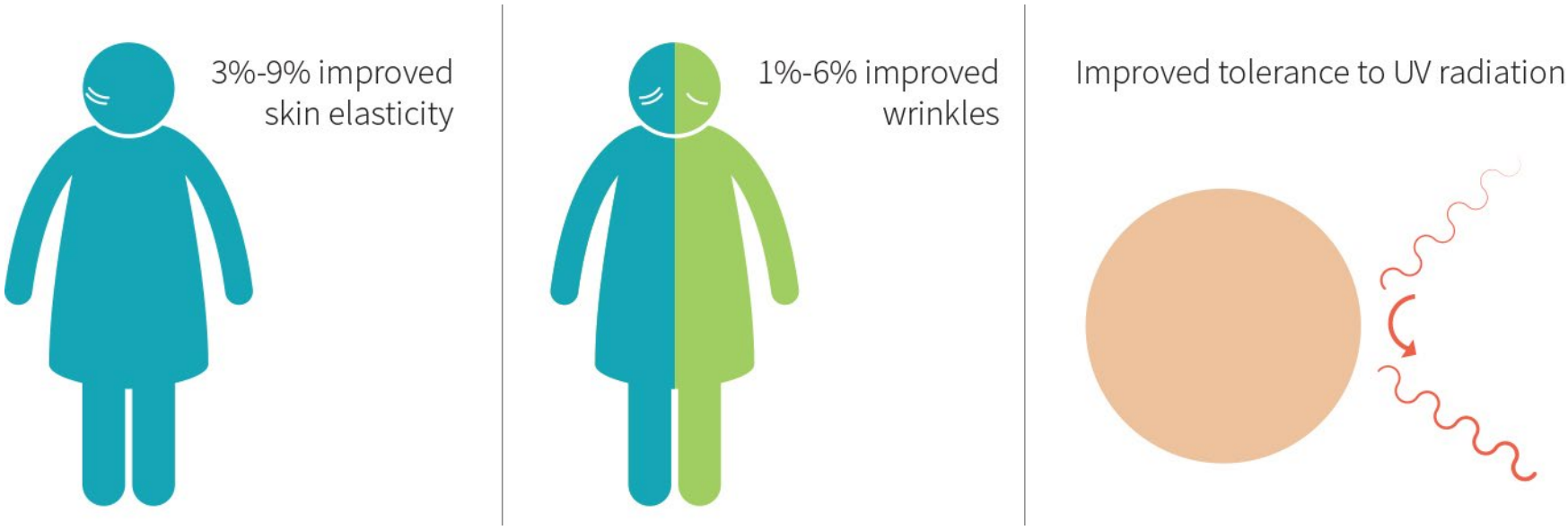
There were no safety concerns, and the compliance rate of the study was extremely high, at around 97-99%. Which is not a surprise, as people tend to enjoy chocolate, with some (non-rigorous) studies showing greater craving in females than in males. What WAS surprising was that a statistically significant difference was seen in the weight of the cocoa group, compared to the placebo group. While the study was not controlled for other environmental factors like diet and exercise, and thus no conclusive findings can be drawn from this particular dataset, the researchers observed that the placebo group gained an average of 1.5 kilograms over the course of the study while the cocoa group, on average, was relatively unchanged, gaining only 0.04 kilograms.

While almost no differences were seen between the treatment and placebo groups after 12 weeks, several measurements of skin roughness and skin elasticity were positively affected by cocoa supplementation after 24 weeks. The women who consumed the cocoa beverage were also able to tolerate a higher dose of UV-B irradiation before their skin became sunburned.

What does the study really tell us?

Overall, the study shows some small, statistically significant changes in skin elasticity, wrinkles, and resistance to UV-B radiation are caused by consumption of cocoa flavanols. It also shows that a longer, 24 week period is needed to see statistically significant differences between the treatment and placebo groups, confirming the researchers' hypothesis that previous studies of shorter duration were not sufficient.

Figure 3: Main effects of 24 weeks of supplementation on skin



An important thing to note about the data is that all the treatment group measurements are reported as percentage changes compared to the placebo group - what you would really want to know as a possible consumer is how it affected your skin, not how your skin compared to someone else's. When you dig into the group's measurements compared to their own baseline, the numbers are slightly less impressive. Over the course of the 24 week study, the improvement in skin roughness (wrinkles) in the cocoa group was only about 1-6% from the group's baseline measurements—a change that may not even have been visible to the casual observer. Skin elasticity fared a little bit better, showing improvements in the range of 3-9%.

The researchers did note in their analysis "... the sizes of effects were smaller than other direct curative strategies such as topical tretinoin, laser resurfacing, and chemical peeling". They also suggested that the cocoa flavanols might be more effective in preventing wrinkles when consumed for a longer duration and starting at a younger age, rather than as a treatment once wrinkles and loss of skin elasticity have already appeared in older women.

The UV-B exposure data hold up slightly better. The median MED for the 19 participants at the start of the study was 160mJ/cm2. The placebo group's MED was statistically unchanged compared to baseline after the 24 week study, while the 65 mJ/cm2 increase in the cocoa group's MED was not only statistically significant, but also represented a 40% increased tolerance compared to baseline - basically a modest sun protection factor (SPF) of 1.4.

The researchers noted that the study took place in the winter, which may have had an effect on some of the measurements, particularly skin hydration. However, the length of the study does provide a benefit over previous studies that had much shorter durations (six to 12 weeks).

One other benefit of the study was that it was conducted in a homogenous population in terms of race, age, and gender. This eliminated some of the factors that may have confounded the results of previous studies. The downside, of course, is that the results can't be readily applied outside of this specific study population, namely, middle-aged and elderly Korean women.

The length of the study is its main strength. Its main weakness is that while the data for skin roughness and skin elasticity are statistically significant, cocoa supplementation may not have produced any visible changes in wrinkles or skin appearance because the differences from baseline measurements in the treatment group were small. This lends some support to the idea that cocoa flavanols may be more useful for preventing wrinkles rather than treating existing wrinkles. The specific study population likely eliminated some noise from the data collection, but also limited its applicability more broadly.

The big picture

The data from this study support many of the conclusions from previous trials, including the fact that nearly no statistically significant effects were seen at the 12 week mark, where many other earlier studies stopped. The fact that skin elasticity showed improvements before skin roughness and wrinkles did is also in line with previous observations.

Regarding the observation that the treatment group maintained their weight while the placebo group gained weight over the course of the study: previous reports have suggested a number of possible mechanisms for cocoa flavanols playing a role in weight-related pathways, including effects on insulin receptors that alter the development of fat cells, and affecting the digestion of fats and carbohydrates, possibly increasing satiety. Researchers have investigated the role of cocoa flava-

nols for weight loss in rats, and in a dietary assessment of over 1000 healthy people, a positive correlation was observed between higher frequency of chocolate consumption and lower BMI. But there haven't really been any clinical trials designed to directly assess the effects in humans. So for now, this is still just an interesting isolated observation.

The cocoa flavanols used in this study may be only one of many possible beneficial antioxidants for improving skin's appearance. A number of facial creams have antioxidants added to them to deliver these nutrients directly to the epidermis, and dietary nutrients such as beta carotene (and other carotenoids) and lycopene have previously been shown to have photoprotective effects. Even resveratrol, one of the antioxidant molecules found in red wine, is being investigated for topical application. A 2013 review reported 14 different dietary or topical antioxidants that have evidence for protective effects on the skin, and suggested that combinations of multiple antioxidants may have synergistic effects (that is, a larger effect than the individual effects added together).

In short, antioxidants are probably good for the skin regardless of what dietary source they come from, and the more the merrier. But some people happen to think chocolate tastes better than carrots.

Data from this study support previous conclusions from earlier trials. While cocoa flavanols may provide some benefit to the skin, they are likely only one of many antioxidants that may improve the skin's appearance and protect from sun damage.

Frequently asked questions

How much chocolate would I have to eat to experience the same benefit as the participants in this study?

You'd need about 320 milligrams of cocoa flavanols, or somewhere between eight and 25 grams of dark chocolate (70%+). That works out to roughly 50-150 calories (a couple of "fun sized" bars or a quarter to a half of a regular sized chocolate bar). The higher the cocoa percentage, the less you'd have to eat. Other studies have used higher doses of cocoa flavanols, which could equate to nearly twice as much chocolate consumption.

Would cocoa flavanols be effective for men?

Since this study was only conducted in women, it's harder to draw support from the data for a similar supplementation strategy in men. Aging skin is the result of a number of different environmental and biological factors. Some of those biological factors have gender differences like hormonal patterns and gene expression. As previously mentioned, there are a number of other flavanols that might be beneficial to the skin's appearance. So it's possible that there could be a similar effect in men, or there may be a completely different mechanism in males that could be unaffected by the cocoa flavanols specifically. More research is needed in different study populations to tease out broader applicability.

What should I know?

Korean women over the age of 40 saw a modest but statistically significant improvement in facial skin surface roughness and skin elasticity after consuming a flavanol-rich cocoa beverage for 24 weeks. The women who consumed the cocoa flavanols also had a mild "internal sunscreen" effect and were able to tolerate a higher dose of UV-B irradiation before producing a sunburn than those who consumed a daily beverage without cocoa flavanols. ◆

There's more information about cocoa extracts on Examine.com. To discuss this study and your love of chocolate, visit the ERD Forum on Facebook.

Not-so-safe supplements

Emergency Department Visits for Adverse Events Related to Dietary Supplements

Introduction

Dietary supplements are sometimes erroneously perceived as inherently healthy. And because of the way many supplements are advertised, it's easy to overlook that improper administration can lead to adverse outcomes.

The classification of a supplement is defined in the United States Dietary Supplement Health and Education Act of 1994 (DSHEA) as a vitamin, mineral, herb or botanical, amino acid, and any concentrate, metabolite, constituent, or extract of these substances. In the U.S., the Food and Drug Administration (FDA) is the governing body that oversees the regulation of dietary supplements. If a supplement has been reported to be causing serious adverse events or reactions, the FDA has the authority to pull it from the market. However, no safety testing or FDA approval is required before a company can market their supplement. The lack of oversight authority given to the FDA has even drawn the attention of late night talk shows hosts like John Oliver, who humorously covered the issue in this YouTube video.

Many adults are using one or more supplements to address illnesses or symptoms, and to maintain or improve health. Half of all U.S. adults have reported using at least one supplement in the past 30 days. Twelve percent of college students have reported taking five or more supplements a week. Now, more than ever, there are seemingly endless options to choose from. The number of supplement products currently available on the market is thought to be in excess of 55,000. Compare that to the mere 4,000 available in 1994, when DSHEA was passed.

Furthermore, confidence in the safety and efficacy of these supplements is very high despite the lack of rigorous oversight by the FDA. A survey conducted by the trade association, Council for Responsible Nutrition, found that "85% of American adults … are confident in the safety, quality and effectiveness of dietary supplements." An independent survey has echoed these results, finding that 67.2% of respondents felt extremely or somewhat confident in supplement efficacy and 70.8% felt extremely or somewhat confident about their safety.

While the majority of Americans trust in their supplements, more than one-third have not told their physician about using them. There are numerous documented drug-supplement interactions ranging from the mild to the severe. The herb St. John's Wort is thought to be able to reduce symptoms in people with mild to moderate depression. But this 'natural' supplement also has 200 documented major drug interactions, including some with common depression medication. However, no good data currently exists to document how common adverse events related to dietary supplements may be. The authors of the present study have used surveillance data to try and fill this knowledge gap.

Due to DSHEA, supplements remain largely unregulated by the FDA. But dietary supplements are becoming ever more popular, as about half of U.S. adults report using one or more in the past 30 days. Trust in the safety and efficacy of these supplements also remains high. The authors of this study aimed to investigate how many annual adverse events are caused by improper supplement usage.

Who and what was studied?

The researchers looked at 10 years of data (2004-2013) to estimate the adverse events associated with dietary supplements in the United States from 63 different hospitals. The selection of these hospitals was meant to be nationally representative and included locations that had 24-hour emergency departments. Trained patient record abstractors reviewed the reports from each hospital to identify cases where supplements had been implicated as the likely source of the adverse event. These abstractors have been trained to analyze and compile medical information contained in patient records.

Cases were scanned for emergency room visits where the treating clinician had explicitly ascribed dietary supplements as the root cause of the medical issue. This included herbal or complementary nutritional products such as botanicals, microbial additives, and amino acids, in addition to micronutrients like vitamins and minerals. Products that may typically be classified as food were excluded, like energy drinks and herbal tea beverages. Topical herbal items and homeopathic products were included in the analysis even though they do not fall under the regulatory definition of dietary supplements.

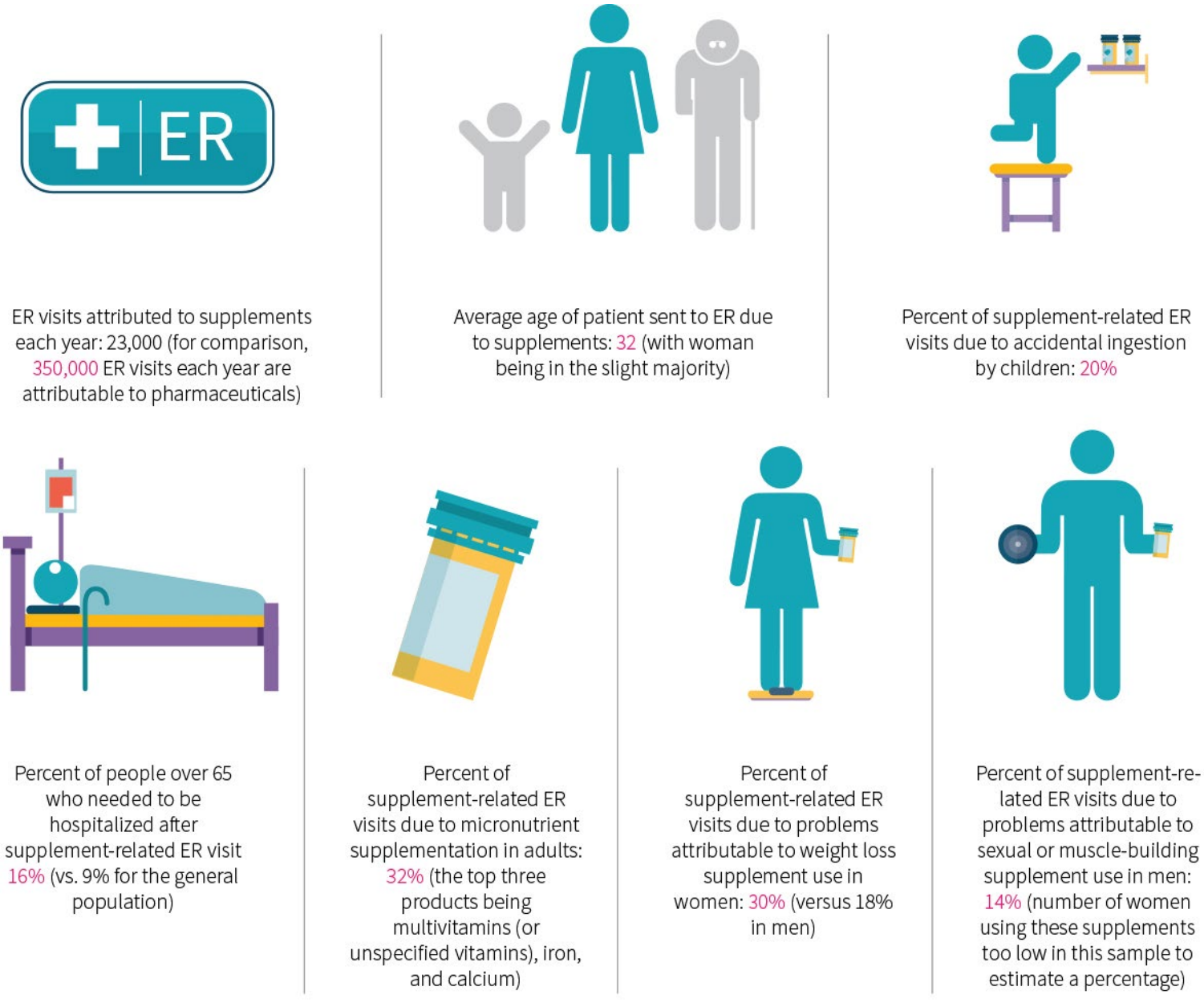
Adverse events were classified as anything causing adverse or allergic reactions, excess doses, unsupervised ingestion by children, or other events like choking. Due to the non-standard death registration practices among different hospitals, cases involving a mortality were not included, as were any cases involving intentional self-harm, drug abuse, therapeutic failures, nonadherence, and withdrawal.

Researchers examined patient records from 2004 to 2013 from 63 different hospitals. Cases where the treating clinician had identified a supplement as the cause of the medical emergency were extracted from the dataset. However, deaths associated with or caused by supplements were not included, as hospitals differ in their practice of registering mortalities.

What were the findings?

Some of the major findings are summarized in Figure 1. Over 3,600 cases were identified within the predetermined 10-year period. The researchers extrapolated from these data that the U.S. experienced an average

Figure 1: Supplement safety by the numbers

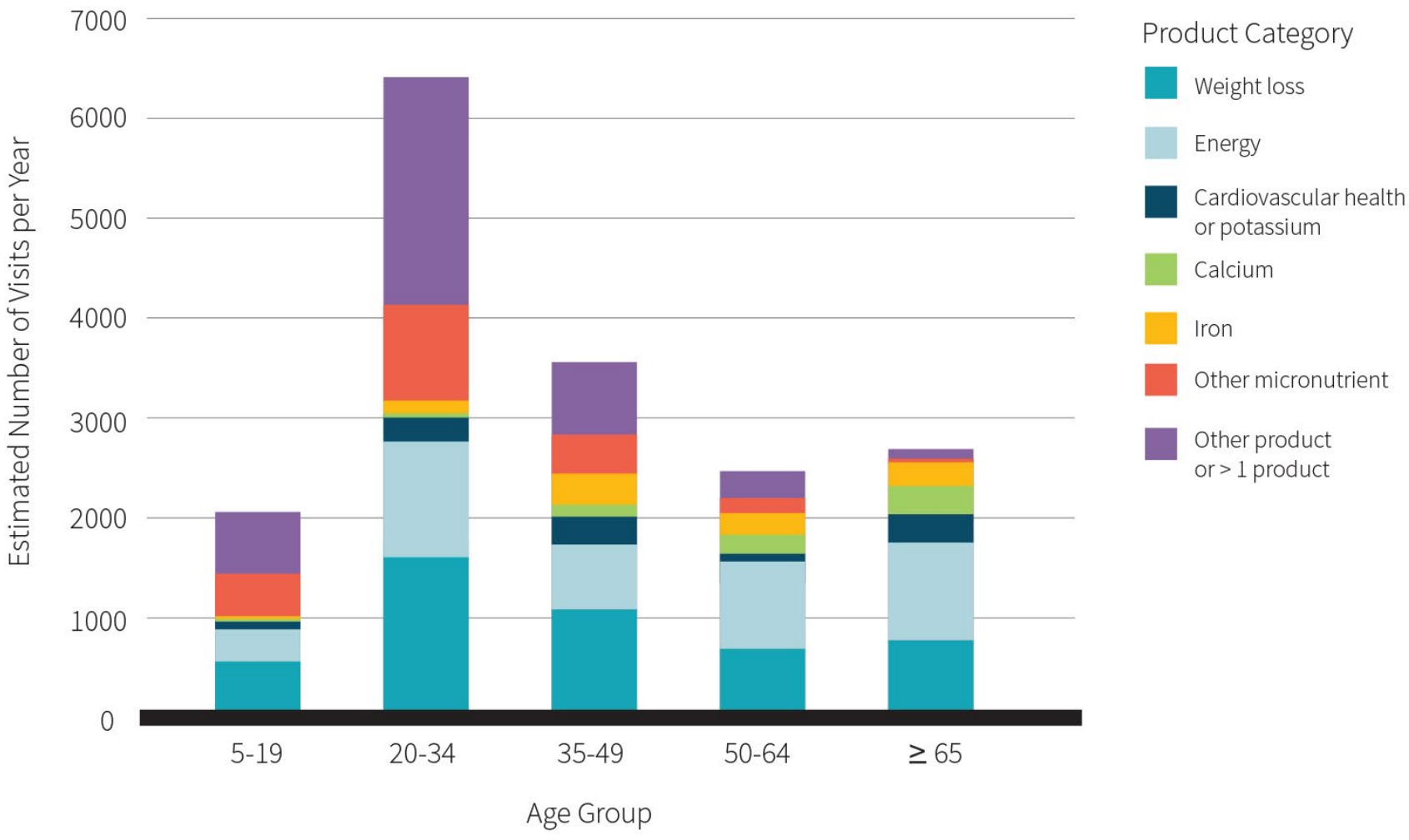


of 23,000 supplement-related emergency department visits per year, with estimates ranging from 18,600 to 27,400. Of these 23,000 emergency room visits, it was calculated that about 2,150 (9.4%) of these result in hospitalization. About 88% of these ER visits were attributed to a single supplement, as opposed to interactions or mixtures of multiple supplements. The average age of patients treated for supplement-related adverse events was 32 years, and the majority of these cases were female.

Figure 2 shows age and supplement category related results. About a quarter of ER visits involved people between the ages of 20 to 34, but people older than 65 years old were more likely to have a visit that resulted in hospitalization. Of patients above 65 admitted to the ER, 16% had to be hospitalized. Surprisingly, one-fifth of supplement-related ER visits were due to accidental ingestion by children. When the data covering unsupervised ingestion of dietary supplements by children was not included, the researchers found that the majority of ER visits (65.9%) were due to herbal or complementary nutritional products. The top five products in this category included the following: weight loss (25.5%), energy (10.0%), sexual enhancement (3.4%), cardiovascular health (3.1%), and sleep, sedation, or anxiolysis (i.e. anti-anxiety) (2.9%). Multivitamins or unspecified vitamin products were the biggest contributors to ER visits under the micronutrient product category.

ER visits also varied according to gender and age. Weight loss and micronutrient supplements disproportionately landed females in the ER, while sexual enhancement and bodybuilding products largely affected males. Among patients younger than four years old and adults over 65, micronutrients were the number one cause of emergency department visits. This is in contrast to the other age groups, where herbal and complementary nutritional products were the biggest contributor. In people ages five to 34, weight loss products or energy products were implicated in more than 50% of ER visits. Weight loss products mostly affected

Figure 2: Summary of which types of supplements lead to ER visits by age



Source: Geller AI et al. N Engl J Med. 2015 Oct.

patients from 20 to 34 years of age, while the micronutrients iron, calcium, and potassium mostly affected those older than 65.

About 23,000 people go to the ER for supplement-related visits every year. The biggest contributors to this are herbal or complementary nutritional products like weight loss and energy supplements, which largely affect people between the ages of five to 34. Females are more likely than males to end up in the ER due to adverse supplement reactions. Those over the age of 65 are most at risk for an ER visit due to micronutrient supplements such as iron, calcium, and potassium.

What does the study really tell us?

While 23,000 annual supplement-related emergency visits may sound high, this is less than 5% of pharmaceutical product-related ER visits. However, these ER admittance rates do not line up with the marketing that has promoted dietary supplements as fundamentally healthy. That is, the general public overwhelmingly perceives these products to be safe and effective, but the present data does not support this notion (ERD readers excluded. We think you are all ahead of the curve on this one).

However, it should also be noted that overall incidences of supplement-related ER visits have remained constant over time. No significant changes were detected between 2004 and 2013 when accounting for population increases. The only increase that occurred was ER visits associated with micronutrient supplements, which jumped 42.5%, from 3,212 to 4,578 cases in this same time frame.

Unlike their highly regulated pharmaceutical counterparts, there are no legal requirements for dietary supplements to identify any potential adverse effects or major drug interactions on their packaging. The lack of adequate warning labels may be a contributing factor to why histories of dietary supplement usage are rarely obtained by clinicians. This can be due to a combination of clinicians not asking proper patient screening questions and to a lack of disclosure by the patient.

Proprietary Blends

The FDA has established labeling standards dictating what must appear on a supplement's packaging. Manufacturers must list out each ingredient, and are required to display the amount or percentage of daily value of those ingredients.

A proprietary blend falls under a slightly different set of regulations. Blends are a unique mixture of ingredients that are typically developed by the manufacturer. The FDA requires that all ingredients of a proprietary blend be listed on the label in descending order according to predominance of weight. While the amount of the blend as a whole must be listed, the amount of each ingredient included in the blend does not.

Blends are used to help prevent the competition from knowing what the specific formulation is. But it can also hide the fact that very little of an active ingredient may be in the bottle. So while a proven performance enhancing ingredient like creatine may be listed in a proprietary blend, it could be well below what is considered to be an effective dose.

Given that there is a tendency to underreport supplement usage, the researchers have noted that their calculations of emergency department visits attributed to supplement-related adverse events are probably an underestimation. A further limitation was the relatively small sample of hospitals used. But this method of data collection is likely to yield more accurate results over voluntary reporting despite the fact that voluntary reporting would have likely allowed for a larger sample population.

While 23,000 annual supplement-related emergency visits may not be a large contributor to ER visits in the larger scheme of things, it does provide a counter-narrative to the marketing that often portrays supplements as always health promoting. Supplements are not required to come with labels warning of adverse events or potential drug interactions, which can be a contributing factor to supplement-related ER visits.

The big picture

The supplement industry is the wild west of nutrition. By and large, DSHEA has hampered the ability of the FDA to adequately regulate supplements. If you have ever taken a supplement that makes a health claim, you may have encountered this statement on the label: "These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease." While all ingredients must be declared on the label, there is little oversight to ensure that these ingredients are present in the supplement, at the doses that are advertised on the packaging. Under DSHEA, there is no requirement for companies to provide any data to the FDA showing that their supplement is safe and effective, unless they are introducing a new or novel ingredient. It falls on the FDA to show that a supplement is unsafe before any action can be taken.

In light of this lack of regulatory oversight, if you are currently taking or thinking about adding a supplement to your diet, be sure to notify your doctor. Supplements can interact with prescription medication or could exacerbate certain medical conditions. Warfarin (Coumadin) is a good example. It is a blood-thinning medication that can be prescribed to people at risk of forming blood clots. To ensure that the medication works properly, these patients are usually placed on a low vitamin K diet, as vitamin K plays an essential role in forming blood clots. If these patients do not disclose that they are taking a multivitamin with vitamin K, multivitamins being one of the most commonly used supplements, they could be putting themselves at risk for developing unwanted clots.

Currently, the supplement industry is partially policed by itself. Companies that market and sell supplement products do not have to show the FDA data of safety or efficacy in the same fashion that pharmaceutical companies do. The FDA can step in when a supplement has been shown to cause harm and pull it from the market. It is important to discuss all supplements you may be taking with your doctor to avoid unpleasant or dangerous interactions. Be sure to tell them even if they do not ask during your screening.

Frequently asked questions

Is there any way to ensure that I'm purchasing a quality supplement??

There are companies out there that do supply third-party certifications to supplement manufacturers. These companies will verify that the supplements listed on the ingredient list are present in the concentrations claimed. There are four major companies that provide these certifications, which are shown in Figure 3: NSF International, Informed Choice, Consumer Lab, and U.S. Pharmacopeia. With the exception of Consumer

Lab, all of these third-party certifiers print their seal on the products they have screened.

The testing process often involves looking at the purity, strength, and bioavailability of the product. Good manufacturing practices, which help to provide systems that track proper design, monitoring, and control of the manufacturing process and facilities, are also frequently taken into account. Many employ continuous random testing in order for a given supplement to remain certified. It is very important to note that these companies do not test for efficacy. That is to say, these certifications do not ensure that any health claims made about the supplement are truthful.

What should I know?

While 23,000 dietary-supplement related ER visits may not seem like a lot when compared to something like the 610,000 deaths caused by heart disease every year in the U.S., it is something that can be easily prevented with education and awareness. Although supplement related deaths were not included in the ER visit projection, which could lead to an underestimation, it is also possible that emergency department physicians may have incorrectly ascribed certain signs and symptoms to supplements, which could consequently lead to overestimation. Essentially, the 23,000 annual ER visits should be viewed as a very rough estimation.

If you are currently taking or planning to introduce a supplement to your diet, be sure that you are consuming the recommended dose for that product and consult your doctor before hand. Supplements are not automatically beneficial for health, no matter what the marketing says. Treat dietary supplements the way you would treat medication, with caution and respect for their ability to both help and harm your health. ◆

An incredibly effective supplement may also be incredibly harmful given the right (well … wrong) context. Talk about the under-discussed issue of supplement safety at the ERD Facebook forum.

Figure 3: Third-party supplement certifications

Better living through cherry juice

Consumption of anthocyanin-rich cherry juice for 12 weeks improves memory and cognition in older adults with mild-to-moderate dementia

Introduction

Plant-based foods have been contributing positively to human health since time immemorial. More recently, these health effects have been widely attributed to phytochemicals, a group of non-nutritive bioactive compounds generally found in fruits, vegetables, whole grains, nuts, and legumes.

In the fields of neuroprotection and cognitive functioning, plants are once again at the forefront of cutting-edge science: flavonoids, a category of phytochemicals, have been associated with improved cognitive function and reduced neurodegenerative decline in old age. In fact, two studies reported that daily consumption of either wild blueberry juice or concord grape juice for 12 weeks led to improvements in verbal learning and memory in older adults with mild cognitive impairment. A more recent study extended these findings to older adults with no sign of cognitive impairment, reporting that daily consumption of flavanone-rich orange juice for eight weeks seemed to improve overall cognitive performance.

As promising as this sounds, the research is still lacking in individuals that have dementia, a blanket term for various neurodegenerative diseases that are believed to compromise the areas of the brain associated with "higher brain functions," such as language, memory, learning, and self-awareness. Dementia progresses to the point that the individual eventually finds it difficult to perform day-to-day activities and live independently.

Alzheimer's disease (AD), the most common form of dementia, is the sixth leading cause of death in America. At the time of this writing, approximately 5.3 million Americans live with AD. By 2050, this number is projected to increase to about 15.3 million (almost a 300% increase) as members of the baby boomer generation age. In light of this rapid rise of AD and the lack of effective treatments, it's important to conduct further studies examining the effect of fruit flavonoids on cognitive function in individuals with AD.

Therefore, the authors of this study sought to analyze the effects of sweet cherry juice, another flavonoid-abundant fruit (primarily through flavonoid subgroup anthocyanins) on the cognitive performance of individuals with mild-to-moderate AD.

Many of the health-conferring effects of plant-based foods may be attributed to their phytochemical content. Fruits rich in flavonoids, a class of phytochemicals, have recently shown promise in improving cognitive function and attenuating neurodegenerative decline. Unfortunately, research on this topic is lacking in people with Alzheimer's disease, the sixth leading cause of death in America. The purpose of this study was to analyze the effect of daily consumption of flavonoid-rich sweet cherry juice for 12 weeks on the cognitive performance of elderly adults with mild-to-moderate Alzheimer's disease.

Who and what was studied?

Forty-two elderly adults (age 70 and over) with mild-to-moderate Alzheimer's disease participated in this study. Individuals with any other physical or mental ailments were excluded.

Participants were randomized to receive either 200 milliliters of sweet cherry juice a day or 200 milliliters of apple juice a day for 12 weeks. The assigned juice was delivered to the homes of the participants on a weekly basis and was to be consumed in one sitting at any time of day. A cup marked with a 200 milliliter fill line was provided for accurate daily dosing.

The sweet cherry juice (derived from Bing sweet cherries) was provided by a research company based in Australia known as Agritechnology, and was

produced in such a way that allowed for greater retention of flavonoids. Using High Performance Liquid Chromatography (HPLC), it was confirmed that the sweet cherry juice contained 69 milligrams of anthocyanins (red pigments) per 100 grams (100 milliliters), whereas the apple juice only contained 0.02 milligrams per 100 milliliters. No information about other flavonoid groups was provided. The cherry juice also proved to have greater antioxidant activity than the apple juice, measured by oxygen radical absorbance capacity (3200 vs. 15.55 µmol Trolox equivalents/g).

All outcome variables were measured at baseline (before the study began), week six, and week 12. An interview was also conducted at each meeting, which included a nutritional status assessment and a questionnaire report-

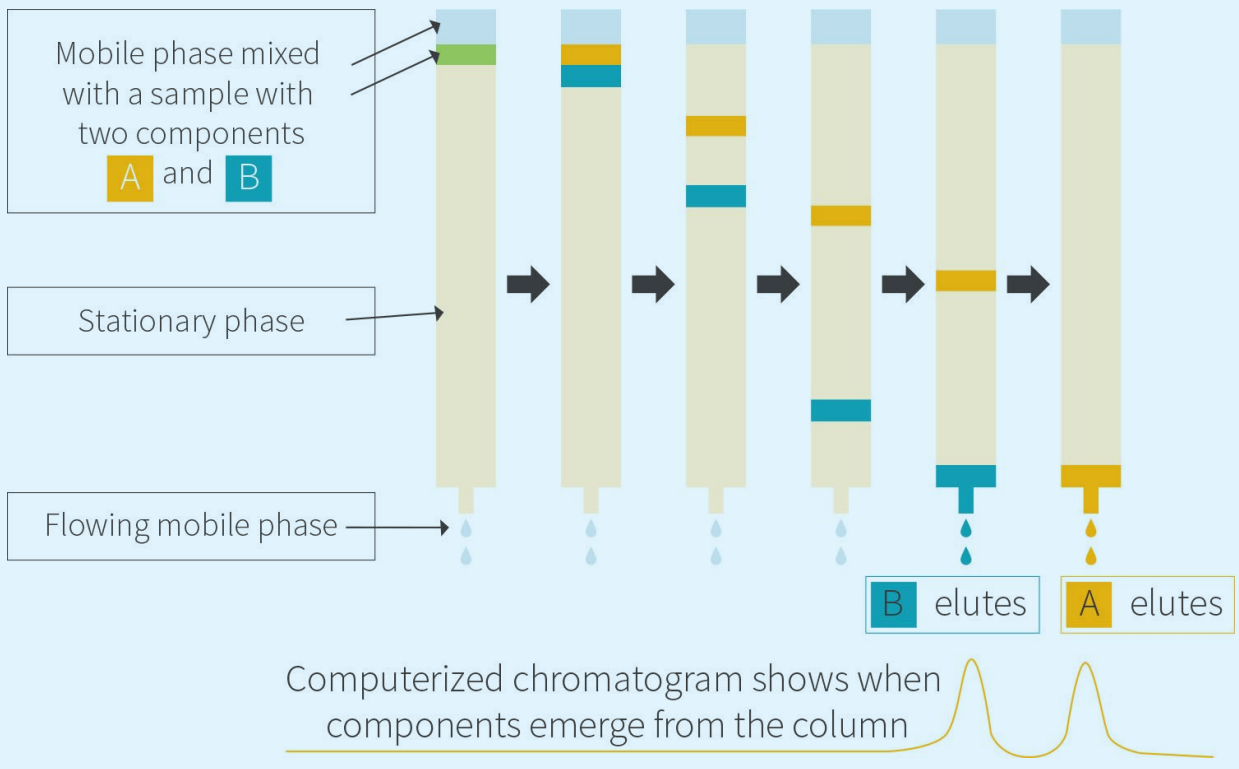
What is High Performance Liquid Chromatography (HPLC)?

Chromatography is the collective term representing various laboratory techniques used to separate mixtures. High Performance Liquid Chromatography (HPLC, depicted in Figure 1) is an improved version of column chromatography, as it is faster, extremely sensitive, automated, and allows for better separation.

In column chromatography, the mixture containing the chemicals of interest is dissolved in a fluid called the mobile phase (which is basically the solution with all the solvents needed to separate the chemicals of interest from the rest of the mixture), and is then applied to the top of the column (tube). As this mixture travels through the tube, it goes through a stationary phase that separates the solutes based on either size, solubility, or binding capacity. Chemicals with greater affinity for the stationary phase will come out of the column after the chemicals with a lesser affinity.

In other words, each molecule in the sample mixture will interact differently with the stationary phase—some will "stick" more than others. The molecules that "stick" less end up moving through the tube at a faster rate and can be isolated in a test tube at the bottom of the column.

Figure 1: Basics of how HPLC works



ing demographic characteristics, alcohol consumption, tobacco use, supplement habits, and medications.

Seven cognitive tests that measured verbal learning and memory, executive function, working memory, confrontational naming (related to semantic memory), and short-term memory were used to assess cognitive performance.

Resting blood pressure, heart rate, and anthropometric measurements, including height, weight, and mid-calf and mid-arm circumference were measured.

Blood samples were taken at baseline and at 12 weeks in order to measure C-reactive protein (CRP) and interleukin-6 (IL-6) levels to assess changes in inflammation. Vitamin C levels were also measured.

Forty-two elderly adults (age 70 and over) with mild-to-moderate Alzheimer's disease were randomized to receive either 200 milliliters of sweet cherry juice or 200 milliliters of apple juice a day for 12 weeks. A battery of cognitive tasks were used to assess cognitive performance.

What were the findings?

At baseline, before the trial had even started, the sweet cherry juice group was found to consume about 40% more flavonoids per day than the control group. However, the change in cognitive test results was assessed (rather than a comparison just at the final time point), mitigating the importance of this difference.

At 12 weeks, the sweet cherry juice group showed improvement in most cognitive tasks compared to their baseline performance. However, the improvement only reached statistical significance in the areas of verbal learning and memory, as well as executive function.

The sweet cherry juice group also reported a statistically significant decrease in systolic blood pressure at weeks six and twelve, compared to baseline. Diastolic blood pressure decreased as well, but statistical significance was not reached, although a trend towards significance was noted. The control group showed no statistically significant difference from baseline in any of the outcome measures.

Neither group showed a statistically significant change in any of the inflammatory markers, although both groups did experience a decrease in plasma Vitamin C levels.

Despite the sweet cherry group showing a trend for improvement in the majority of cognitive tests, statistical significance was only reached in the areas of executive function, and verbal learning and memory. The sweet cherry juice group also experienced a statistically significant drop in systolic blood pressure and a non-statistically significant decrease in diastolic blood pressure. The control group reported no statistically significant difference from baseline in any of the outcome measures.

What does the study really tell us?

Statistical significance does not relate to the magnitude of effect. Rather, it tells us how likely it would be to see the results observed in the study by chance. Therefore, even though the sweet cherry juice group showed a statistically significant improvement in certain aspects of cognition, we cannot, based solely on statistical significance, be certain that these improvements are large enough to be clinically relevant.

To account for this, the authors conducted a test to measure the effect size and found it to be either large or moderate for verbal learning and memory, and executive function — the same tasks found to be statistically significant.

So, not only was the improvement in cognition most likely a result of the sweet cherry juice, but it was also large enough in magnitude to be clinically relevant. Not to mention, the only noted side effect was a drop in plasma Vitamin C levels, and the participants only had to consume less than a cup of the sweet cherry juice a day, making this a safe and practical way of potentially enhancing cognition in elderly adults with mild-to-moderate Alzheimer's disease.

Keep in mind that the sweet cherry juice used in this study is not identical to the cheap cherry juice you find at your local supermarket. The manner in which it was processed enabled it to retain a large proportion of its flavonoid content. In fact, according to the authors, the sweet cherry juice group actually had a daily anthocyanin intake that was 46 times greater than the Australian national average for adults 65 years and older (138 mg vs. 3.02 mg/day).

With that in mind, and also considering that the chief flavonoid in sweet cherries are anthocyanins, it seems safe to hypothesize that the improvement in cognition was likely attributed to the anthocyanin content of the sweet cherry juice. However, the bioactive effects of other flavonoids cannot be dismissed, especially considering that previous trials have noted similar improvements in cognitive performance with fruits rich in other flavonoids, as seen with consumption of a flavanone-rich orange juice.

The authors reported a dip in serum vitamin C in both groups. A possible explanation for this is that the participants replaced their usual commercial drinks that are often fortified with vitamin C for the study juices. Another explanation is that flavonoids could potentially inhibit dietary vitamin C absorption, although only preclinical evidence exists to substantiate this. The authors also mention that the chemicals they used to analyze serum vitamin C levels may have degraded over the study period.

The study also has several limitations that need to be considered. The chief limitation of this study is that, despite

"[...] the bioactive effects of other flavonoids cannot be dismissed, especially considering that previous trials have noted similar improvements in cognitive performance with fruits rich in other flavonoids, as seen with consumption of a flavanone-rich orange juice."

randomization, the sweet cherry juice group consumed more flavonoids and performed better on the majority of cognitive tasks than the control group at baseline. While this doesn't directly impact changes in cognition test results, it's hard to know if it had any impact.

This study also had a relatively small sample size (n=42) and short timeframe (12 weeks). The former made it difficult to detect a relatively small difference in diastolic blood pressure, so a positive effect of sweet cherry juice on diastolic blood pressure cannot be completely ruled out based on the insignificance of the value that was found. In regard to the latter, a study of longer length is necessary in order to observe if the cognitive improvements are long-lasting or diminish over time, and also to gauge to what extent, if at all, sweet cherry consumption can offset the progression of Alzheimer's disease.

The large and moderate effect sizes for the cognitive tasks assessing verbal learning and memory and executive function suggest that the effects of sweet cherry juice on cognition are clinically relevant. Limitations include a relatively small sample size, a short sample period, and the fact that the sweet cherry juice group consumed more flavonoids and performed better on the majority of cognitive tasks than the control group at baseline.

The big picture

The current study is the first to look at the effect of a flavonoid-rich sweet cherry juice on cognitive function in elderly adults with mild-to-moderate Alzheimer's disease. These findings are in line with previous trials analyzing the effect of other flavonoid-rich foods on cognitive performance.

In addition to the trials mentioned in the introduction on blueberry, concord grape, and orange juice, two other recent studies found that daily consumption of a flavanol-rich cocoa beverage (990 mg flavanol) for eight weeks resulted in a statistically significant improvement in areas of executive function and verbal fluency in older adults that were either healthy or had mild cognitive impairment.

The trials analyzing the acute effects of flavonoid-rich food consumption on cognitive function have mixed results. On the one hand, a recent study found that acute consumption of orange juice (240ml) with an added 5.5 grams of orange pomace (providing 272 mg flavonoids) led to a significant improvement in tasks related to executive function and psychomotor speed in healthy middle-aged males. On the other hand, two other studies — one analyzing both apples and spinach, and the other analyzing the same sweet cherries as the current study — found no improvement in cognitive performance.

While the difference in findings could possibly be attributed to the different fruits used, as each would have a unique flavonoid composition that could affect the body differently, it is more likely the case that it takes an extended period of consumption before fruit flavonoids can significantly benefit cognitive function. In fact, pre-clinical studies have indicated that it may take several weeks before berry flavonoids can accumulate in the brain regions associated with cognition.

The mechanism by which flavonoids may improve cognitive function are still poorly understood. Previous trials have postulated that the improvements in cognitive performance from consuming flavonoid-abundant foods is likely attributed to reduced inflammation. One study specifically found that daily supplementation with 280 grams of sweet cherries decreased various inflammatory markers, including CRP, in healthy adults. The present study, however, found no statistically significant changes in markers of inflammation (CRP or IL-6), suggesting that the benefits of sweet cherry juice may be attributed to a different mechanism, such as protecting neurons against injury from

toxins, improving cerebral blood flow, and activating synaptic signaling. The authors noted it is also possible that the anti-inflammatory effects of sweet cherry juice could have been masked by the progressive nature of the inflammation associated with AD. Accordingly, it is evident that further trials are necessary before we arrive at a solid understanding of the mechanisms by which flavonoids affect cognition.

Previous trials have reported a beneficial effect on cognitive function from long-term consumption of flavonoid-rich foods in older adults that were either healthy or had mild cognitive impairment. The present study extends these findings into older adults with mild-to-moderate dementia. Further trials are necessary, however, in order to elucidate the exact mechanisms by which flavonoids affect cognitive function.

Frequently asked questions

How many sweet cherries would I have to eat to get an equivalent dose of anthocyanins?

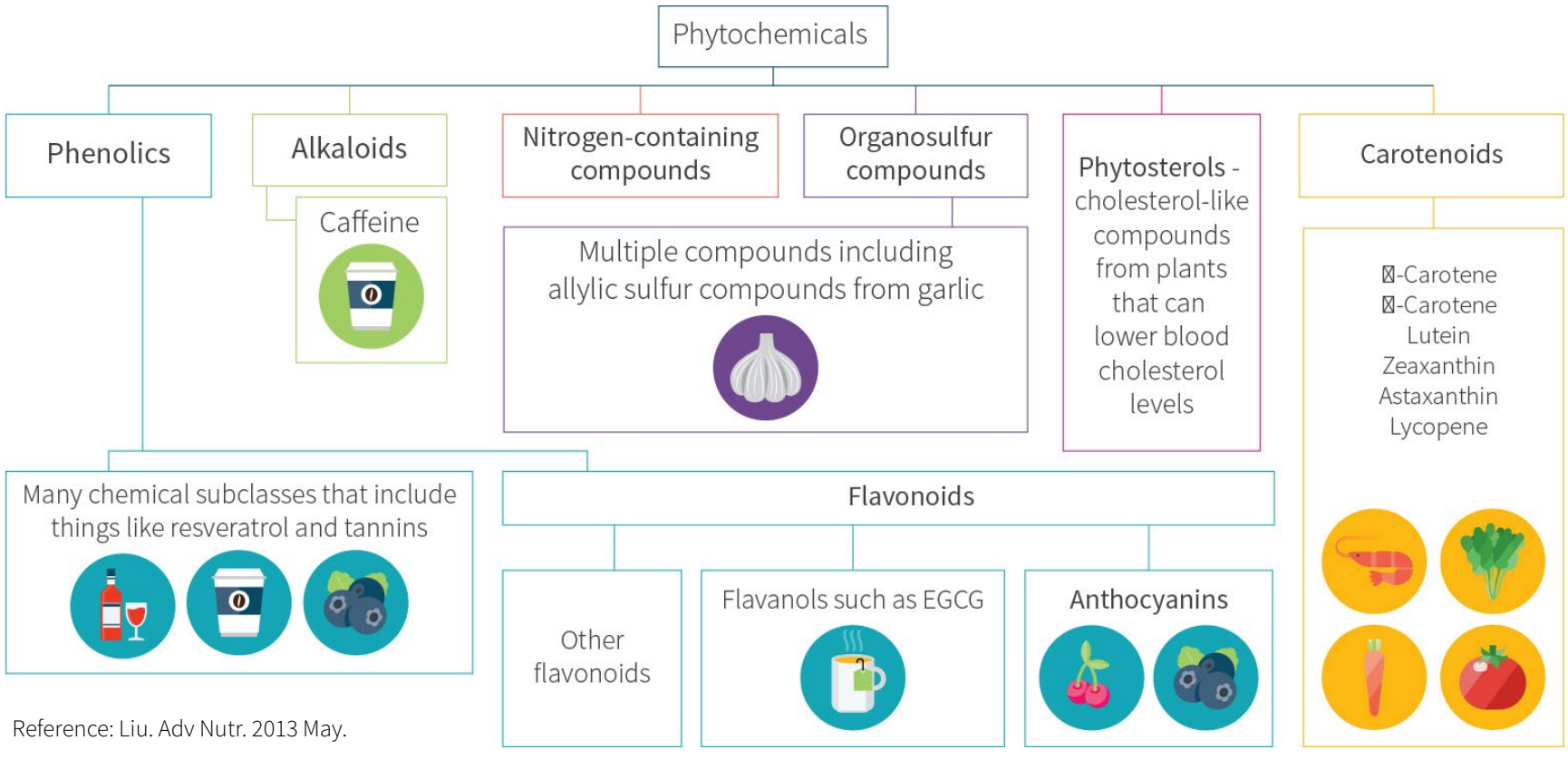
The 200 milliliters of sweet cherry juice used in the study was said to contain 138 milligrams of anthocyanins. According to the USDA, an equivalent dose of anthocyanins can be obtained from eating 113 grams of sweet cherries. For reference, a cup of blueberries weighs about 145 grams.

What is the difference between phytochemicals, flavonoids, and anthocyanins?

Phytochemicals are a group of non-nutritive bioactive compounds generally found in fruits, vegetables, whole grains, nuts, and legumes. Although their mechanisms of action are only partially understood, they are recognized for their health-conferring effects. Over 5000 compounds have been identified, but only a few have been studied extensively. Flavonoids are a type of phytochemical, and anthocyanins are a subtype of flavonoid.

As shown in Figure 2, some of the most well-known phytochemicals are classified into six different categories: phenolics, alkaloids, nitrogen-containing compounds, organosulfur compounds, phytosterols, and carotenoids. Phenolics and carotenoids are the most studied subgroups. Carotenoids include

Figure 2: The relationship between phytochemicals, flavonoids, and anthocyanins



Reference: Liu. Adv Nutr. 2013 May.

beta-carotene (which gives carrots their orange color) and lycopene, which is found primarily in tomatoes. Phenolics have flavonoids as a subclass, and anthocyanins are a subclass of flavonoids.

Each kind of flavonoid has a slight variation in structure, which is responsible for differentiating its mechanism of action in the body, as each molecule has its own specific receptor, quite like a lock and key.

Which foods are rich in anthocyanins?
Fruits and vegetables with a red, blue, or purple color will usually have a notable anthocyanin content. Table 1 below lists fruits and vegetables with the highest anthocyanin content derived from a USDA study.

What should I know?

Daily consumption of sweet cherry juice for twelve weeks, processed in a manner that allowed it to retain a large portion of its flavonoid content, led to improvements in verbal learning and memory as well as executive function in older adults with mild-to-moderate Alzheimer's disease.

These findings corroborate previous trials on other flavonoid-rich foods, further lending credence to the theory that flavonoids have a positive effect on cognitive function, despite their mechanism of action remaining poorly understood. ◆

Hail to the cherry, for it not only tastes good but has measurable health effects. Discuss eating and cognition at the ERD Facebook forum.

Table 1 - Fruits and vegetables with high anthocyanin content

Food	Anthocyanin (mg/100g)
Chokeberry	1480
Elderberry	1375
Black Raspberry	687
Wild Blueberry	486.5
Black Currant	476
Cultivated Blueberry	386.6
Red Cabbage	322
Marion Blackberry	300.5
Blackberry	245
Cranberry	140
Black Plum	124.5
Sweet Cherry	122
Concord Grape	120
Red Radish	100.1

The newest index on the block… the hydration index!

A randomized trial to assess the potential of different beverages to affect hydration status: development of a beverage hydration index

Introduction

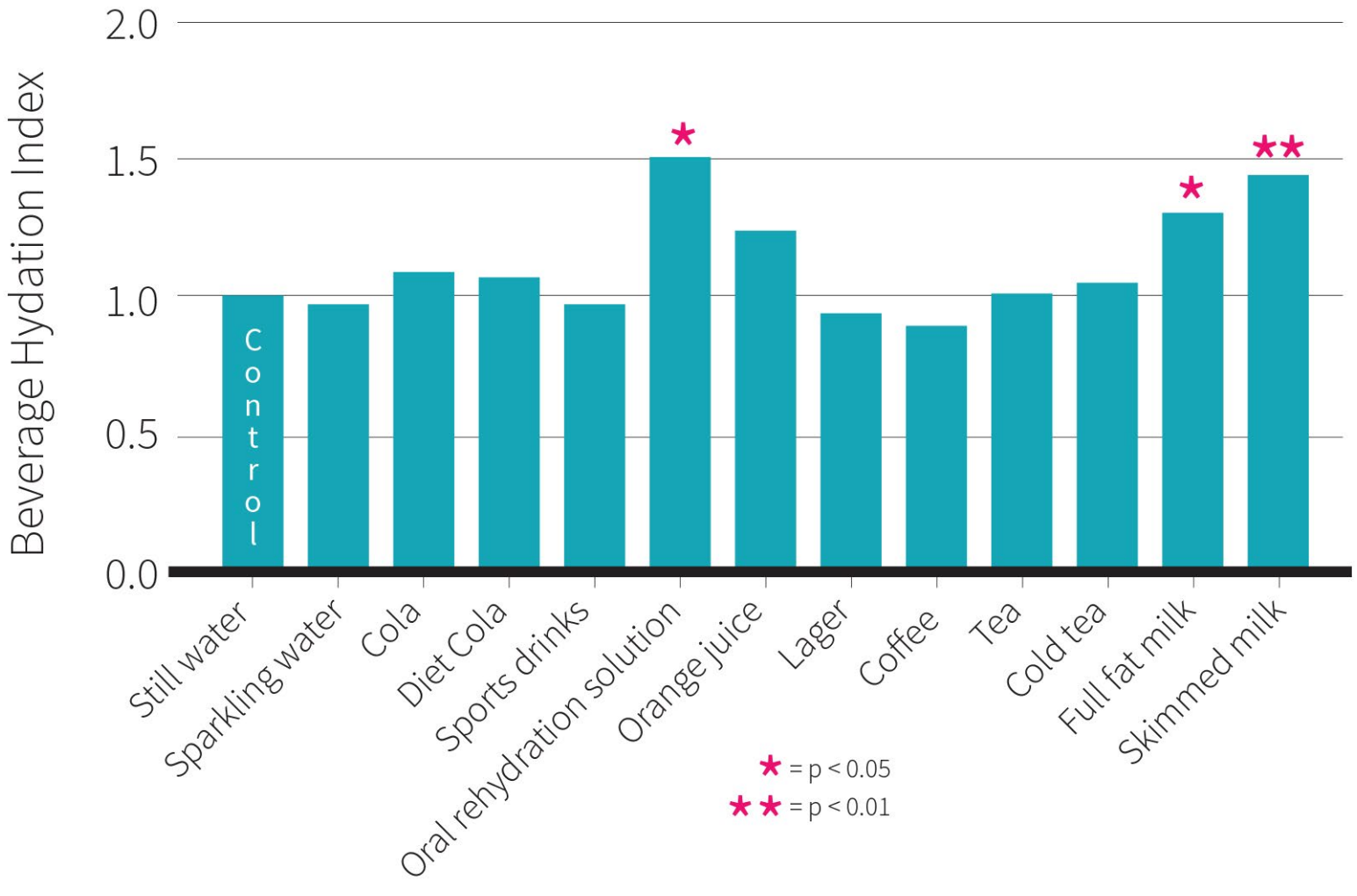
ERD has previously covered the glycemic index and the insulin index, but beverages now also have their own index: namely, the new "hydration index". People usually think about hydration in the context of sports and exercise, so it may be beneficial to know which beverages can best hydrate you when access to fluids (or bathrooms, see Figure 1 for a rough guide to bathroom-guided hydration statuses) is limited.

Not all beverages are created equal from a hydration standpoint. Absorption is affected by the amount of fluid ingested, electrolyte and carbohydrate content, and the presence of diuretic agents (substances that promote urine production). For example, milk has been shown to be more effective than both water and sports drinks for rehydration after strenuous exercise.

The rehydration process is affected both by the volume of fluid ingested as well as the sodium content. It has long been known that the presence of carbohydrates and electrolytes in a drink increase the rate of fluid absorption after drinking. Coffee is often thought of as negatively affecting hydration status, but this is based on studies examining the acute effects of high levels (more than 300 mg) of caffeine on individuals who had been deprived of caffeine for a period of days or weeks. A tolerance to the diuretic actions of caffeine develops with regular intake, and the amounts of caffeine found in normal sized servings of tea, coffee, soda, etc., do not have diuretic effects.

This study is the first to develop a method for systematically quantifying values for hydration and fluid balance. Similar to how the glycemic index is intended to define the blood glucose response to the ingestion of foods compared to a white bread or glucose standard, a beverage hydration index (BHI) could serve to quantify water excretion from the kidneys in response to various beverages compared with still water. The cumulative

Figure 1: BHI for tested drinks



Reference: Maughan et al. Am J Clin Nutr. 2015 Dec.

volume of urine passed over a fixed period of time can be measured as a marker of fluid absorption and retention. The aim of this new study was to determine the fluid balance responses to the ingestion of a set amount of commonly consumed beverages ingested in a euhydrated state (a normal fluid balance).

The volume and amount of electrolytes and sugars of ingested fluids affect their absorption and retention, but various beverages have yet to be systematically compared. This study set out to determine if a beverage hydration index, similar in principle to the glycemic index, could be established.

Who and what was studied?

This study recruited 72 recreationally active, healthy male participants between the ages of 18-35. A large number of participants were needed due to the study design, which tested 13 different beverages. Each participant completed a maximum of four experimental trials that included water along with three other test drinks. Participants recorded their diet and exercise during the two days before the first trial and were asked to replicate it before their subsequent visits. They were also asked to avoid strenuous exercise and alcohol in the 24 hours preceding all trials.

Participants consumed 500 milliliters of still water over the course of 15 minutes, one hour before arriving at the laboratory. This is potentially problematic because they were self-guided, so compliance could have been poor. After using the bathroom and performing baseline bodyweight measurements at the lab, participants ingested one liter of the assigned test drink over a 30-minute period (four equal servings administered 7.5 minutes apart). They were then asked to empty their bladder at the end of the drinking period and again at the end of each hour for the next four hours.

The following drinks were tested:

- Still water - Sparkling water - Coca-Cola - Diet Coke
- Sports drink (Powerade) - Oral rehydration solution (Dioralyte) - Orange juice
- Lager beer (Carlton) - Hot black coffee - Hot black tea - Cold black tea
- Full-fat milk - Skim milk

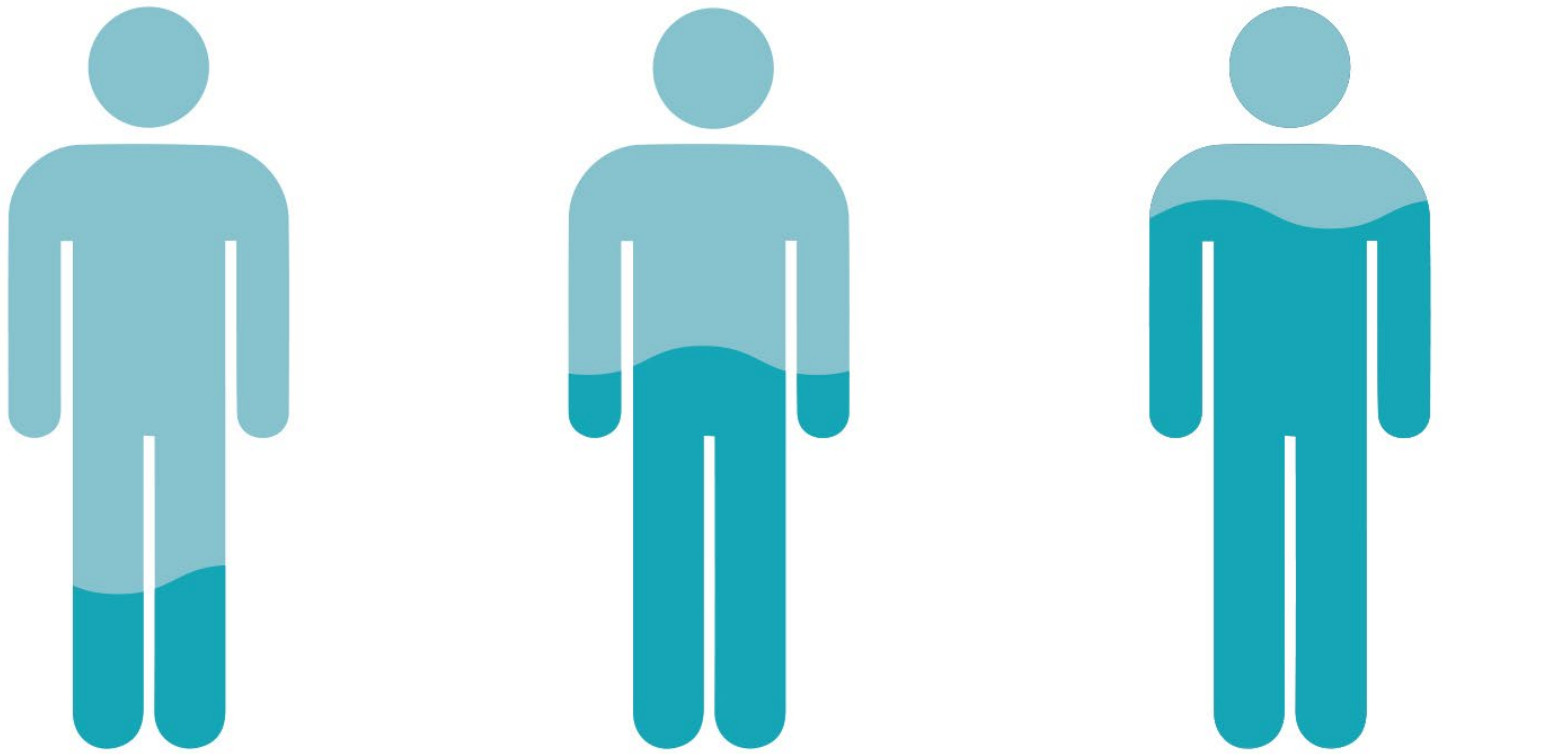
Even though a set volume of each beverage was consumed, the presence of other components (e.g. fat, carbohydrate, protein) means that the actual water content of the drinks was between 88-100%. Results are presented both corrected and uncorrected for the differences in water content, as practical use would dictate the uncorrected values.

The main outcome measure was the amount of urine passed after ingestion of a given beverage. A beverage hydration index (BHI, as shown in Figure 2) was estab-

> “[...] milk has been shown to be more effective than both water and sports drinks for rehydration after strenuous exercise.”

Figure 2: BHI calculation

$$\text{Beverage Hydration Index} = \frac{\text{Urine mass post water consumption (control)}}{\text{Urine mass post test beverage (intervention)}}$$



Low BHI = lesser water retention

Control (water)

High BHI = greater water retention

lished by dividing the urine mass after consuming still water by the urine mass for each test beverage. A high BHI means more water is retained in the body than if the drinker had drank an equal volume of still water.

This study examined the effects of 13 different beverages on urine output in order to establish a beverage hydration index. This index was based on the amount of urine produced after drinking each beverage compared with the amount produced after drinking still water.

What were the findings?

Urine output from ingestion of full-fat milk, skim milk, and the oral rehydration solution was lower than that from ingestion of still water, translating to a higher hydration index. Interestingly, orange juice showed a statistically significant reduction in urine output between the second and third hour, but was no longer statistically different at the end of the four hour collection period. The average differences in cumulative urine output compared with still water were 294 grams for full-fat milk, 339 grams for skimmed milk, and 362 grams for the oral rehydration solution, which amounts to an approximately 25% decrease in urine output compared to still water.

To establish a beverage hydration index (BHI), still water was used as a control and is thus assigned a value of 1.0. Since the water content of the drinks varied from 88-100%, the BHI was calculated with and without an adjustment for the amount of water ingested from each drink. These results are shown in Figure 3. Using unadjusted values, a hydration index that was higher than water was observed for full-fat milk (1.50), skim milk (1.58), oral rehydration solution (1.54), and orange juice (1.39). However, after adjustment for water content only full-fat milk (1.32), skim milk (1.44), and oral rehydration solution (1.50) were significantly different from water. None of the beverages tested (including coffee) had a significantly lower hydration index than water.

Figure 3: Am I hydrated? A urine color chart

The electrolyte content of each beverage was also measured. The three drinks that provided the greatest degree of hydration (both types of milk and the rehydration solution) also had the greatest levels of electrolytes (sodium and potassium).

Urine output over four hours was lower after drinking full-fat milk, skim milk, or an oral rehydration solution, compared with drinking the same amount of water. There were no differences in urine output after ingestion of cola, diet cola, hot tea, iced tea, coffee, lager, orange juice, sparkling water, or sports drink, compared with still water.

What does the study really tell us?

This study takes the important first step toward establishing a beverage hydration index, which can be used to compare the short-term hydration potential of different beverages. This can serve a similar purpose as the glycemic index and insulin index: a way to compare how different liquids get processed and absorbed by our bodies. Note that hydration prior to the test was controlled for, so participants were in a euhydrated state. It is possible that there would be some different results in the rehydration potential if participants had been dehydrated, like after exercise or an overnight fast, for example.

The water content of the test beverages ranged from 100% (still water) to 88% (full-fat milk), but participants consumed exactly one liter of each. This is why the researchers reported the BHI both unadjusted and adjusted for water intake. The adjustment made very little difference: orange juice was on the fence of statistical significance, with only unadjusted values being significantly different from water.

This is the first study to establish an index for short term-hydration. It measured urine output in euhydrated individuals, so applicability to other situations, like after exercise, is unknown.

The big picture

Classifying beverages according to their ability to hydrate can serve a number of purposes. Beverages that promote fluid retention may be beneficial in situations where there is limited access to fluids, or when frequent bathroom breaks would be undesirable. The researchers that conducted the study under review are very experienced in the world of hydration research, so it's appropriate that they are creating a novel BHI. Incidentally, one of the co-authors also conducted a study on carb intakes that was covered in ERD #10.

Fluid absorption is affected by a number of factors,

including electrolyte content (mainly sodium and potassium) and glucose content. The BHI can recognize and quantify the effect that these various factors may have on an individual's hydration status. The results of this study are in line with previous research in the area. The drinks with the highest BHI also had the highest electrolyte content. Acute ingestion of a high-sodium beverage has been shown to result in an increase in total body water. People often associate sports drinks with having a high electrolyte content, but in reality it contains less sodium than milk, and less potassium than seven of the other tested beverages, including tea and coffee, making its total electrolyte content quite low. Previous research has also shown that milk, and milk with added sodium are both more effective for rehydration (as measured by cumulative urine output) than either water or a sports drink.

In contrast to the enhancement of fluid absorption by electrolytes are the known diuretic effects of caffeine and alcohol, which act by inhibiting arginine vasopressin (also called anti-diuretic hormone). No effect from the caffeine was observed from any of the drinks in this study, which ranged from 96-212 milligrams. A measurable effect on urine output would typically require over 300 milligrams of caffeine, while the coffee used in this study was reported as having a caffeine content of 212 milligrams per liter. Although this is on the low side for coffee (which would be expected to range from 250-1000 milligrams per liter), the researchers performed their own analysis using HPLC to get this value. The alcohol content in one liter of lager beer also did not increase urine output in this study. A previous study looking at fluid balance in response to alcohol in both euhydrated and hypohydrated states found an increased urine output after alcohol ingestion when euhydrated, but no differences when hypohydrated.

While the urine output of each participant was collected for four hours, the BHI values were based on the net fluid balance after two hours. The researchers stated a number of reasons for this decision. The majority (82%) of urine output over the four-hour period was collected after two hours, most people would typically not go longer than two hours without access to fluids, and differences between beverages are evident by two hours. Also, they report that there was very little difference in the calculated BHI whether it was based on the first two hours or the entire four-hour period. With that said, it does seem a bit strange that they would ignore half of their data points, particularly in light of the fact that the original description of the trial states that they would calculate the BHI at each hour over the four hours.

Other considerations with this type of research include gender differences. The diuretic response to a water load can be greater in women than men, suggesting that women turn water over more quickly than men. Determining if the measured BHI values would be the same for women requires further research.

A variety of factors can influence fluid absorption. Electrolyte content is a primary factor, and the presence of electrolytes in beverages such as milk explains their higher hydration index score, even compared to sports drinks that are marketed for hydration purposes. Due to potential sex differences in fluid balance, further research in women would be helpful.

Frequently asked questions

Would the results of this study (done over a four-hour window) hold true over a 24-hour time period?

Possibly. A previous study that had participants consume water or various combinations of caffeinated or non-caffeinated beverages (sodas and coffee) found no significant differences on 24-hour hydration status. Neither milk nor an oral rehydration drink was included in that study, however. Additionally, a 2015 study found no differences in 24-hour hydration when consuming various combinations of water, cola, and orange

juice. It is unclear what the effect of hydrating only with milk or the oral rehydration drink throughout an entire day would be, but that situation is also quite unrealistic.

What effects would protein, fat, and carbohydrate content of a drink have on BHI?

Very little fluid absorption takes place in the stomach, so the ingested fluid needs to empty into the small intestine before it can be absorbed. Solutions that include carbohydrates at a concentration of 1-4% can be absorbed faster, but higher concentrations than that could impair absorption. There are a number of moving parts to this mechanism, however, as evidenced by the fact that there were no differences in BHI for regular or diet cola. It is also known that fat and protein can delay gastric emptying time, and could potentially have an effect on BHI.

Would the temperature of a drink affect BHI?

Not likely, based on the results of this study that showed no differences in BHI between cold and hot tea. Although people often claim that certain temperatures are better for fluid absorption, there are likely no differences.

What should I know?

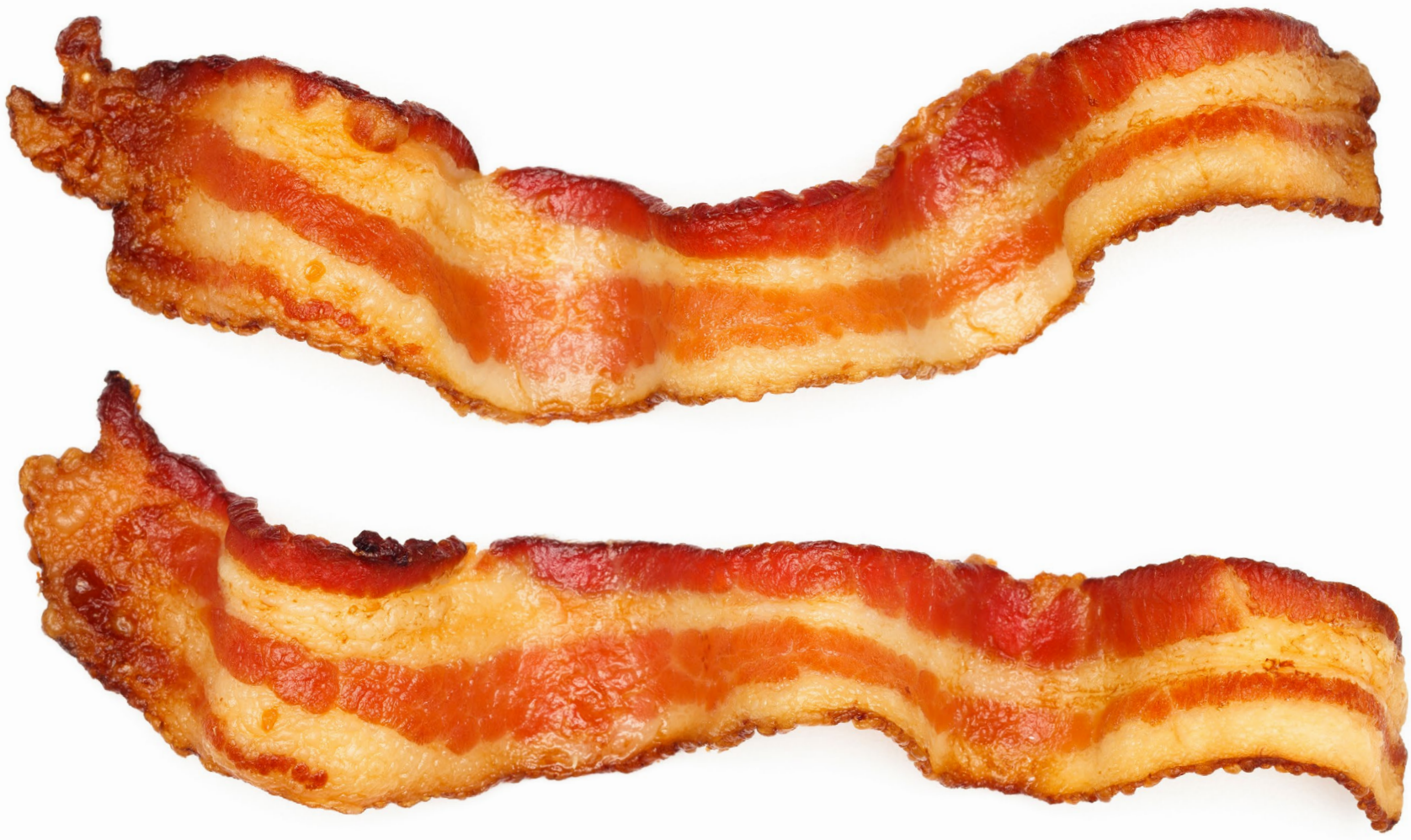
This study established a new method for quantifying the effect of various beverages on hydration. No differences were found compared to water after ingestion of cola, diet cola, hot tea, iced tea, coffee, lager, orange juice, sparkling water, or a sports drink. Only full-fat milk, skim milk, and an oral rehydration solution led to a reduced urine output after drinking one liter, compared with drinking the same amount of still water. The hydration index established by this study may be useful in situations with limited access to fluids or bathroom breaks. ◆

Now that liquids have their own index, how and where will the index be used? Talk about this study, hydration, and your favorite beverages at the ERD Facebook forum.

> “The diuretic response to a water load can be greater in women than men, suggesting that women turn water over more quickly than men.”

Carbs-protein or protein-carbs … does food order matter?

Food Order Has a Significant Impact on Postprandial Glucose and Insulin Levels



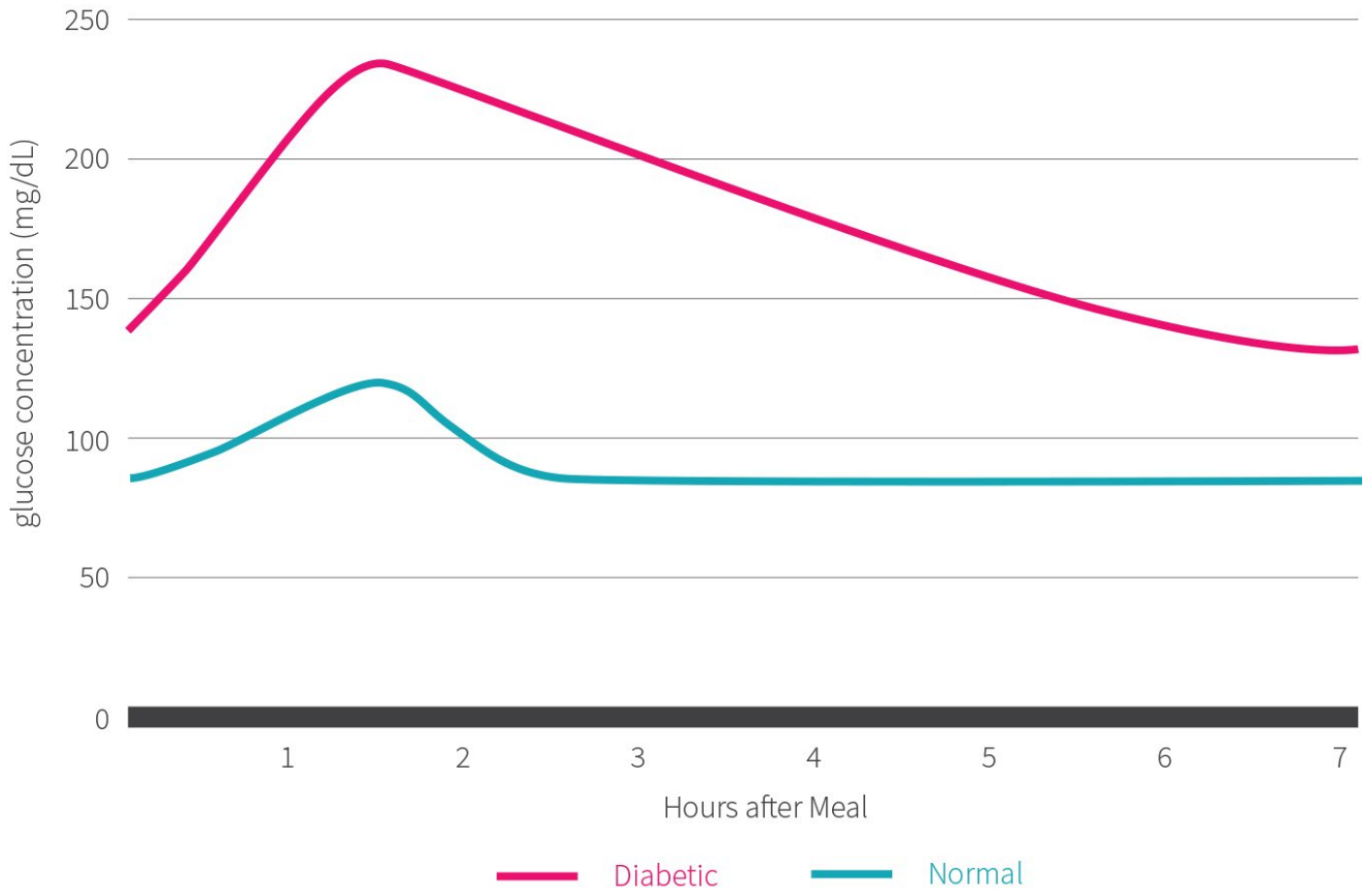
Introduction

The glycemic index gets a lot of attention. However, as you may have learned in ERD #4, this focus may be potentially overrated as a tool for managing blood sugar levels. In its position statement on dietary carbohydrate and the prevention and management of type 2 diabetes, the American Diabetes Association (ADA) emphasizes that the amount of *total carbohydrate* in a meal is one of the strongest predictors of the blood glucose response. This is correct, but ignores the non-negligible influence of food order on the blood glucose response to meals.

Postprandial hyperglycemia refers to a state after consuming a meal in which blood glucose levels elevate beyond a healthy range. Normal blood sugar values after eating are between 120-140 mg/dl. For people with diabetes, the ADA recommends keeping postprandial glucose levels below 180 mg/dL, since those with diabetes can experience much higher than normal levels after eating (as shown in Figure 1). Observational as well as interventional studies have shown that postprandial hyperglycemia, yet not high fasting glucose levels, is an independent risk factor for vascular diseases, due in part to increased oxidative stress. Interestingly, even in people with normal glucose tolerance, having glucose levels greater than 155 mg/dL one hour after eating is correlated with an increased risk for nonalcoholic fatty liver disease as well as having early atherosclerosis.

Against that background, it is all the more important to know that the GI is not very useful in making food choices because it's typically used for individual foods and not meals, and thus ignores the significant effect of fat and protein from mixed meals on postprandial glucose. It is well established that fiber, fat, and protein will all slow down gastric emptying and thus delay the rise in blood sugar following a meal. What has been missing, though, is data regarding the effect of food order on postprandial blood sugar responses in people with type 2 diabetes. This pilot study measured the effects of varying food order on the glucose and insulin responses to a meal in overweight and obese adults with type 2 diabetes.

Figure 1: How diabetics and nondiabetics respond to a meal



The macronutrient content can change the way carbohydrates are absorbed by affecting the digestion process. This suggests the order in which macronutrients are consumed during a meal may affect blood sugar levels. This study explored this possibility as it applies to diabetic people.

Who and what was studied?

This cross-over design pilot study recruited eleven participants (six female), all of whom had type 2 diabetes and were being treated with metformin, a widely-used diabetes drug that reduces the amount of glucose produced by the liver and may improve insulin sensitivity. Participants were an average of 54 years old with a BMI of 32.9 (BMI of greater than 30 classifies someone as 'obese'). They had been diagnosed with type-2 diabetes for an average of 4.8 years and had a mean HbA_{1c} score of 6.5% (which is very good for a person with diabetes). HbA1c is a marker for long-term blood glucose control. Current guidelines for people with diabetes recommend maintaining levels at or below 7.0%.

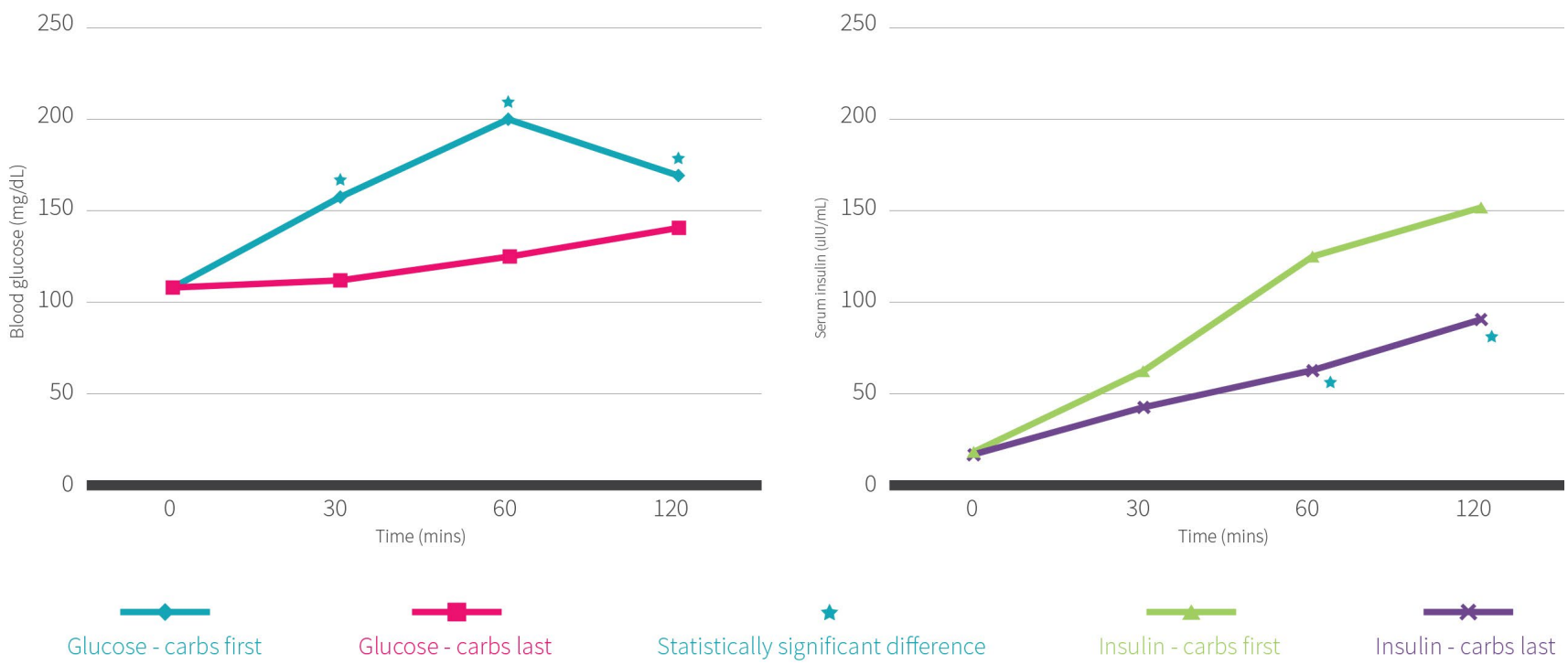
On two separate occasions (one week apart) participants visited the lab after an overnight fast and consumed a 628 kcal meal (35% protein, 43% carb, 22% fat). On the first visit, the carbohydrates were consumed first (ciabatta bread and orange juice), followed by a 15 minute break, after which the participants ate grilled chicken breast, salad, and broccoli with butter. The order of the food was reversed on the second visit. Blood samples were taken to measure the participants' glucose and insulin levels just prior to meal ingestion, as well as 30, 60, and 120 minutes after starting the meal.

Eleven people with diabetes being treated with metformin were randomized to be given a meal either with carbs first followed by protein and vegetables or vice versa. Their blood sugar was measured before and after the meal. One week later, the food order was reversed and blood sugar was measured again.

What were the findings?

The order in which the food was consumed had significant effects on blood glucose and insulin levels. The results are summarized in Figure 2. In line with what the scientists had expected, the mean glucose levels after eating decreased by 28.6% (30 min.), 36.7% (60 min.), and 16.8% (120 min.) when protein and vegetables were consumed first.

Figure 2: Mean values of blood glucose and insulin



Additionally, the glucose incremental area under the curve (iAUC, a way to quantify the total amount of glucose absorbed) was 74% lower after 120 minutes when protein and veggies were consumed first, compared with when the carbs were consumed first.

Post-meal insulin levels were decreased by 49.6% (60 min.) and 40.2% (120 min.) and the insulin iAUC was 49% lower after 120 minutes on the trial in which protein and vegetables were consumed first, compared to the trial in which the opposite order of carbohydrates, proteins, and vegetables was used.

Notably, measurements ceased at the 120 minute mark, while both glucose and insulin were still elevated above their baseline levels. This means that we are getting an incomplete picture for the glucose and insulin curves as well as the total area under the curves. It is possible the total AUC would have evened out to a degree between the groups (meaning they absorbed a similar amount of glucose), even though the shape of the curves look different. This is something the authors have acknowledged, and provides a great example of why a smaller pilot study is done before doing a larger and more expensive full study.

Blood sugar levels were lower after meals that started with protein and veggies before carbs, compared to eating carbs first. Post-meal insulin release was also decreased when the carbs were eaten last.

By eating the carbs at the end of the meal, participants with diabetes were able to maintain their blood glucose levels below 141 mg/dL. This is not only well below the previously mentioned upper guideline of 180 mg/dL suggested by the ADA, but also below the levels associated with a plethora of health problems (155 mg/dL). In contrast, when these same participants consumed the carbs first, their blood sugar peaked at 199 mg/dL and stayed above 155 for over 90 minutes!

It is very important to note, however, that there was a 15 minute break between the carbohydrate portion of the meal and the rest of the food. The authors used a 15 minute break to allow the food to pass through the very first steps of the digestive process and thus stimulate the release of gut hormones that may impact glucose regulation. It is unfortunate that this study did not also include a group that ate the whole meal all at once, for comparison. While most people aren't going to wait 15 minutes to have their breadsticks, real life implications could mean that saving carbs for dessert may be an effective strategy to maintain healthy blood glucose levels.

This pilot study suggests that further research in larger populations would be useful in determining if altering food order would be helpful in managing blood sugar in people not on metformin. Also, the large time gap between eating the two parts of the meal may limit the practicality of these results.

What does the study really tell us?

This pilot study shows that the timing of carbohydrate intake, before or after eating protein and vegetables, has significant effects on postprandial insulin and glucose responses in people with type 2 diabetes who are being treated with metformin. Eating carbs at the end of a meal could be a very effective way to improve glycemic controls in people with diabetes.

The big picture

The improvements in post-meal blood sugar control between these two treatments rival or exceed those seen with add-on drug therapies aimed at regulating postprandial glucose levels. The idea of consuming protein and vegetables before carbohydrates during a meal represents a simple approach to managing blood sugar in people with diabetes.

No attempt was made to examine the mechanisms of action in this study, but there are several possible reasons for improvements in glucose response when protein and vegetables are followed by carbs (some of which are depicted in Figure 3). These include a reduced transit time due to high amount of fibers in the vegetable part of the meal, as well as additional stimulation of incretin hormones, which can stimulate insulin release, suppress glucagon secretion, and inhibit gastric emptying. Cholecystokinin is one such hormone that could be involved in these beneficial effects. The release of cholecystokinin from the small intestine results in delayed gastric emptying and reduced glycemic increase.

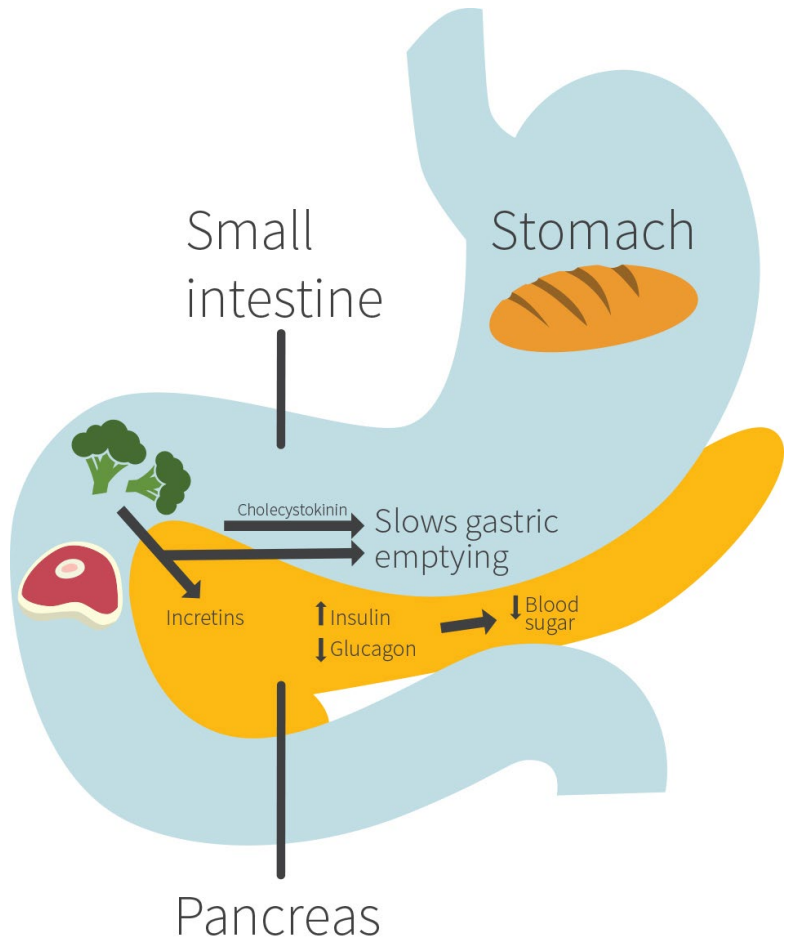
There is also a direct relationship between satiety and cholecystokinin release. Put simply, when you eat carbs first, they're near the pylorus (the part of the stomach that connects to the small intestine) and they exit first. When you eat carbs last they're on top of a bunch of other food, and partially mixed with other food, and thus exit the stomach more gradually.

It is not easy to contextualize these results due to the limited research on the effects of food order on blood sugar management. One of the few pertinent studies evaluated the blood glucose and insulin response of 15 Japanese participants with type 2 diabetes who ate either carbohydrate (rice) before vegetables or vice-versa for four weeks. The researchers found that the consumption of vegetables before rice was able to successfully reduce postprandial glucose and insulin levels. The same paper reported a larger and longer-term study where one group of diabetics (n=196) received instruction to consume their veggies before carbs while the diabetic control group (n=137) simply continued their regular doctor visits. This long-term study (30 months) was able to confirm that a long-term change in food order will also affect the overall, not just the acute, blood glucose management, as is suggested by significant decreases in HbA1c in the group of participants who ate the vegetable content of their meals before the rice.

At least acutely, a bolus of whey protein consumed prior to a complex meal can can have a similar beneficial effect on the postprandial glucose levels of people with type II diabetes. As previously hinted at, this beneficial effect is paid for with a significant increase in insulin. Despite the decrease in gastric emptying and the area under the glucose curve, whey does not trigger the same acute increase in insulin sensitivity the scientists observed for the vegetable and protein preload in the study under review.

The effects of food order can extend beyond blood sugar control. A 2013 study of 60 overweight and obese men and women compared the effects of consuming a 150 kcal pre-load of salad, yogurt, and water 15 minutes before eating lunch and dinner while on a hypocaloric diet for three months. Although both groups were instructed to follow a similar caloric deficit, the group eating the pre-load consumed fewer total calories and had greater decreases in body weight, waist circumference, triglyceride, total cholesterol and systolic blood pressure.

Figure 3: Possible mechanism for why carbs-last lowers blood sugar



Plausible mechanisms exist for the effect of meal timing on postprandial glucose and insulin release. The results of this study seem to be in line with the limited previous research on the matter.

Frequently asked questions

Do I need to wait 15 minutes before eating the carbohydrate portion of my meal?

This study did use a fairly unrealistic period of time between sections of the meal in order to magnify any effects that may be seen with changing food order. It is still possible that beneficial effects would be seen with shorter time gaps within the meal. There may also be an interaction between the amount of fiber in the first portion and the length of the delay, but further research is needed to investigate this hypothesis. What we can say with some certainty, though, is that shorter time intervals will probably reduce the effect sizes.

Would these results be similar in people without diabetes?

While the differences may not be as pronounced in healthy people, it is possible that differences would still be observed. A previous study using a slightly different protocol measured the postprandial responses of vegetables before carbs (and vice-versa) in people with type 2 diabetes and people with normal glucose tolerance, and reported similar improvements in postprandial glucose and insulin levels in both diabetic and non-diabetic subjects.

What should I know?

Traditional diabetes counseling focuses on carb counting. The idea of consuming food in a particular order represents a fairly novel approach to balancing blood sugar. More specifically, this pilot study showed statistically significant and practically relevant improvements in both blood sugar and insulin levels when the carbohydrate portion of the meal was consumed 15 minutes after the protein and vegetable content.

Postprandial blood glucose values peaked at 199 mg/dL when carbs were consumed first, as opposed to 141 mg/dL when the same amount of carbs were consumed last. In addition, the overall blood glucose response was 74% lower and the insulin response 49% lower (measured by area under the curve for 120 minutes after eating) when carbs were consumed at the end of the meal. Altering food order still hasn't been thoroughly tested in many large trials, but it appears to be a simple and safe option for blood sugar control in diabetic (and likely non-diabetic) populations. ◆

To get the most out of a nutrition discussion, try altering the typical order many people employ: FIRST read an in-depth analysis of a topic, and THEN discuss the topic after you're armed with knowledge … perhaps in the ERD Facebook forum.

In closing...

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