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Research Digest

Stephan Guyenet ◆ 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.

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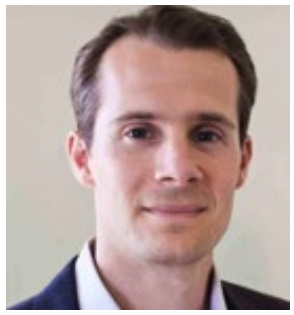

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Something fishy: How a component of fish oil may counteract the effects of some chemotherapy

Increased Plasma Levels of Chemoresistance-Inducing Fatty Acid 16:4(n-3) After Consumption of Fish and Fish Oil

Introduction

Cancer is an incredibly broad group of diseases characterized by similar features, the most notable being uncontrolled cell growth. Although researchers have made great strides in understanding the molecular mechanisms behind various cancers, they are still working on creating effective therapies that specifically target these mechanisms. This means that many therapies rely on relatively old-fashioned treatments: chemo or radiation, which kill the tumor cells faster or more effectively than they kill normal cells. As might be expected from such harsh therapies for such serious diseases, many of these cancer therapies are associated with severe side effects.

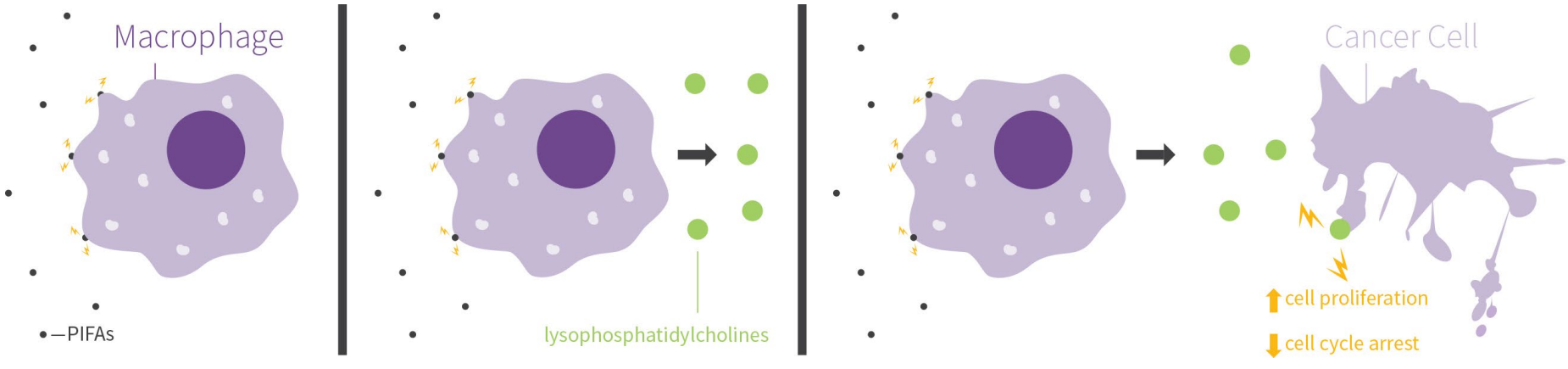
To address these side effects (and possibly as a result of newfound interest in their health), many patients turn to dietary remedies, including a variety of supplements. Fish oil is one of the most popular choices, and it is used by an estimated 20% of cancer patients. However, relatively little work has been done to assess fish oil's interactions with common cancer treatments like chemotherapy.

Fish oil is a common supplement, but its sources and processing can vary greatly. It can come from any oily fish, including eel, herring, and mackerel. The specific fatty acids components in fish oil can vary, depending on the species and diet of the source fish. Since the benefits of fish oil supplementation and oily fish consumption have been widely researched for decades, scientists are now beginning to assess the components of fish oil in more detail, especially as they pertain to specific populations or interactions with medications.

The group who conducted this study was the first group to identify certain fatty acids called platinum-induced fatty acids (PIFAs) that can induce resistance to chemotherapy in mice. Specifically, they identified 12S-HHT and 16:4(n-3) as two fatty acids that can cause resistance to chemotherapy by altering DNA damage repair mechanisms. Figure 1 depicts how PIFAs may interact with macrophages to ultimately induce some level of chemoresistance. This study is a follow-up to the previous mouse-based report and aims to examine the fish oil supplementation habits of cancer patients, as well as further clarify the effects of fish oil supplementation on chemotherapy resistance.

Fish oil supplementation is relatively common in cancer patients. The researchers conducting this study recently identified certain components of fish oil (especially platinum-induced fatty acid 16:4) that can promote chemotherapy resistance in mice, so they sought to understand whether these effects could also be seen in human tumors.

Figure 1: Possible mechanism for PIFA-induced chemoresistance



Reference: Houthuijzen et al. Nat Commun. 2014 Nov.

How fatty acids are named

BASIC FATTY ACID STRUCTURE

Fatty acids are primarily long chains of carbon and hydrogen atoms strung together at the end of a carboxyl group (COOH), which is why they are called "acids." The first level of complexity among fatty acids is their differences in length. This is what researchers are referencing when they discuss short-chain and medium-chain fatty acids.

GETTING TURNED AROUND

The second level of complexity among fatty acids is the introduction of double bonds between carbon atoms, which produces a "kink" in the fatty acid chain. Saturated fats don't have any double bonds, monounsaturated fats have one, and polyunsaturated fats have many. An "omega-3 fatty acid" or "n-3" is a fatty acid with a double bond on the third carbon of the chain.

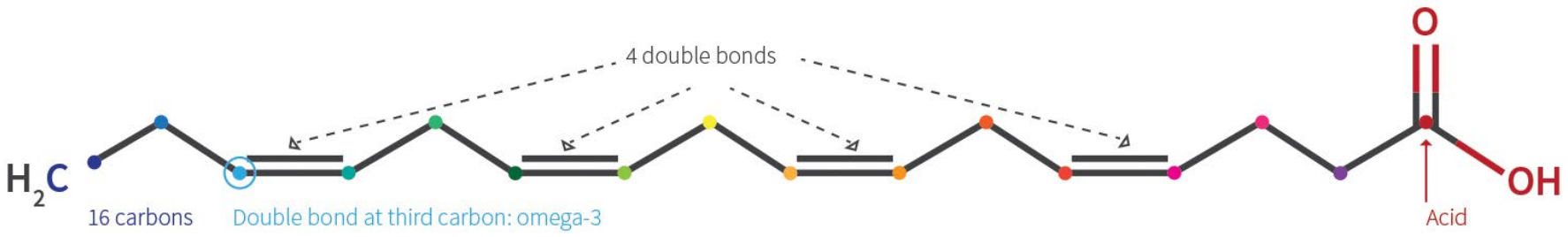
A NUMBERS GAME

The naming system described above is common, but many scientists rely on a more complete lipid number naming convention. For example, the fatty acid discussed in this paper, 16:4(n-3), is a 16-carbon fatty acid chain with four double bonds and a double bond at the third carbon (making it a type of omega-3 fatty acid). A depiction is shown in Figure 2.

GETTING CONFUSED

Aside from the lipid number system, there are also systematic names, which follow organic chemistry naming conventions and turn out tongue-twisters like hexadeca-4,7,10,13-tetraenoic acid, which is the chemical name for the 16:4(n-3) acid mentioned above. Then there's the "trivial" naming system that follows historical names. For example "arachidonic acid" is widely used but doesn't actually describe any of the features of the fatty acid.

Figure 2: 16:4(n-3) fatty acid



Who and what was studied?

The design of this study is somewhat different than most clinical studies because it assesses supplementation habits that could negatively affect life-saving therapies. It would be incredibly unethical to treat chemotherapy patients with fish oil and assess whether or not their disease progressed, so instead, the study authors assessed many of the most important aspects of fish oil's interaction with chemotherapy without actually conducting a clinical trial.

As a first step, the investigators tried to understand whether consuming fish oil or fatty fish actually increased PIFA levels in healthy volunteers. Thirty healthy volunteers who had not recently consumed fatty fish or fish oil were given either 10 or 50 milliliters of fish oil from one of three different brands of commercially available fish oil (six in each group). Twenty other healthy volunteers were fed 100 grams of either tuna (a relatively lean fish that served as a sort of control), salmon, smoked mackerel, or cured herring (five participants in each group). Blood was collected from all participants before consumption as well as 1, 2, 4, 6, 8, and 24 hours after consumption of the fish oil or fish.

All of the supplements were also analyzed separately for PIFA content.

To assess whether PIFAs could induce chemoresistance in human cancers, the researchers used a mouse cancer model in which colon cancer cells are implanted under the skin of the mice, so that the researchers can study the growth of the tumors. Once the tumors reached a certain size, the researchers treated the mice with a variety of chemotherapies, as well as a variety of PIFA sources. These mice were either studied for tumor growth over time or for pharmacodynamic studies of the levels of chemotherapeutic and PIFA over time. Similarly, the tumor-bearing mice were also treated with purified eicosapentaenoic acid (EPA) to assess whether mice can convert EPA into PIFAs and whether those resultant PIFAs affected chemotherapy resistance.

Finally, to understand how patients actually use fish oil, the researchers conducted a survey of over 400 patients, to which only 118 patients responded. The questionnaire assessed whether or not patients used nutritional supplements, which they used, and whether or not they reported that use to their doctors.

It is difficult to study supplements that may minimize the effectiveness of lifesaving therapies. To do so, the researchers studied whether fish oil or fish consumption translated into increases in blood PIFA content in healthy volunteers, whether PIFA ingestion induces chemoresistance in a mouse model of tumor growth, and whether or not cancer patients use fish oil supplements.

What were the findings?

The researchers found significant levels of 16:4(n-3) fatty acids in all of the commercial fish oils they tested, so they chose to focus the rest of their studies on that specific fatty acid. In the mouse study, chemotherapy

> “[...] the addition of purified 16:4(n-3) caused the tumors to grow at a rate comparable to that of tumors from mice not treated with chemotherapy at all.”

controls effectively reduced cancer growth, but the addition of purified 16:4(n-3) caused the tumors to grow at a rate comparable to that of tumors from mice not treated with chemotherapy at all. This effect was also seen when mice were treated with fish oil in doses equivalent to about three milliliters, or roughly 2.5 grams, for a human. This is about double the dosage recommended by the American Heart Association, although even larger doses are often taken.

To assess the levels of fish oil required to induce chemoresistance, the researchers administered 100, 10, 1, and 0.1 microliters of fish oil to mice and assessed tumor

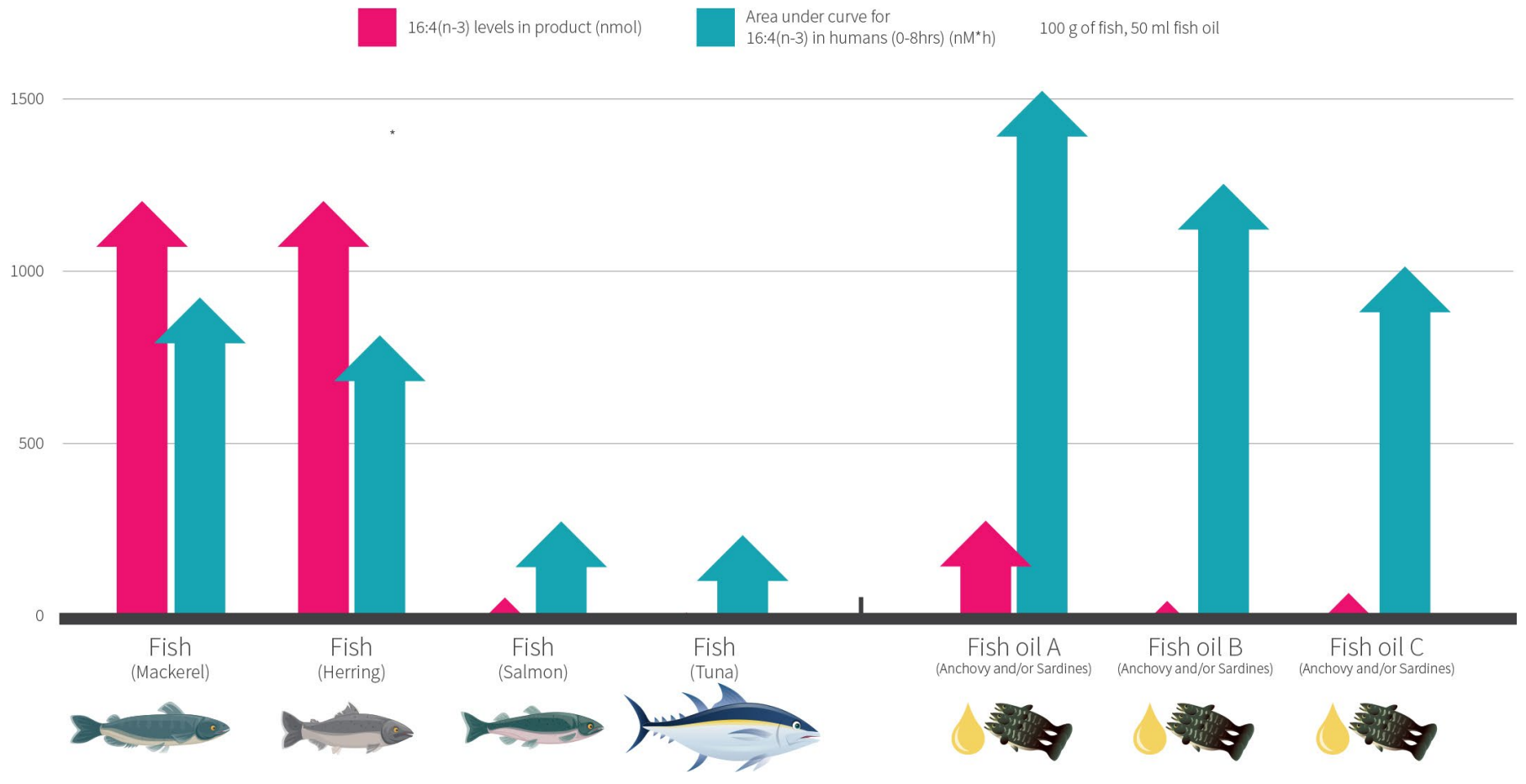
growth. Fish oil supplementation as low as one microliter (again, equivalent to about a three milliliter dose for humans) showed a significant reduction in chemotherapy effectiveness. Finally, when the researchers administered EPA to mice with tumors and assessed both their serum 16:4(n-3) content as well as its ability to induce chemoresistance, they found both elevated 16:4(n-3) and tumor sizes similar to untreated tumors in mice that received EPA.

In healthy volunteers, fish oil administration increased 16:4(n-3) levels in participant blood samples for up to eight hours. It may have increased these levels for even longer in some cases, but the trial only evaluated up to eight hours. In the fish studies, participants who ate mackerel or herring had increased levels of 16:4(n-3), whereas participants who ate salmon had lower levels, and participants who ate tuna had levels similar to baseline. As seen in Figure 3, fish oil increased human blood levels of 16:4(n-3) to a greater degree than did fish, relative to the amount that existed in the fish or oil itself.

The patient questionnaire revealed that 30% of patients regularly used nutritional supplements, and 11% regularly used fish oil or other supplements containing omega-3 fatty acids. Eleven of the 13 patients (85%) who regularly used these supplements continued to use them during therapy, but only six of them (55%) reported their supplementation habits to their doctors.

Fish oil and 16:4(n-3) administration induced tumor chemoresistance in mouse models. Fish oil administration and oily fish consumption increased 16:4(n-3) blood levels in healthy volunteers. 11% of cancer patients used fish oil or omega-3 supplements, and most of these patients used them during chemotherapy, with only about half reporting supplementation to their doctor.

Figure 3: 16:4(n-3) levels in humans - higher than expected with fish oil compared to fish



What does the study really tell us?

Although this study is unable to directly address whether or not fish oil supplementation reduces the effectiveness of chemotherapy in humans, it makes a compelling case for chemotherapy patients to avoid fish oil and oily fish consumption, at least in the days surrounding chemotherapy treatment.

Using a relatively standard tumor model that is known to respond to chemotherapy, the researchers found that 16:4(n-3) or fish oil administration reduces the effectiveness of a variety of chemotherapies to the point that the mouse tumors grew at the same rate as untreated tumors. They observed similar effects from purified EPA administration, which seems to indicate that, at least in mice, EPA can be converted to 16:4(n-3) through an unknown mechanism.

In humans, the researchers found that ingestion of fish oil or oily fish increases levels of 16:4(n-3) in the blood of healthy volunteers. Although this might seem like a relatively straightforward finding, it is critical to provide evidence that human ingestion and digestion of fish oil results in the presence of a specific fatty acid in the blood.

Finally, the researchers found that most patients who use fish oil continue to do so during chemotherapy, and patients often don't report fish oil usage to their doctors.

Although the experiments in this study were somewhat disparate, they do form the basis for a preliminary body of evidence. The study showed that fish oil and oily fish consumption could reduce the effectiveness of chemotherapies in mice, that fish oil and oily fish consumption in healthy volunteers increases blood concentration of what is presumably the causative agent of this chemoresistance, and that a relatively large percentage of cancer patients take dietary supplements, which include fish oil.

Added together, the experiments reported in this paper provide a strong preliminary base of evidence suggesting that cancer patients receiving chemotherapy may want to avoid taking fish oil supplements around the time of their chemotherapy treatments.

The big picture

Chemotherapy is a balancing act. Since cancer is a disease state characterized by uncontrolled cell growth, it makes sense that targeting uncontrolled growth would be a good therapeutic strategy. Unfortunately, there aren't any good ways to specifically target uncontrolled growth, so instead, chemotherapy targets rapid cell growth. Although this makes it very good at killing

> "One example is St. John's Wort, which causes upregulation of enzymes that process a variety of drugs, including some chemotherapy agents."

cancer cells, it also results in off-target effects in other rapidly dividing tissues, such as intestinal cells. This is why many standard chemotherapeutic agents cause a variety of gastrointestinal side effects, including vomiting and diarrhea. One of the key roles of oncologists is to control chemotherapy doses to maximize cancer cell death and minimize side effects. There are also a wide array of supportive therapies available, such as antiemetics, to help doctors control these side effects. In many cases, cancer patients also seek out their own supportive therapies, including supplements, in an effort to enhance their quality of life while receiving cancer treatment.

In most cases, it remains unclear whether supplements are truly beneficial for cancer patients. In some other cases, there is a clear contraindication for the use of certain supplements while receiving certain chemotherapy agents. One example is St. John's Wort, which causes upregulation of enzymes that process a variety of drugs, including some chemotherapy agents. However, researchers have only recently begun studying interactions between chemotherapy and supplements, so there are many other interactions that remain to be discovered.

This study represents a kind of "miniature body of evidence" to support the idea that 16:4(n-3) acids found in fish oil may reduce the effectiveness of chemotherapy. Because cancer is such a lethal group of diseases and because the therapies are already both carefully calibrated and relatively arduous, it is critical to eliminate any agents or habits that could reduce therapeutic effectiveness. Although all of the experiments in this study were preliminary, they support the idea that fish oil supplementation may have a negative impact on chemotherapy effectiveness, thus indicating that supplementation management may be an important topic for patients to discuss with a physician.

However, it is worth noting that most chemotherapy regimens are not continuous, as a result of the side effects they cause. Generally, chemotherapy is an intermittent treatment in which the patient receives chemo drugs for a certain number of days and then takes a break from the treatment in order to recover. This was not really taken into account in the current study, so it may be acceptable for patients to take fish oil or other supplements during the times they are not receiving chemotherapy, but further study is needed to confirm this hypothesis.

“ […] it may be acceptable for patients to take fish oil or other supplements during the times they are not receiving chemotherapy, but further study is needed to confirm this hypothesis. ”

Frequently Asked Questions

What alternative therapies or supplements are safe for cancer patients?

This is a very broad and loaded question, and the answer depends on the nature of a patient's cancer. Because cancers and their treatments are so diverse, their interactions with supplements and alternative therapies are similarly diverse. The most important aspect of any supplementation or alternative therapy regimen for cancer patients is constant and open communication with their oncologist or medical team. In general, it is important for cancer patients to discuss any and all symptoms, medications, and dietary needs with their doctors. This is even more important in the context of clinical trials, which often have very specific requirements and limitations.

If the effects of fish oil are still not fully understood, is it okay for healthy people to take it?

Generally speaking, fish oil is a relatively well-studied supplement in healthy populations. However, fish oil is not a commodity with one uniform composition among all products, and not all omega-3 supplements are even fish oil in the first place.

As an example of how complicated things can get, recent evidence points to possible prostate cancer harms from certain fatty acids found in fish oil, while other fatty acids may benefit prostate cancer. Some people megadose fish oil in an attempt to quickly curb inflammation, and sometime encounter side effects such as increased bleeding risk. So even if you deem yourself "healthy", it is always a good idea to consult with your doctor before taking any supplements, and do research into how supplements may interact with each other, have different effects at different doses, etc. There's even a website to help you with that kind of thing!

What should I know?

Fish oil supplementation and oily fish consumption may negatively impact the effectiveness of chemotherapeutic agents. The presumed causative factor of this interaction, 16:4(n-3) PIFAs, reduced chemotherapeutic effectiveness in a mouse cancer model. These PIFAs are also present in the bloodstream of healthy volunteers after fish oil or oily fish consumption. Up to 30% of cancer patients report using supplements, including fish oil. Based on this evidence, patients supplementing fish oil during chemotherapy should inform the oncologists treating the cancer so they can provide appropriate advice. ◆

Almost everyone has had or knows someone who has had cancer. Supplementation during chemotherapy is rarely discussed … to talk more about this issue, head over to the Facebook ERD Forum.

"Fish oil supplementation and oily fish consumption may negatively impact the effectiveness of chemotherapeutic agents."

Got Milk(fat globule membrane)?

Potential role of milk fat globule membrane in modulating plasma lipoproteins, gene expression, and cholesterol metabolism in humans: a randomized study

Introduction

Cardiovascular disease (CVD) is a general term for any pathological condition that involves the heart or blood vessels. Many of these diseases, and certainly those most commonly associated with Western societies, are a result of atherosclerosis – the thickening of artery walls through the buildup of plaques of fatty material. Although CVD was once thought to be primarily due to elevated cholesterol levels, it is now recognized that inflammation of the arteries is a necessary prerequisite for plaque formation.

That said, LDL infiltration of the artery walls is a major cause of inflammation, and there is little debate among the medical community that high levels of LDL-cholesterol (LDL-c) is a risk factor for CVD. Two recent meta-analyses support this view. The first looked at over 38,000 patients taking statins and found a significant reduction in risk as LDL-c levels moved from above 175 mg/dL to below 50 mg/dL. Achieving an LDL-c below 100 mg/dL through statin therapy was associated with a 44% reduced risk of having a major CVD event, while levels below 50 mg/dL were associated with a 56% reduced risk. The second analysis looked at data from over 10,000 patients enrolled in 24 randomized, placebo-controlled trials of PCSK9 inhibitors and found that treatment reduced LDL-c by nearly half while simultaneously reducing the number of heart attacks by 51% and the odds of death from any cause by 55%.

What these studies serve to illustrate is that we now have two completely different drug therapies, statins and PCSK9 inhibitors, which reduce LDL-c by different methods and reduce the risk of CVD-related events. It stands to reason that other methods that reduce LDL may also reduce the risk of CVD. A first line of defense for the management of blood cholesterol levels is dietary intervention.

Dairy fat is typically around 70% saturated fat and makes up about a fifth of total saturated fat intake in the U.S. diet, making it a prime target for nutritional interventions. However, results from observational and experimental trials that evaluate the impact of dairy products on blood cholesterol levels are not conclusive. Notably, there is a lot of evidence from randomized controlled trials that diets high in saturated fat derived largely from butter fat increases LDL-c, whereas cheese intake results in lower LDL-c compared with butter of equal fat content, and may not increase LDL compared with a diet lower in saturated fat. Similarly, the results are fairly consistent in showing that whole milk

“ Dairy fat is typically around 70% saturated fat and makes up about a fifth of total saturated fat intake in the U.S. diet, making it a prime target for nutritional interventions. ”

increases LDL-c more than low-fat or skim milk, while whole-fat yogurt may reduce LDL-c.

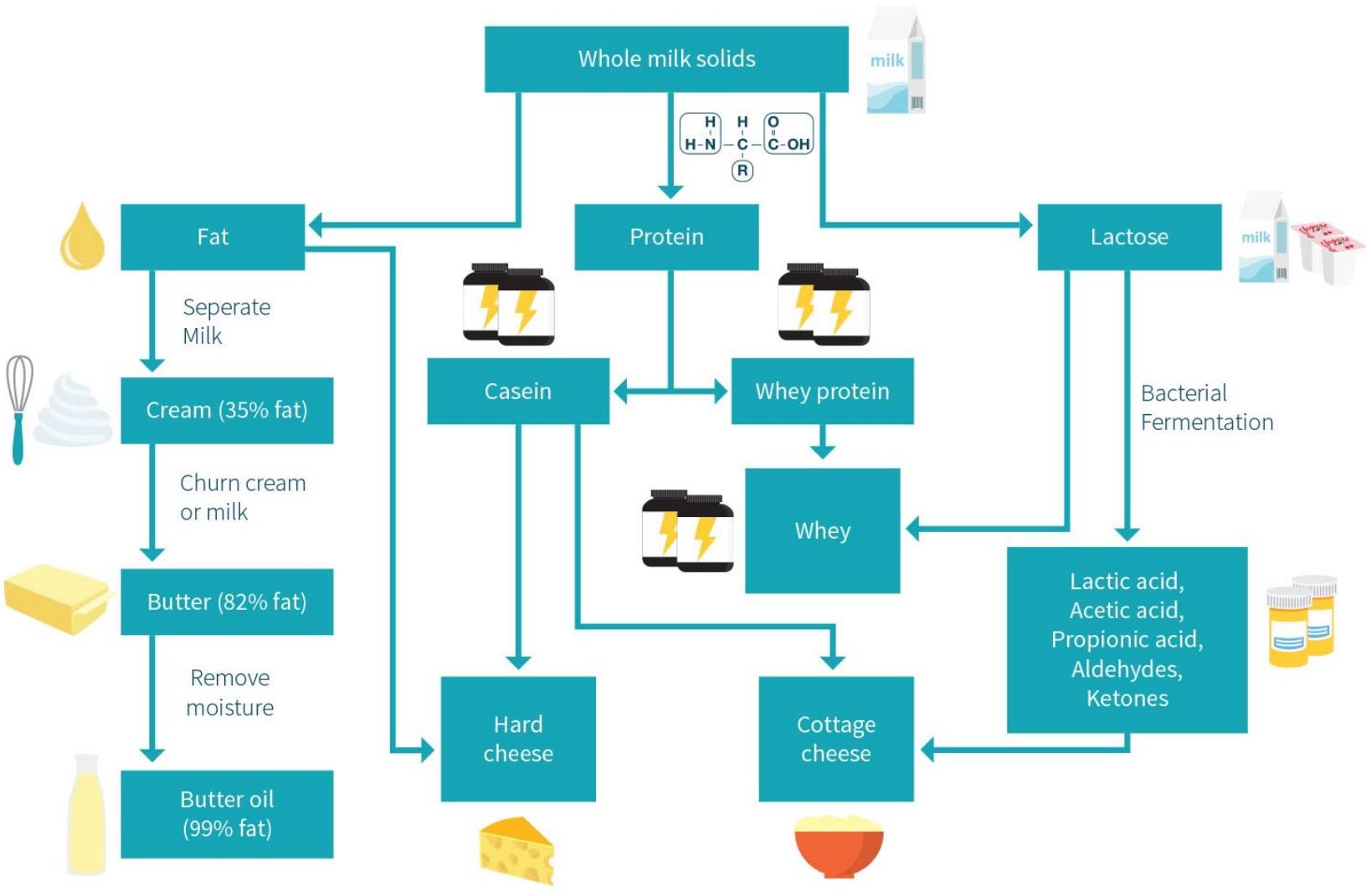
The inconsistent findings with regard to dairy fat's effects on blood cholesterol have been hypothesized to be owed, at least in part, to the milk-fat globule membrane (MFGM) – a three-layered membrane composed of proteins, lipids, and numerous minor bioactive sterols that encloses the milk fat globules. Figure 1 shows the basic processes used to make different dairy products. The MFGM is a very fragile compound that is preserved in cream and cheese, but destroyed during mechanical processing, such as the churning required to make butter or the homogenization of milk. It has been suggested to have numerous health benefits, including cholesterol-lowering effects. The current study was an attempt to test the hypothesis that the effect of dairy fat on serum cholesterol levels is mediated by the presence (or absence) of the MFGM.

Observational and experimental evidence investigating the effect of dairy fat on serum cholesterol levels is conflicting and depends on the dairy product consumed. An intact milk-fat globule membrane (MFGM) present in some dairy foods, such as non-homogenized cream and cheeses, may explain the inconsistencies. The study under review tested this hypothesis.

Who and what was studied?

Local advertising at Uppsala University Hospital, Sweden was used to recruit overweight but otherwise healthy men and women to undergo an eight-week, single-blinded randomized trial. The participants were 50-65 years old, had an average BMI of 28, did not regularly engage in heavy exercise (more than 3 times per week), and had no abnormal blood chemistry. After being stratified by baseline sex, age, LDL-c, and habit-

Figure 1: Dairy products in a nutshell



ual dairy intake (high vs. low), the participants were randomized to a MFGM or control group. Stratification means that the participants were put into categories based on the aforementioned variables, helping ensure an even distribution between groups. A total of 46 people completed the study (26% men and 74% women).

The dietary interventions were essentially the same except for the source of dairy fat. Both groups consumed 100 grams (just under ½ cup) of fat-free milk and one scone prepared by the research staff. The MFGM group also consumed 100 grams (about 6.5 tablespoons) of whipping cream (40% fat) per day, which was confirmed to have intact MFGMs, while the control group consumed 40 grams (about three tablespoons) of butter oil that had no MFGMs present, and a few grams of whey protein isolate to match up the protein and calcium content of the groups. The butter, oil, and whey were baked into the scones of the control participants. All participants were allowed to eat their food however and whenever they wanted through the day, provided the whipping cream was not heated, mixed, or whipped.

The participants were all free-living adults who visited the research clinic weekly for weight measurement, food distribution, and general support. They were instructed not to change their usual dietary habits, but to avoid consuming any dairy or margarine products not provided by the researchers.

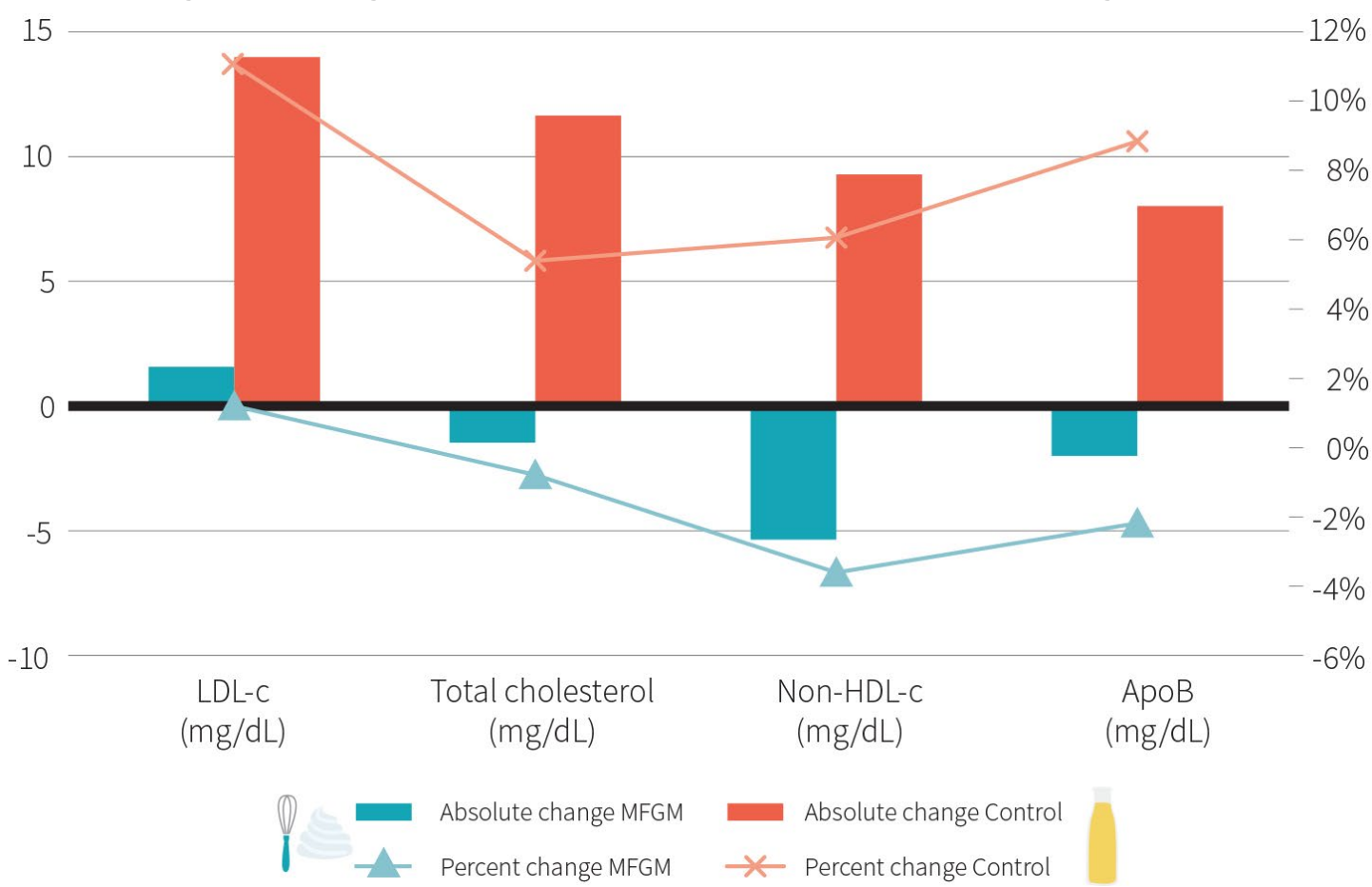
Table 1: Nutrient content of the intervention food items

	MFGM diet	Control diet
Energy, kcal	805	794
Carbohydrate, g	88.9	86
Fat, g	41.8	41.4
Protein, g	16.7	16.7
Phospholipids, mg	19.8	1.3
Cholesterol, mg	100	120
Calcium, mg	687	677

What were the findings?

The researchers evaluated numerous metabolic biomarkers, but the treatment affected only a few, which are shown in Figure 2. While the control group showed

Figure 2: Significant differences between study groups



a rise in total-, LDL-, and non-HDL-cholesterol and apolipoprotein (Apo) B, the MFGM group did not, and there was a significant difference between the groups after the eight week intervention.

The researchers also analyzed peripheral blood mononuclear cell (PBMC) gene expression in the women of each group and found the expression of 19 genes to be significantly reduced in the MGFM group and increased in the control group. Changes in most of these genes correlated with changes in one or more of the changes in blood lipids. Though the scientific understanding of most these genes is poor, some of them have been implicated in the regulation of the cell life cycle, including apoptosis (programmed cell death), and in the regulation of protein breakdown within cells.

What does this really tell us?

This is a limited but informative study. It shows that replacing the habitual dairy fat intake of older overweight-obese Swedish men and women with 40 grams of dairy fat from pasteurized but not homogenized cream has no effect on blood cholesterol levels and down-regulates the expression of numerous PBMC genes. However, replacing dairy fat with butter oil significantly increases blood cholesterol levels and PBMC gene expression. The small sample size, ethnical and geographical homogeneity, and inability to know how, when, and with what exactly the test products were consumed are significant limitations to the study. Although the presence of the MFGM in the cream is a plausible explanation for the outcomes, it is also possible that the physical state of the fats (fat globules vs. isolated fat) influenced the results.

“ The small sample size, ethnical and geographical homogeneity, and inability to know how, when, and with what exactly the test products were consumed are significant limitations to the study. ”

Nonetheless, a strength of this study is that the results are directly translatable to common foods, although the effects may have been different if butter, rather than butter oil, was used in the control group. Still, the LDL-c-raising effects of butter oil are in line with those observed with butter. Of the most commonly consumed sources of dairy fat, butter and butter oil have the lowest MFGM content (see FAQ).

Another strength of the study was that plasma phospholipid and cholesterol fatty acid composition were unchanged in both diets throughout the intervention without any differences between the diet groups, suggesting that the milk fat dose used (40 grams a day) was

similar to the habitual dairy fat intake of the participants. This helps minimize the possibility that changes in dietary fat intake influenced the results.

In sedentary, overweight-obese Swedish people, consuming pasteurized but non-homogenized cream instead of butter oil prevented increases in blood cholesterol concentrations, possibly due to the intact MFGM within the cream. However, the small sample size and lack of geographic and ethnic diversity makes it difficult to generalize the results of this study.

Big picture

The potential mechanisms through which MFGM counteracts the cholesterol-raising effects of dairy fat are not well established, but animal models suggest that it involves reduced cholesterol absorption or phospholipid-induced alterations in liver gene expression. For instance, rats fed a high-fat diet supplemented with MFGM phospholipids display a 15% to 30% increase in fecal cholesterol excretion and a 20% to 60% decrease in liver cholesterol. In a separate rodent study, where the consumption of phospholipids was set to the estimated intake of a typical human, overall and per meal cholesterol absorption were reduced by half. Although the current study did measure surrogate markers of cholesterol absorption and synthesis and found no changes among the participants, the possibility of reduced cholesterol absorption and increased cholesterol excretion cannot be ruled out until more direct measurements in humans are made.

Rats that consume a high-fat diet supplemented with MFGM-rich milk extract display a reduction in liver fat accumulation and blood lipid levels attributed to a significant reduction in the expression of hepatic genes that regulate cholesterol synthesis (HMG-CoA reductase), bile acid synthesis (cholesterol 7α-hydroxylase), and fatty acid synthesis. This is in accord with the current study, which found all 15 tested PBMC genes to be down-regulated in the MFGM group. It has been suggested that PBMC gene expression after dietary interventions reflect changes within the liver and can be used for studying the response of certain genes related to fatty acid and cholesterol metabolism.

“ The potential mechanisms through which MFGM counteracts the cholesterol-raising effects of dairy fat are not well established, but animal models suggest that it involves reduced cholesterol absorption or phospholipid-induced alterations in liver gene expression. ”

The current study is novel in its attempts to test the MFGM hypothesis, but falls short of providing concrete evidence that the group differences are owed to it. Unfortunately, there are no other human studies on the MFGM. The main confounding variable was the different dairy sources used, which could be overcome in future trials by using products only differing in their level of processing (e.g., homogenized vs. non-homogenized whole milk). Of course, adding more strict dietary control would also aid in isolating the MFGM. Allowing the consumption of MFGMs through their natural food sources provides a degree of generalizability to the foods themselves. Future trials should also evaluate if supplementation with a MFGM extract would have similar effects on blood cholesterol and interact with other fat sources in the diet.

> “The world enjoys gravitating to the extremes of issues, and blood cholesterol levels are no exception.”

Frequently Asked Questions

If inflammation is a necessary prerequisite for atherosclerosis, then why worry about LDL-c?

The world enjoys gravitating to the extremes of issues, and blood cholesterol levels are no exception. Although many “anti-mainstream” nutrition enthusiasts claim that hypercholesterolemia doesn’t play a role in heart disease, understanding how arterial plaque forms may aid in illustrating why we should care about LDL-c and especially LDL particle count (LDL-p).

After an artery is damaged through any of the many risk factors for CVD (hypertension, free radicals, etc.), it begins to express certain proteins that allow for the accumulation of white blood cells. As the white blood cells arrive, they begin releasing chemicals (cytokines; this is the inflammation part) that signal more of their brethren to stop by. Under normal circumstances, the damage would resolve and the blood cells would leave: mission accomplished. However, under conditions of continuous damage through, for example, chronic inflammation, the artery will never fully repair and the white blood cells will continue to accumulate. This is where LDL-c and LDL-p come into play.

LDL-cholesterol enters the damaged area, where it is more prone to becoming oxidized. The oxidation signals to the white blood cells that they need to eat it, so as to protect the body. But this LDL-c-engulfing process turns white blood cells into “foam cells,” which can be thought of as obese white blood cells. That is, they are giant lipid-filled cells that can’t function properly and are ultimately part of what forms the plaque seen in atherosclerosis. So while inflammation is indeed necessary, if there there are fewer LDL particles with overall lower LDL cholesterol in the blood, then there is a reduced likelihood of it entering the damaged area and being oxidized and consumed. Similarly, if someone has a boatload of LDL-c in their blood along with high LDL-p, there is a far greater likelihood that some of it will become oxidized and consumed by white blood cells, even if the damaged area is only temporarily (i.e. no systemic inflammation present) damaged. So, the best bet against heart disease is keeping both inflammation and LDL-c / LDL-p low.

What dairy products contain an intact MFGM?

The MFGM in dairy fat prevents lipid droplets from grouping together, therefore they remain dispersed in the milk. Only after destruction of the structure of the MFGM through mechanical force like churning do lipid droplets aggregate and subsequently form large fat clumps (i.e., butter). This is why MFGMs are only present in dairy products that contain dairy fat and have not been mechanically altered through churning or homogenization. For example, whole milk, cream, and cheese all contain MFGMs, whereas butter, butter oil, butter milk, whey protein, and any fat-free dairy products do not.

That being said, MFGM is only one of the many differences between dairy products that may influence their differential impacts on heart disease. For example, cheese and milk are more nutrient-dense than butter. Additional differences are shown in Figure 3.

What is the difference between butter and butter oil?
Butter oil is the fat concentrate obtained primarily from butter or cream by the removal of practically all the water and proteins. The terms anhydrous milk fat, dry butterfat, and dehydrated butter fat are used synonymously with butter oil, but the raw material used for their preparation is mainly cream. Ghee is also a form of butter oil.

What should I know?

Non-homogenized milk fat (cream) does not increase cholesterol levels, which, ironically, is the main reason we are told to avoid high-fat dairy foods. The MFGM may explain the inconsistencies of observational and experimental studies evaluating the impact of dairy fat on blood lipid levels, and this study provides preliminary evidence to support this hypothesis. However, no concrete conclusions can be made because of a handful of study limitations, such as the physical state of the dairy products used. Animal research suggests any potential effects may be owed to the ability of the MFGM to reduce cholesterol absorption and synthesis and increase excretion. ◆

Figure 3: Differences between butter and cheese impact health effects

	CHEESE	BUTTER
CHOLESTEROL EFFECT	LOW/ MODERATE	MODERATE/ HIGH
MFGM	HIGH	LOW
PROTEIN	MODERATE	ABSENT
VITAMINS/ MINERALS	MODERATE	LARGELY ABSENT
FERMENTATION	PRESENT	ABSENT

Turns out that demonizing "Dairy" as a category probably isn't the best approach. Maybe demonizing isn't the best approach, in general. Head over the Facebook ERD forums to talk about dairy and heart disease.

I get by with a little help from my friends: probiotics and depression

A randomized controlled trial to test the effect of multispecies probiotics on cognitive reactivity to sad mood

Introduction

For thousands of years, clinicians have observed a connection between the gut, brain, and overall health. Hippocrates is famously quoted as saying "all disease begins in the gut." This should not come as a surprise to anyone who has ever experienced gastrointestinal (GI) symptoms like diarrhea, indigestion, or abdominal discomfort in response to changes in their emotional state. Studies in both healthy patients and in people with functional bowel disorders have confirmed connections between emotional state and GI function.

The gut and brain communicate through neural, endocrine and immune pathways. It has become increasingly clear that interactions with intestinal microbiota are also an important part of this communication. A number of animal and human studies have examined the relationship between gut bacteria and mood symptoms such as anxiety and depression, leading to the idea that probiotic supplementation may be a potential strategy for reducing or preventing depression.

According to the cognitive theory of depression, an individual's negative and distorted thinking is the basic psychological problem at the root of depressive syndrome. Cognitive reactivity refers to the activation of dysfunctional patterns of thinking triggered by subtle mood changes. This is a key feature in the development and occurrence of depression, and as such would be a relevant target for interventions. Dysfunctional patterns of thinking can include thoughts of hopelessness, thoughts of hurting oneself or others, ruminating on the causes and consequences of anguish, and a general loss of motivation for life. These responses are thought to come from underlying negative thought patterns that get brought to the surface during times of low mood. Cognitive reactivity appears to be a cause of, rather than simply an association with, depression, since higher cognitive reactivity scores precede and predict the onset of depression, even in people with no prior incidence of depression.

Considering the vast potential to treat and prevent mood disorders by improving gut health, the objective of this Dutch study was to determine the effects of a probiotic supplement on cognitive reactivity to sad mood, as well as symptoms of depression and anxiety in non-depressed, healthy adults.

"Cognitive reactivity appears to be a cause of, rather than simply an association with, depression, since higher cognitive reactivity scores precede and predict the onset of depression, even in people with no prior incidence of depression."

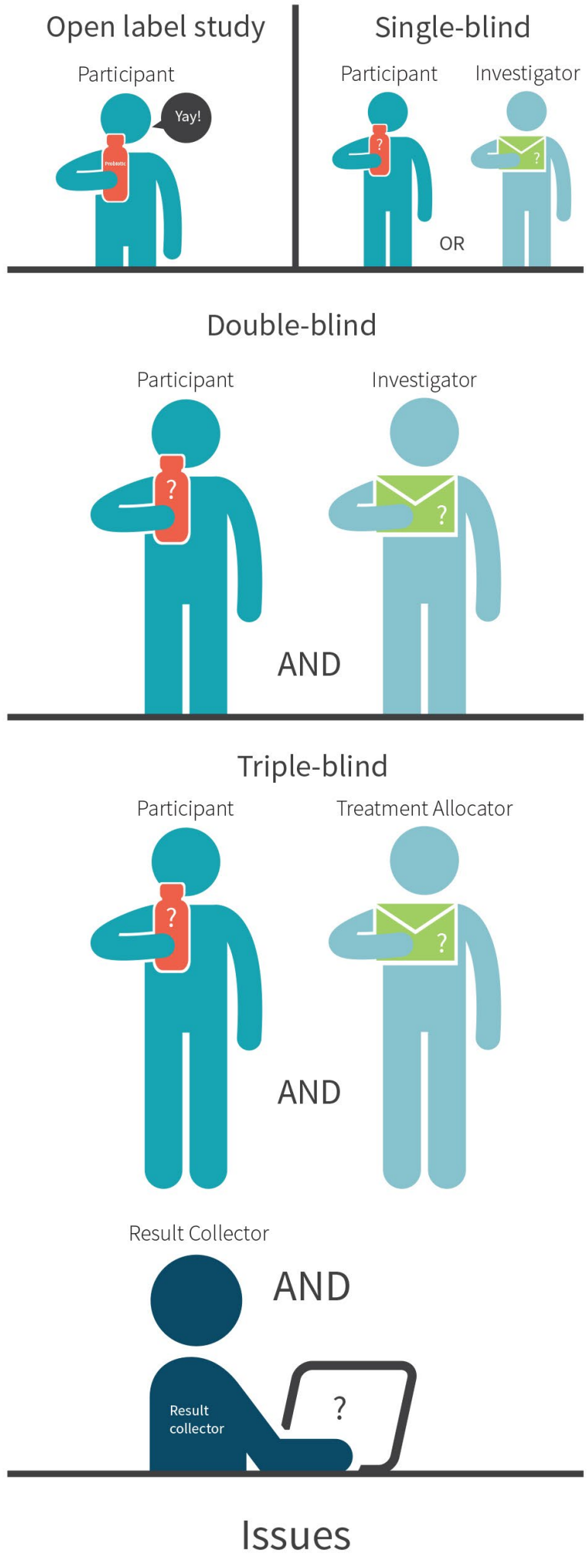
Cognitive reactivity, which involves negative thought patterns triggered by mood change, has been shown to predict the onset of depression. Since the brain and gut communicate through several pathways and the gut microbiome has recently been found to influence this communication, it is possible that probiotic supplementation could affect cognitive reactivity. This is what this study set out to test.

Who and what was studied?

Forty healthy, normal weight college-age adults participated in this triple blind study. A triple blind study means neither the participants, researchers, nor the people who organize and analyzed the data knew which group a participant was in. Different types of study blinding are depicted in Figure 1. The participants did not smoke, had no reported medical conditions, food allergies, medications, or drug use, and consumed no more than three to five drinks per week. Participants also did not have any psychiatric or neurological disorders, or any personal or family history of depression or migraines. They were randomly assigned to receive either a probiotic supplement (n=20, five males) or placebo (n=20, three males) for four weeks. The menstrual cycle was not controlled for in the female participants.

Interestingly, all participants were told they were receiving the probiotic supplement. This is different from many other trials, as participants would normally be told they have an equal chance of receiving the supplement being studied or placebo. The probiotic used was a mixture that is commercially available in the Netherlands, containing *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W52, *Lactobacillus acidophilus* W37, *Lactobacillus brevis* W63, *L. casei* W56, *Lactobacillus salivarius* W24, and *Lactococcus lactis* (W19 and W58). The participants consumed either supplement or placebo for four weeks.

Figure 1: Triple blinding vs other blinding



*Definitions are not standard. Sometimes the other blind is an investigator rather than treatment allocator, for example.

**The term "Masking" has been proposed, given the number of people with serious visual impairments (e.g. blindness)

Three different questionnaires were used before and after the intervention period to quantify the outcomes. The revised Leiden Index of Depression Sensitivity (LEIDS-r) measured the perceived cognitive reactivity to transient changes in sad mood, which indicates vulnerability to depression. The LEIDS-r is made up of 34 questions that assess the extent to which dysfunctional thoughts are activated when someone is experiencing a mild state of dissatisfaction with their life. Example questions include "*when in a low mood, I take fewer risks*," or "*when in a sad mood, I more often think about how my life could have been different*." Responses are given on a 5-point scale, with 0 being "does not apply to me" and a score of 5 meaning "very strongly applied to me." The scale measures vulnerability to depression overall, and consists of six different subscales: regard to aggression, hopelessness/suicidality, acceptance/coping, control/perfectionism, risk aversion, and rumination.

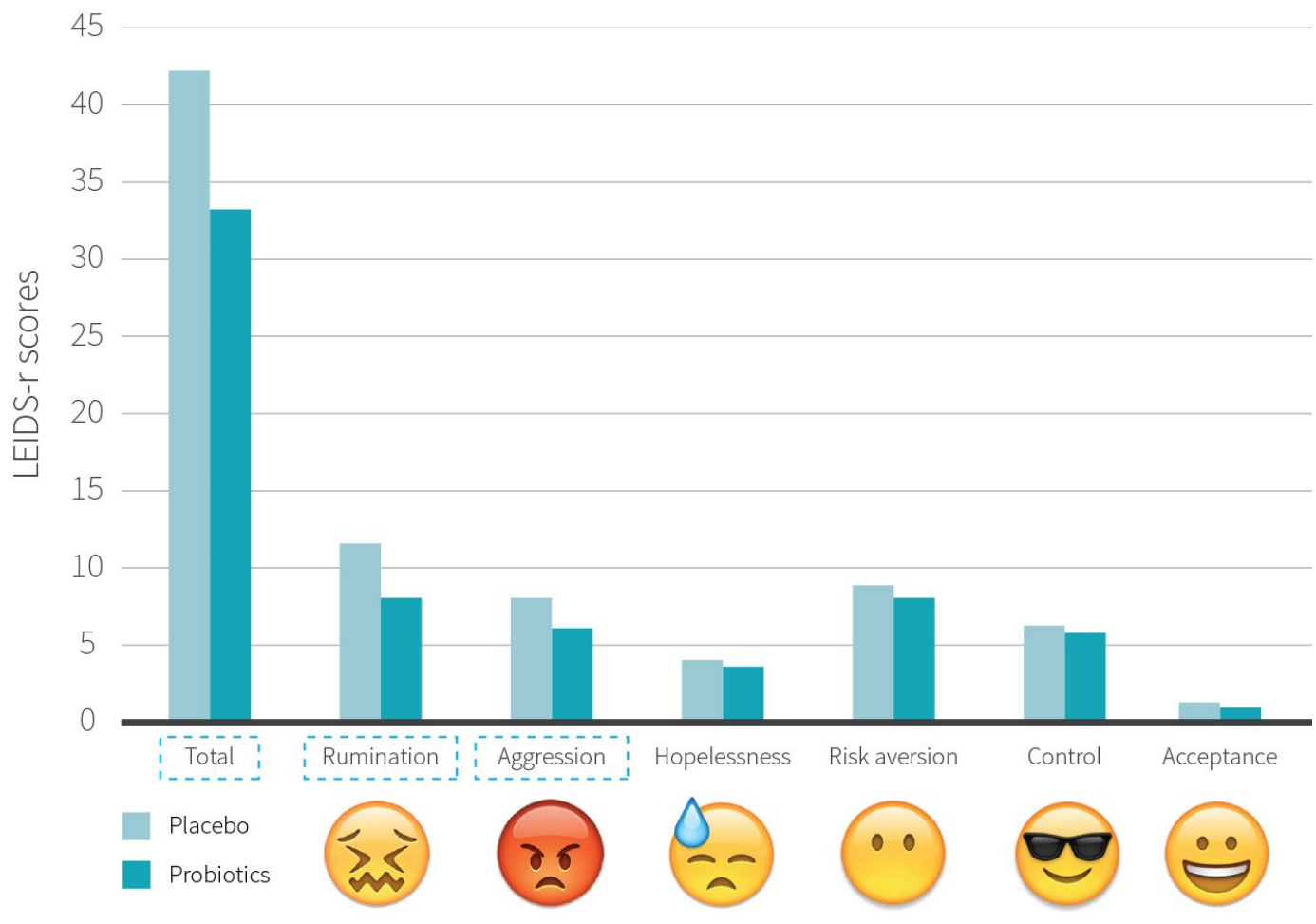
The Beck Depression Inventory II (BDI-II) is a 21-item questionnaire that assesses the existence and severity of depressive symptoms occurring during the previous two weeks. Similar to the LEIDS-r, questions are rated on a 4-point scale ranging from 0 to 3 in terms of severity, and the total score is added up to classify the level of depression (minimal, mild, moderate, or severe). The Beck Anxiety Inventory (BAI) is also a 21-item questionnaire, used to assess the existence and severity of anxiety symptoms occurring during the previous week. Questions are also answered on a 4-point scale ranging from 0 to 3 in terms of severity.

Forty healthy college-age adults with no personal or family history of depression took either placebo or a probiotic mixture. Cognitive reactivity was measured with the LEIDS-r questionnaire before supplementation began and after four weeks of supplementation. Anxiety and depression were also measured using questionnaires.

What were the findings?

The study findings are summarized in Figure 2. None of the participants (in either group) showed any signs

Figure 2: Study results



of depression (using the BDI-II) or anxiety (using BAI) at baseline or follow-up. Differences were seen on the LEIDS-r, however, which measures vulnerability to future depression. Participants who received the four-week probiotic supplement showed a significantly lower score for overall cognitive reactivity to sad mood, mainly accounted for by reduced rumination and aggressive thoughts. No differences were found between groups for hopelessness, control, risk aversion, or acceptance.

What does the study really tell us?

"*The present results indicate, for the first time, that probiotics intervention can influence cognitive mechanisms that are known to determine vulnerability to mood disorders.*"

This study set out to determine the effects of a multi-species probiotic supplement on cognitive reactivity, an important marker in predicting future depression, in healthy young men and women without any personal or family history of mood disorders. Though none of the participants showed any signs of current anxiety or depression, a four-week probiotic intervention showed significantly reduced cognitive reactivity scores, suggesting a reduced vulnerability to future depression. Reductions in total cognitive reactivity score were largely due to decreases in the aggression and rumination subcategories. This is relevant because the people who ruminate about the causes of being in a sad mood may have a harder time recovering from depression.

These participants were healthy and had no diagnosable anxiety or depression at baseline, so improvements in these scores would not necessarily be expected. The lack of any existing mood disorders in the participants is important because it allows the researchers to test for any influence on *future* depression, which the LEIDS-r questionnaire has been shown to do. Of course, further long-term studies using the probiotic interven-

> "Participants who received the four-week probiotic supplement showed a significantly lower score for overall cognitive reactivity to sad mood, mainly accounted for by reduced rumination and aggressive thoughts."

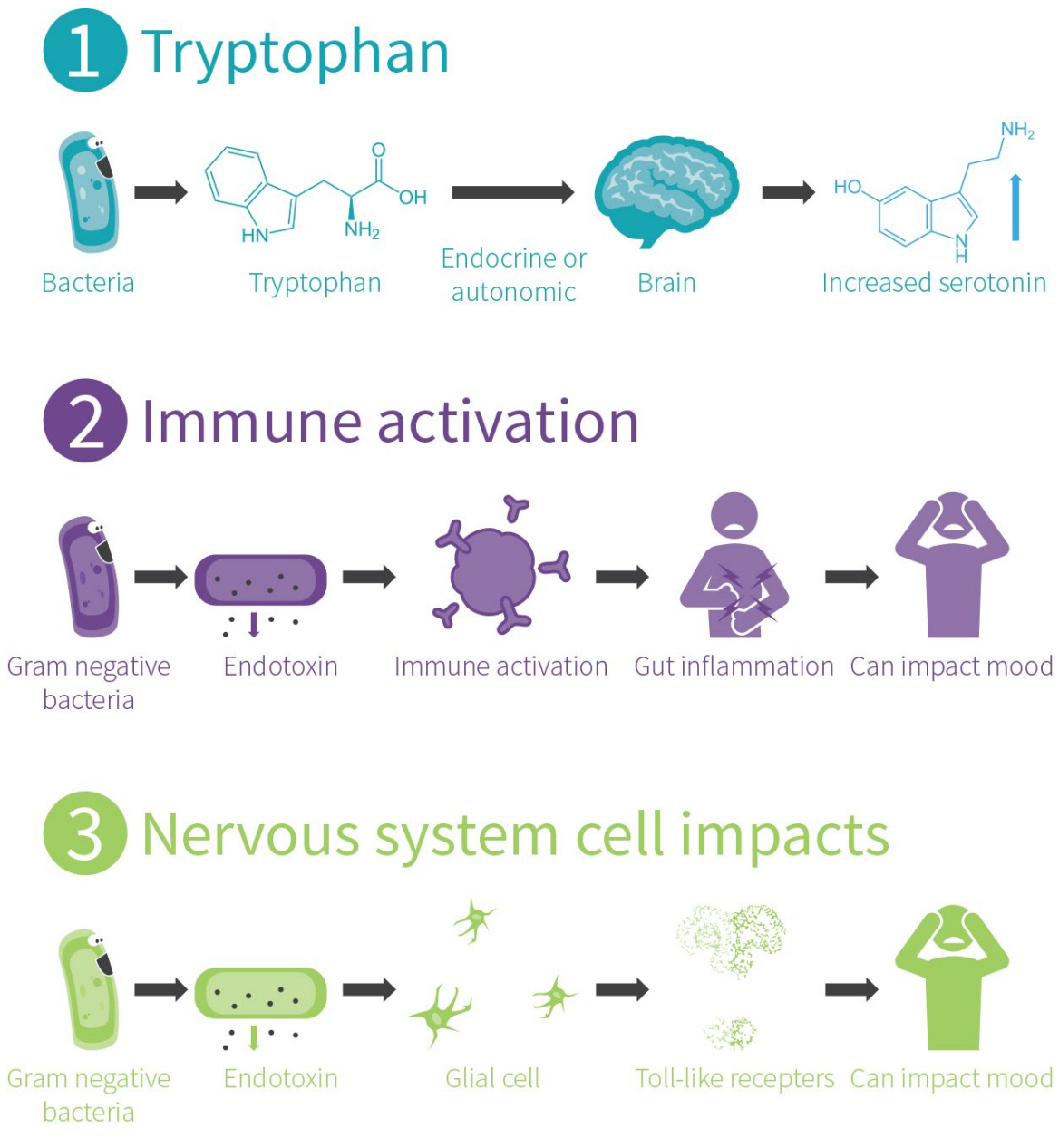
tion would be needed to confirm if these predictions become clinically relevant.

However, we can calculate a guesstimate of the odds reduction of developing depression based on the LEIDS-r score. The roughly nine-point reduction in the LEIDS-r score seen in this study due to probiotic supplementation translates to an odds ratio of 0.76, in terms of developing depression over a two-year period, based on previous research.

While no mechanisms of action were studied, a number of hypotheses can be considered, which are shown in Figure 3. Cognitive reactivity scores can predict the depressive response to serotonin depletion, and gut bacteria may increase serotonin in the brain by increasing plasma tryptophan levels. Decreased intestinal permeability from the probiotic supplementation could also play a role, as increased gut permeability can lead to symptoms of depression. A review of the effects of probiotic supplements on intestinal permeability found a positive effect in 48% of the controlled studies.

While compliance was not confirmed by stool analysis and dietary control did not include consideration for other probiotic-rich foods (i.e. yogurt), the biggest limitation in being able to draw wider conclusions from this study is the disproportionate female to male balance. Participants in this study were 80% female, which is opposite to the male gender bias often found in the scientific literature. This is relevant because men and women have different gut microbiomes due to differences in sex hormones, and we are also somewhat different both emotionally and cognitively. This is also a fairly small study in a young population, which makes generalization difficult. Although ethnicity wasn't

Figure 3: Three of the ways that microbiota can impact the brain



explicitly mentioned in this study, this study was conducted in the Netherlands, which may warrant caution when generalizing to broader populations As we've seen in ERD #6 in "The gut microbiome's role in type I diabetes," nationality and ethnicity can correlate with microbiome differences.

This study suggests that a multispecies probiotic supplement reduces cognitive reactivity, which is associated with a lower risk of future depression. This is plausible, since there are several mechanisms by which the gut microbiome may affect vulnerability to depression, although these mechanisms were not examined in the study under review. The small sample size and limited diversity in age, gender, and ethnicity makes the results difficult to generalize.

The big picture

A number of human and animal studies show reduced signs of depression and anxiety with probiotic supplementation, though improvements are often seen only with pre-existing anxiety or depression.

Taking a probiotic supplement made up of multiple strains of bacteria can have increased effectiveness through an additive or synergistic effect of the individual strains, compared with mono-species supplements. However, some probiotics may work in an antagonistic manner, so combinations of strains should be studied both individually and in combination before creating a multispecies product. A previous study by one of the co-authors of this study reported improvements in intestinal barrier function by each probiotic strain used in this study separately, as well as in the combined product. Another study that included that same co-author found a decrease in migraines during the second and third month of taking the same supplement. However, no control group was used and no placebo was given.

As mentioned in last month's ERD article on HMB supplementation, the fact that a company sponsors the research does not automatically taint the results. However, it is worth noting that the aforementioned study about intestinal barrier function was done by the company's own internal research and development scientists. Both the study about migraines, as well as the study under review, featured the same employee from Winclove Probiotics as a co-author. Despite this, the authors of this paper state that "no competing interests exist."

Conflicts of interest

Conflicts of interest occur when the people who design, conduct, or analyze research have a motive to find results that suit their needs. The most obvious source of a conflict of interest is monetary. Sometimes, such as in this paper and the vitamin K2 study reviewed in this issue of the ERD, possible conflicts may exist even though the authors claim there are none. But these authors aren't alone. One study suggests that nondisclosure of possible conflicts of interest is somewhat common.

However, having competing interests doesn't automatically negate the results of studies. For instance, one review of major cardiovascular trials found that conflicts of interest had no impact on the results.

Conflicts of interest must be evaluated carefully. Don't automatically assume that they don't exist just because they're not disclosed, but also don't assume that they necessarily influence the results if they do exist.

Many studies to date have suggested that probiotics may have an effect on anxiety and depression, especially in animals, although human trials were mostly conducted on populations with pre-existing anxiety or depression. Multistrain probiotics could be more beneficial than individual strains in some, but not all, cases. Ideally, research should compare single versus multi-strain supplementation.

Frequently asked questions

Would probiotic supplementation have the same effect in men and women?

This study recruited both men and women, though it was predominantly (80%) made up of women and results were not listed separately by gender. Other trials using probiotic supplements have found both similar and differing effects among men and women. It is difficult to say how this product would compare between genders.

Could the benefits of this supplement extend beyond depression and anxiety?

Previous research using the same supplement has shown improvements in gut barrier function and a reduction in migraines. Additionally, a number of the species used in this product (but different strains) have shown cholesterol lowering effects, as well as contributing to improved immune function.

What I should know?

This study showed that healthy individuals consuming a multispecies probiotic for four weeks experienced a reduction in cognitive reactivity scores, which are a marker of vulnerability to future depression. In particular, these reductions were characterized by reduced aggressive and ruminative thoughts in response to sad mood.

This trial could provide a basis for larger trials in more diverse populations, possibly also testing the efficacy of multi-strain versus single species probiotics. ◆

We'll certainly be covering more trials on the gut-brain axis in future issues of ERD. In the meantime, discuss the ones we've already reviewed over at the ERD Facebook forum.

> "Previous research using the same supplement has shown improvements in gut barrier function and a reduction in migraines."

Beyond ‘eat less, move more’: treating obesity in 2016

By Spencer Nadolsky, DO

The mainstay therapy for obesity management among clinicians and researchers that don't specialize in obesity treatment is providing advice along the lines of eating fewer calories and/or burning more calories. Obesity is not thought of as a disease, but as a sequelae of laziness and lack of willpower. Many people say "put the fork down" or "push yourself away from the table," implying that these are ways to manage obesity. Unfortunately, following this advice has a very low success rate, which is why we need to shift the way we think about obesity management.

To shift our perception of how to manage obesity, we must first change our views of obesity itself. Instead of being a result of sheer laziness, the pathophysiology of obesity is actually quite complex. Sure, there is an energy imbalance, leading to more energy stored as opposed to burned, but the complexities go much deeper than this. Why does this happen? Does it happen the same way in every person? Why can't people just lose weight and keep it off? These questions are a good starting point to getting a deeper understanding of obesity.

Obesity as a disease

There was an uproar in the fitness community in 2013, when the American Medical Association declared obesity a disease. Many people questioned why someone who eats too much and moves too little should be classified as having a disease. I can understand where this sentiment comes from, when it is said by someone that does not understand obesity. However, the term disease describes obesity very well.

A disease is defined as "a condition of the living animal or plant body or of one of its parts that impairs normal functioning and is typically manifested by distinguishing signs and symptoms." In what ways does obesity not fit this? How do other chronic diseases like hypertension and type 2 diabetes differ from obesity? You don't die from hypertension, you die from the end result of hypertension (e.g. myocardial infarction (MI) or a cerebrovascular accident). Same with type 2 diabetes.

"Many people say "put the fork down" or "push yourself away from the table," implying that these are ways to manage obesity. Unfortunately, following this advice has a very low success rate, which is why we need to shift the way we think about obesity management."

Obesity doesn't kill us through excess adipose tissue. We die from the sequelae: obesity leads to hypertension, which ends with an MI. If we aren't looking at mortality, but instead quality of life, then think about type 2 diabetes leading to neuropathy, which causes awful pain. Obesity also results in a lower quality of life due to conditions like obstructive sleep apnea and osteoarthritis, not to mention the many other affected aspects of health and quality of life.

Obesity is the leading precursor to many of these chronic diseases. If we want to prevent these diseases, shouldn't we be treating the underlying cause? The answer is yes, of course. If we wouldn't hold back giving someone with type 2 diabetes a medicine, then why would we not provide someone with obesity effective treatments? We will get into effective treatment options later.

"But fat just sits there as an energy storage depot!" This is where the pathophysiology of obesity gets really interesting. We used to think of adipose tissue as an inert substance, basically serving as a warehouse for energy until when we needed it later. Researchers have found that our fat is the largest endocrine organ in our body! As readers of ERD are aware, there are hormones called adipokines that our fat tissue releases. These adipokines have various effects on our bodies, some good, some bad. Where we store our fat has an effect on the types of adipokines released as well. People with an "apple" shape, with fat stored centrally (visceral) tend to have the more deleterious types of adipokines, whereas people with a "pear" shape (subcutaneous) tend to have the more benign adipokine profile.

People with central obesity and the metabolic derangements that result from this condition are said to have adiposopathy, or sick fat. This term was coined by obesity researcher and clinician Dr. Harold Bays. Not only is the fat hormonally active, but due to its location (near the liver and portal vein), a higher flux of free fatty acids throughout the body is stored in the muscle, heart,

"People with central obesity and the metabolic derangements that result from this condition are said to have adiposopathy, or sick fat."

and other area of the body. The increase in free fatty acids and adipokines are thought to be the cause of the metabolic issues we see with obesity, like insulin resistance, dyslipidemia, hypertension, and other conditions. The idea of inert fat is old and needs to be buried.

What about people with the pear shape and subcutaneously stored adipose? The metabolic issues described above may not be as relevant, but these people still have a condition called fat mass disease. This is the consequences of having too much body mass, as mentioned above, and it includes osteoarthritis, obstructive sleep apnea, and even symptoms like reflux.

Either way, obesity be considered a disease. If we think issues caused by lifestyle shouldn't be called diseases, then we should stop calling type 2 diabetes and hyper-

tension diseases too. Yes, there are non-lifestyle causes of the aforementioned diseases, but the same can be said for obesity.

The cause(s) of obesity

Much to Gary Taubes' dismay, the fault of obesity doesn't rest on the shoulders of a single macronutrient like carbohydrates. While refined carbohydrates play a role in the disease, there are many other strong factors pushing us towards larger waistlines.

Obesity researcher and ERD reviewer, Dr. Stephan Guyenet, often discusses food reward and hyper palatability of food. What seems as simple as avoiding certain high caloric foods becomes a much tougher task when scientists are trying to create foods that cause our brain wiring to short circuit and crave more of them.

Our appetite regulation also doesn't rely only on the volume of food we eat. The layers of complexities run much deeper. The adipokines mentioned above and the subsequent inflammation can disrupt our appetite and food reward signaling. This partially explains why it might be hard to lose weight once we have gained it.

The microbiome is also involved (another favorite of ERD readers). It's possible the bacteria in our guts control part of our appetite and cravings. Even viruses have been implicated in weight gain, like adenovirus-36.

As a physician, I often see patients who are taking multiple medicines that are thought to be helpful for certain symptoms or disease, but which cause weight gain as a side effect. Kids are being put on powerful antipsychotics for an off-label use, without regard that they will likely experience weight gain and metabolic derangement. Heck, many of my patients use over the counter antihistamines, which could account for a few pounds of weight gain if used chronically. For an exhaustive list of medicines that cause weight gain, refer to my book, *The Fat Loss Prescription*.

Of course, genetics also play a role in our body weight. Researchers are constantly finding various single nucleotide polymorphisms (SNPs) related to our weight. We can't do anything about our genetics. Even more annoying, we don't have control over what our parents and grandparents did, which may have had a large effect on our weight, too. Epigenetics, another fun ERD topic, has been studied more recently in the context of obesity. Turns out the effect our parents had on us in utero was stronger than we once thought, and we may be more likely to store fat than if our parents had chosen different lifestyles.

> "[...] many of my patients use over the counter antihistamines, which could account for a few pounds of weight gain if used chronically."

What can we do though?

Inevitably when I discuss this topic with someone who is an "eat less, more more" pusher, they point out that

we still do need to "eat less and move more." They are absolutely correct, but we also need to find out how to get the individual to be able to actually do so.

There is a reason that weight regain after initial weight loss is so common. The environment, genetic, epigenetic, biological, physiological, and psychological drivers all collaborate to force us back the wrong way. Think about all of the people you know that have obesity. Think of those with obesity who have lost weight. Have most kept it off successfully? If most of the people you know that have had obesity in the past have now lost the weight and kept it off, then I want you to find out their secret and patent it. Research shows that unfortunately lifestyle counseling by itself is not very successful. This is due to the factors described above.

> "Let's face it, dieting is not fun and often our hunger and cravings get the best of us. The forces that drive us to regain are strong and we need strong treatments to combat them."

Let's face it, dieting is not fun and often our hunger and cravings get the best of us. The forces that drive us to regain are strong and we need strong treatments to combat them.

As an obesity medicine specialist, my goal is to find the linchpin in a patient's road map for long-term obesity success. This includes creating a lifestyle they can follow for life, making sure they are not on any medicines that cause weight gain or inhibit weight loss, and deciding on whether they need a medicine and/or surgery that will help them with their lifestyle.

Many fitness professionals balk at the idea of a medicine that helps with weight loss. The truth is that these medicines work in the brain to actually help you "eat less and move more." Instead of feeling miserable on a diet and feeling driven to eat highly palatable foods, these medicines work in the parts of the brain that contain our appetite and food reward centers to take the edge off. As explained above, our brains may not be functioning properly due to our weight and other factors. Why not use a deemed safe medicine to push back the other way, toward weight loss?

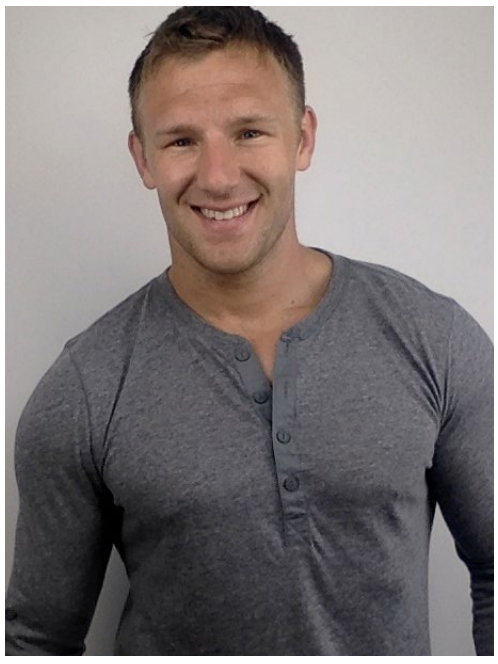
There are currently four medicines approved for long-term weight loss in the U.S. Each work in different ways in our brain to help with lifestyle adherence. Since safety is a concern, there are long-term trials currently going on to ensure the adverse effects of these medicines are minimal and that our treatment of obesity is saving lives and/or improving quality of life.

While I am a medical bariatrician (nonsurgical weight loss physician), I do understand that weight loss surgery is actually the most powerful tool we have when fighting obesity. Just like medicine, the surgery isn't a magical procedure that automatically makes someone lose weight and keep it off forever. Surgical weight loss

is another method that allows patients to stick to a lifestyle over the long term and have a much higher chance of success than without (in many cases). In fact, weight regain (bariatric surgery recidivism) is common when the new lifestyle is not adhered to.

There are multiple bariatric surgeries available today, but the most common are the roux en y gastric bypass and the vertical sleeve gastrectomy. It was thought these worked by shrinking the size of our stomach and therefore our ability to eat large portions, but we are now finding these procedures also affect the aforementioned drivers of obesity (adipokines, gut hormones, micro biome, etc). No matter the reason they work, they are the most efficacious treatment we have right now for obesity.

So, do we still believe that obesity is just a matter of "pushing ourselves away from the table?" As heard from ERD reviewer and renowned obesity researcher Dr. Arya Sharma at an obesity conference, we wouldn't tell someone with depression to just "cheer up." Why would we tell someone with obesity to just "eat less and move more?" ◆



Dr. Spencer Nadolsky is a board certified Family Medicine Physician and a Diplomate of the American Board of Obesity Medicine. He is the medical editor for Examine.com. Dr. Nadolsky is the author of *The Fat Loss Prescription*, now available on Amazon.com.

His love for lifestyle as medicine began in athletics, where he worked using exercise and nutrition science to succeed in football and wrestling. After wrestling at UNC Chapel Hill as a Tar Heel heavyweight and earning a degree in exercise science, he headed to Edward Via College of Osteopathic Medicine in Blacksburg. During medical school, Dr. Nadolsky attended multiple obesity medicine conferences and realized that he wanted to apply the same nutrition and exercise information he learned during his athletics to the general population and health. After medical school, he attended VCU's Riverside Family Medicine Residency in Newport News to hone his skills. He is currently practicing in Olney, Maryland. He launched the book Skinny on Slim and has a blog called Through Thick and Thin.

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.

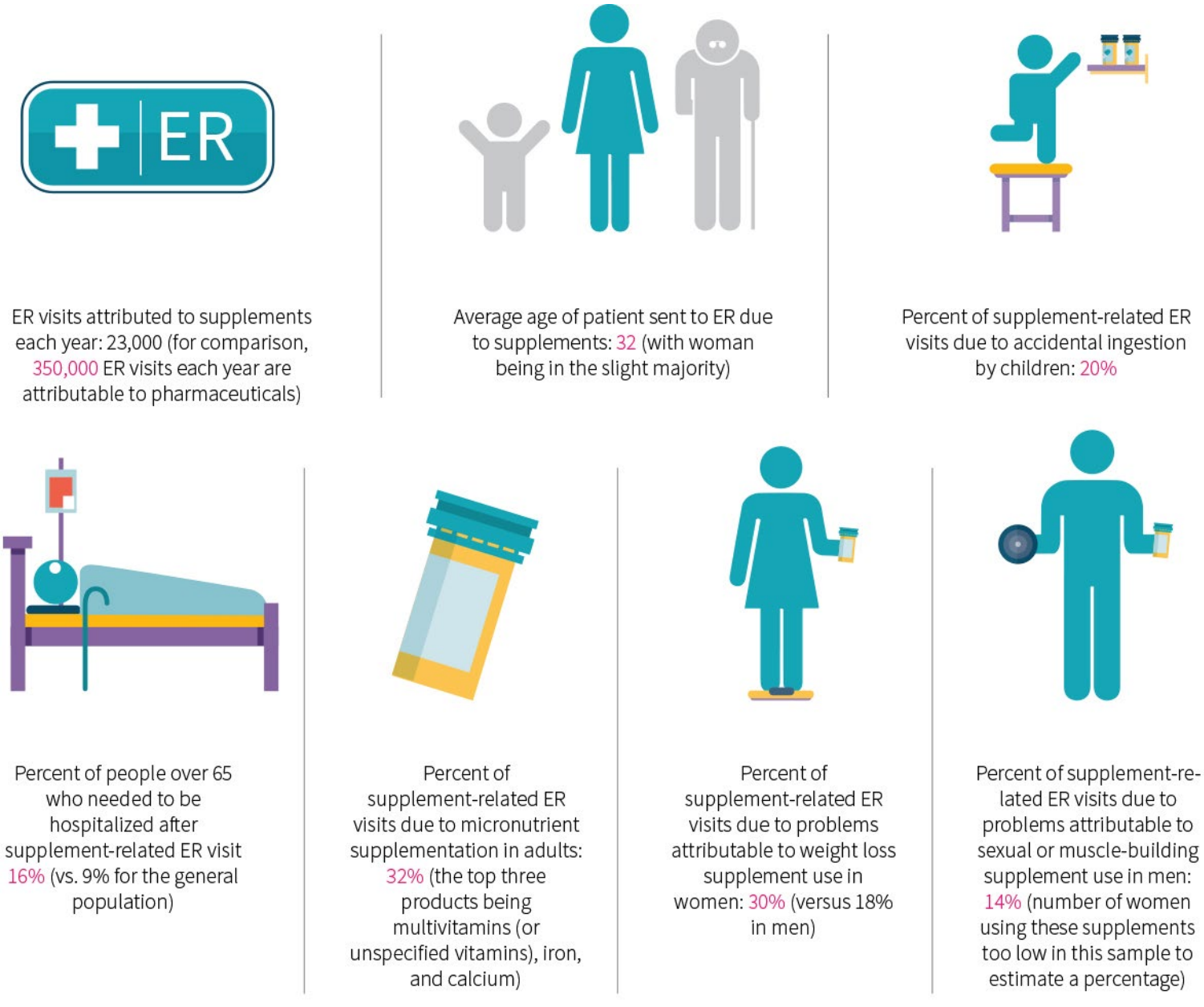
Adverse events were classified as anything causing adverse or allergic reactions, excess doses, unsupervised ingestion by children, or other events like choking. Due to the non-standard death registration practices among different hospitals, cases involving a mortality were not included, as were any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

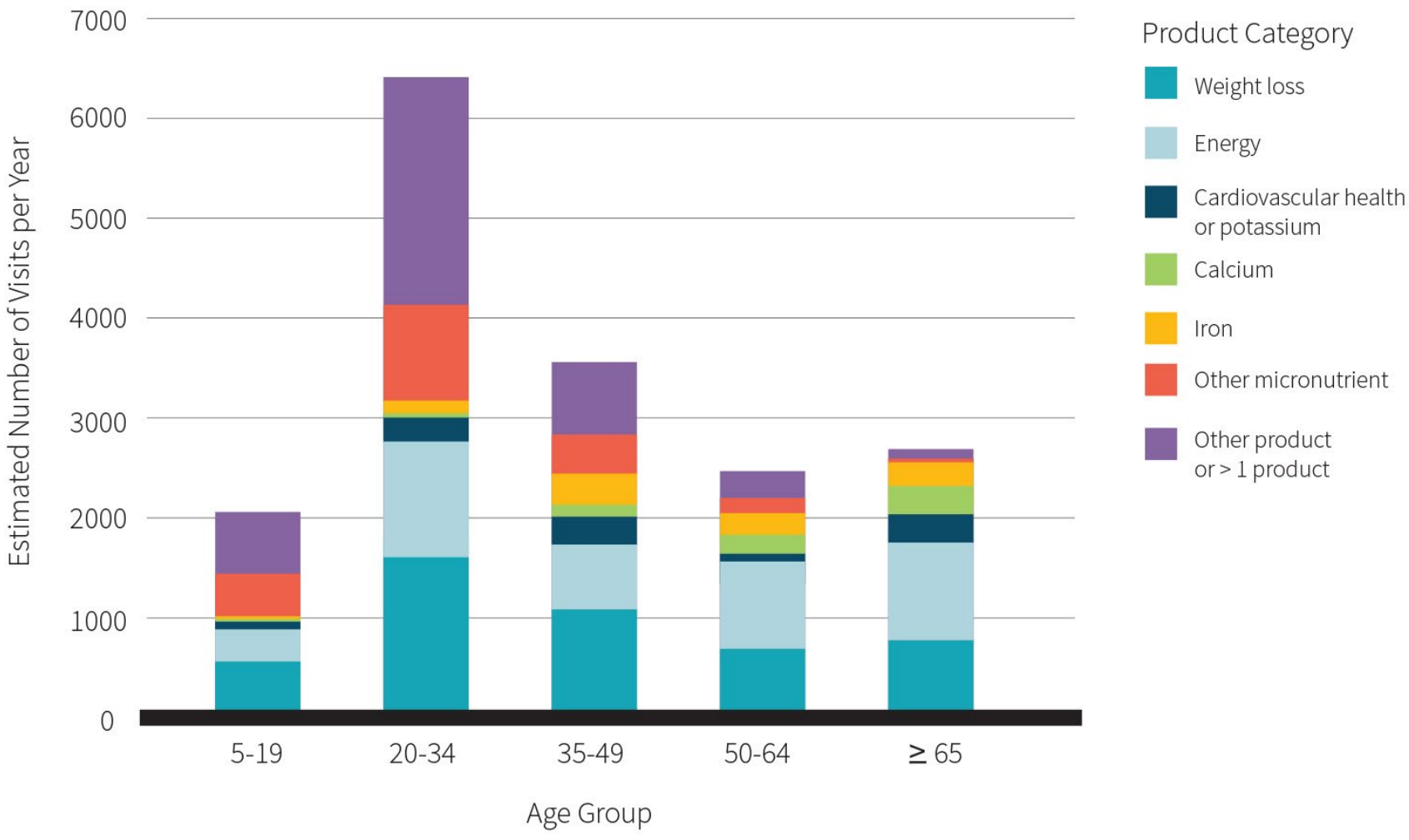


of 23,000 supplement-related emergency department visits per year, with estimates ranging from 18,600 to 27,400. Of these 23,000 emergency room visits, it was calculated that about 2,150 (9.4%) of these result in hospitalization. About 88% of these ER visits were attributed to a single supplement, as 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

In closing...

Thanks again for reading ERD. We enjoy helping people stay up to date on research, whether you're dietitians, trainers, physicians, or simply people interested in improving your health.

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