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From the Editor

One of the reasons you read the ERD is probably because you're looking for an unbiased, but in-depth, review of recent evidence about nutrition. Summarizing the evidence that's out there is pretty much Examine.com's *raison d'être*. However, we may have outdone ourselves in reviewing the evidence in this volume, where we review a review of reviews of the evidence.

That's pretty meta, so feel free to take a moment.

The, er… review I'm talking about concerns melatonin, which is a pretty well-studied molecule that may have more uses than just for sleep. Part of this idea is evident from the fact that it's not just humans who make melatonin — even some bacteria and plants synthesize the stuff, so it's clearly not just there to tell them that it's time to stop watching Netflix and go to bed! But it still may impact aspects of their circadian rhythms, even if it doesn't tell them that it's time to close the laptop. For instance, some gut bacteria seem to respond behaviorally to melatonin, which opens up the interesting possibility that our circadian rhythms could influence our microbiome. Plants may use melatonin to regulate reproductive rhythms, regulate growth, and also as an antioxidant.

Melatonin's antioxidant properties may also be useful for human disease as well. And, as we briefly state in our article, circadian rhythm problems may also lead to inflammatory issues and could contribute to diseases like hardening of the arteries. If melatonin can help circadian rhythms get back on track, it could also possibly play a preventive role in disease.

While melatonin *could* do a heck of a lot, the only question that really matters in terms of health is what it *actually* does. The melatonin study that we cover in this volume attempts to find out what the science says by systematically searching the literature for reviews of melatonin's effects in humans, as well as in animals and test tubes, and summarizing the state of the evidence.

In other words, it's an "umbrella review" — a review of reviews. Umbrella reviews are a useful way to answer broad questions for a topic for which a lot of research has been done. The umbrella review we cover in this volume examines a single molecule (melatonin) and looks at the evidence for its possible effects by searching for and summarizing reviews on the topic. However, umbrella reviews can also work the other way around: you can ask what works for a single outcome and search for reviews of all the things that have been tested.

So, now that you've read a summary of a review that reviews a review of reviews, on to the research!

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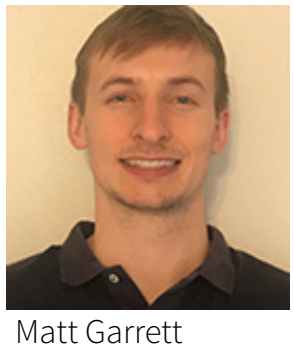

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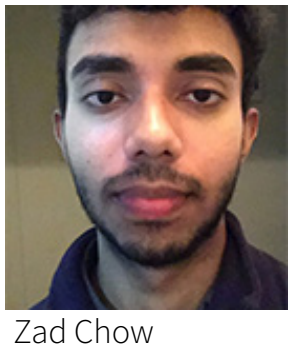

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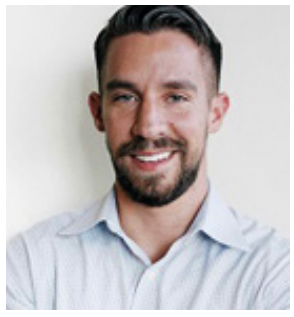

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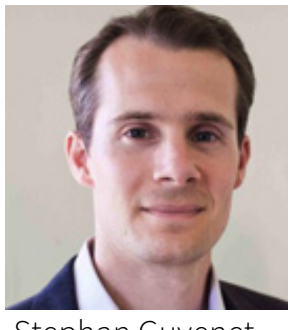

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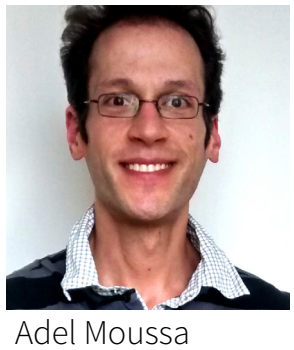

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Do saturated fats fatten up your liver?

Saturated Fat Is More Metabolically Harmful for the Human Liver Than Unsaturated Fat or Simple Sugars

Introduction

About one in four people in the world have non-alcoholic fatty liver disease (NAFLD), a condition characterized by an excessive (more than 5%) infiltration of the liver with fat (steatosis) due to non-alcoholic causes. It is strongly associated with metabolic problems, such as type 2 diabetes, cardiovascular disease, and nonalcoholic steatohepatitis (liver fat accumulation accompanied by inflammation). You can see some statistics about NAFLD's prevalence illustrated in Figure 1.

Liver fat content originates primarily from adipose tissue (59%), with lesser contributions from hepatic *de novo* lipogenesis (DNL, the creation of fatty acids within the liver; 26%), and dietary fat (15%). Still, the roles of DNL and dietary fat in NAFLD have raised questions about how macronutrient composition affects its development.

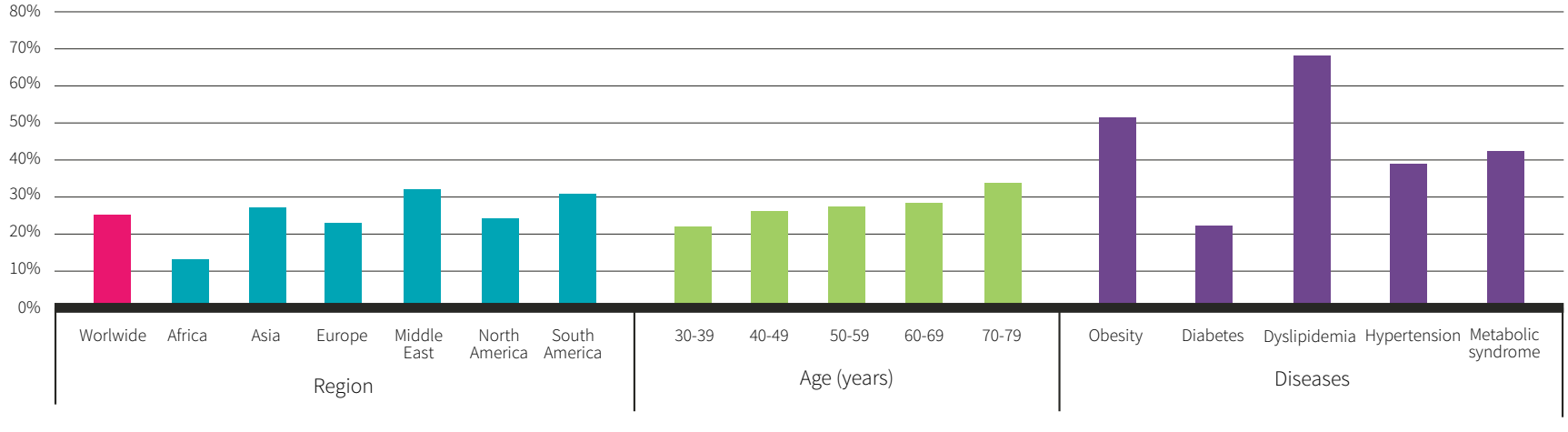
Mechanistic studies have demonstrated that high-sugar diets increase both DNL and liver fat, at least under conditions of calorie excess. Similarly, at least one study has compared the effects of overeating saturated fats (SFAs) or polyunsaturated fats (PUFAs), and found that liver fat increased more with SFA despite similar weight gain between groups.

Ceramides, which are major components of cell membranes derived from SFAs, are a possible explanation for SFA-induced NAFLD due to their involvement in insulin resistance (IR). This, in turn, interferes with glucose metabolism and increases hepatic gluconeogenesis (glucose production by the liver). On top of that, evidence suggests that some lipid-induced inflammatory signals, possibly stimulated by gut microbiota-driven endotoxemia or a crosstalk between gut microbiota and dietary lipids, are stimulating ceramide biosynthesis.

Most of the data regarding the relationship between NAFLD-associated IR and ceramides is from animal studies, and there have not been many studies comparing overfeeding of SFA, unsaturated fatty acids (monounsaturated FA [MUFA] and PUFA), and simple sugars on liver fat content. The study under review aimed to determine the influence of hypercaloric diets with different macronutrient and FA compositions on measures of NAFLD and its associated IR.

Non-alcoholic fatty liver disease (NAFLD), an abnormal buildup of fat within the liver, affects 25% of the global population. It is strongly associated with metabolic dysfunction, and diet is known to play a role in its development. The study under review assessed how hypercaloric diets of different macronutrient and fatty acid (FA) compositions would influence measures of NAFLD and its associated insulin resistance (IR).

Figure 1: Prevalence of NAFLD by world region, age, and health status



Reference : Younossi et al. Hepatology. 2016 Jul.

Who and what was studied?

This was a three-week randomized clinical trial involving 38 middle-aged, overweight and obese adults (21 females and 17 males). Participants were excluded if they had diabetes or other significant disease other than NAFLD. Baseline liver fat concentrations averaged just under the 5% cut-off for NAFLD, ranging 4.3–4.9%.

The participants were randomly allocated to consume one of three hypercaloric diets (more than 1,000 kcal above requirements) in which the additional calories were provided by the research staff. The SAT group overate 30 grams of coconut oil, 40 grams of butter, and 100 grams of blue cheese. The UNSAT group overate 36 grams of olive oil, 26 grams of pesto, 56 grams of pecans, and 20 grams of butter. The CARB group overate 280 milliliters of orange juice, 430 milliliters of sugar-sweetened beverage, and 200 grams of candy. The details of the macronutrient content of the diets are laid out in Figure 2.

Adherence to the diet was reinforced by weekly contact with a study dietitian and verified with three-day dietary records before and after the intervention, and by measuring the fatty acid composition of VLDL-TG as an objective biomarker.

The preregistered primary outcomes were liver fat content, visceral and subcutaneous abdominal fat mass, rates of DNL, and rates of lipolysis. Secondary outcomes included fasting glucose and insulin, C-peptide, liver enzymes, blood lipids, resting metabolic rate (RMR), and subcutaneous abdominal fat cell size and gene expression. The composition of the gut microbiome was also reported, but not preregistered.

This three-week randomized clinical trial involving 38 overweight or obese adults compared the effects of overeating 1,000 kcal per day from primarily saturated fat, unsaturated fat, or simple sugars. The primary outcomes were liver and abdominal fat content, DNL, and rates of lipolysis.

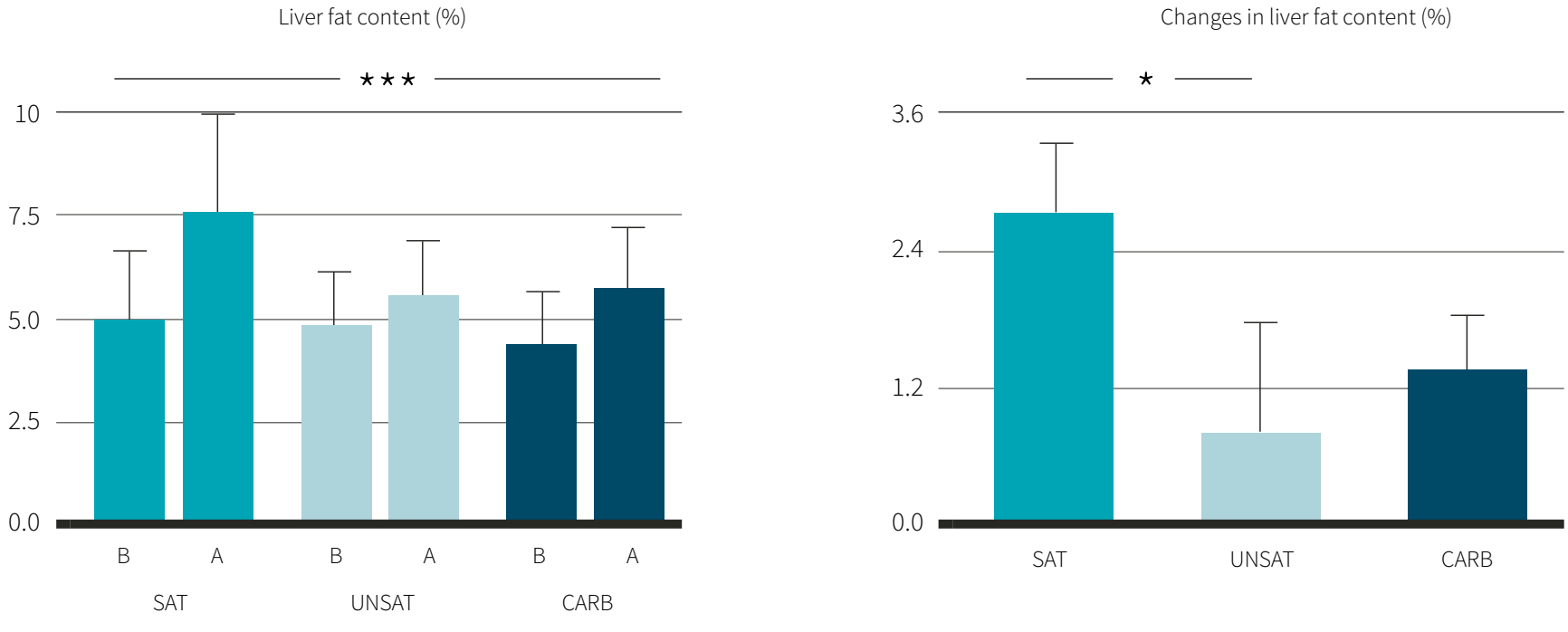
What were the findings?

All overfeeding diets significantly increased liver fat content compared to baseline. The increases were 55% in the SAT group (7.6% vs 4.9%), 15% in the UNSAT group (5.5% vs 4.8%), and 33% in the CARB group (5.7% vs 4.3%). The difference between the SAT and UNSAT groups was statistically significant. The liver fat numbers are illustrated in Figure 3.

Figure 2: Macronutrient composition of the diets

	SAT	UNSAT	CARB
Total fat	58.9%	59.7%	23.8%
Saturated fat	32.7%	14.3%	8.3%
Monounsaturated fat	12.8%	27.7%	8.5%
Polyunsaturated fat	4.5%	11.4%	3.4%
Carbohydrate	25.9%	22.7%	63.7%
Protein	15%	13.2%	11.4%

Figure 3: Liver fat before (B) and after (A) the intervention (left) and its absolute change (right)



Changes in liver fat content were independent of changes in bodyweight, which also increased in all groups by about 1.4%, or 0.9-1.4 kilograms. Both visceral and subcutaneous abdominal fat mass tended to increase in all groups, but these changes did not reach statistical significance.

Rates of DNL nearly doubled in the CARB group and remained unchanged in the other groups. Fasting lipolysis rates were not affected in any group, but lipolysis rates during a hyperinsulinemic-euglycemic clamp were significantly increased in the SAT group (+11%), reduced in the UNSAT group (-17%), and unchanged in the CARB group. Differences between groups were significant.

Fasting insulin (+17%), HOMA-IR (+23%), and total plasma ceramides (+49%) significantly increased in the SAT group only, with the ceramide increase being significantly greater than in both other groups. The SAT group was also the only group to experience significant increases in HDL-C (+17%), LDL-C (+10%), liver enzymes, and endotoxemia (+9%). No changes in any group were seen for triglycerides.

Finally, the SFA diet upregulated fat cell genes related to promoting inflammation. The CARB group saw some increases in inflammatory gene expression, but most were related to carbohydrate metabolism. The UNSAT group saw the fewest changes in gene expression, with most related to energy production and cell integrity.

The SFA group experienced the greatest increases in liver fat content during overfeeding, followed by the CARB and then the UNSAT groups. The CARB group was the only one to experience an increase in DNL, while only the SFA group experienced increases in insulin resistance, ceramides, and endotoxemia.

What does the study really tell us?

This study suggests that three weeks of overfeeding, regardless of whether one splurges on saturated fats, unsaturated fats, or sugars, will increase liver fat in already overweight individuals. The novelty of this study comes from it being the first human study to compare these groups, and showing that overeating

saturated fats has the most pronounced effect on liver fat accumulation and the most detrimental effect on a variety of other health parameters.

The study is not just the first to investigate the differential effects of overfeeding with saturated fat, unsaturated fat, or sugar — it is also the first human trial to pinpoint the different mechanisms. While the sugar diet triggered an increase in liver fat by increasing liver DNL, overfeeding with SFA increased the liver fat by promoting adipocyte lipolysis. As previous studies have shown, most liver fat accumulates as a result of lipolysis.

Since diabetic individuals were excluded, but fasting serum insulin and HOMA-IR levels increased in the SAT group, this study suggests that saturated fat promotes IR and that replacing SFA with MUFA, PUFA, or even sugar could ameliorate the overfeeding-induced increase in IR. In this context, it is worth mentioning that the SAT group had lower baseline serum insulin and HOMA-IR levels (whether the difference was statistically significant cannot be determined, based on the reported data) and that these measures have demonstrated substantial levels of interindividual and intraindividual variability for diagnosing and/or monitoring IR. Thus, more research may be needed to verify SFA's impact on IR.

One potential reason for the seemingly amplified influence of SFA on NAFLD is the negative effects of SFAs on the microbiome, with the increase in endotoxemia and inflammation contributing to the increased formation of ceramides and the augmented increases in liver fat. Moreover, the fact that the ceramide levels showed no correlation with the weight gain supports the hypothesis that they may be mechanistically involved in the increased liver fat deposition or IR of NAFLD seen with SFA overfeeding.

Even though the study had no rigorous dietary control, several measures were included to ensure compliance. Weekly contacts with a dietitian, analysis of VLDL-TG as an objective biomarker of recent dietary FA intake, and similar increases in bodyweight across groups suggest a high level of adherence.

Despite the sensitive monitoring and quality of biomarkers used to evaluate the influence of the hypercaloric diets on lipid metabolism, along with the effective measures to ensure compliance, the study had some limitations. There was no control group being overfed beyond their habitual diet, physical activity was neither assessed nor standardized, and even though the sample size should be sufficient to detect 1.4% differences in liver fat accumulation when comparing the three groups, the sample size was still quite small. Moreover, the results are limited to overweight, but healthy, individuals and may not translate well to an athlete overfeeding to put on muscle.

This study suggests that overfeeding will increase the liver fat content of healthy overweight participants, regardless of the macronutrient composition of the extra food. Saturated fat appears to have a greater effect on liver fat accumulation. The underlying mechanisms for liver fat accumulation between diets appear to be fundamentally different; while sugar overfeeding seemed to increase liver fat via *de novo* lipogenesis, saturated fats increased lipolysis, inflammation, endotoxemia, and ceramides. The study also suggested that saturated fact could impact IR, but more work is needed to verify this.

The big picture

Overfeeding and obesity, as well as the excessive consumption of fructose, trans-fatty acids, and saturated fat, is associated with NAFLD, while caloric restriction appears to reduce NAFLD and associated symptoms. Even short-term caloric restriction provides positive temporal changes regarding liver fat content, hepatic insulin sensitivity, and glucose production. Before the

results from the study under review, the influence of the macronutrient and FA composition of the diet was known only for SFA and PUFA, with SFA demonstrating greater increases in liver fat. Even in an isocaloric diet, SFA-enriched diets appear to increase liver fat content compared to PUFA — a result that is in line with the epidemiological observation that people with NAFLD tend to have a reduced PUFA:SFA ratio in their diets.

One of the postulated mechanisms through which SFAs contribute to greater liver fat accumulation is through increased lipolysis. High-saturated fat diets have been shown to stimulate lipolysis via inflammatory mediators in mice. The study at hand seems to confirm the existence of a similar mechanism in humans. In fasted participants with NAFLD and obesity, adipose tissue lipolysis, DNL, and dietary fat supply accounted for about 59%, 26%, and 15% liver fat accumulation, respectively. Simple sugars, which produced a measurably lower increase in liver fat (33%) compared to SFA (55%) in the study at hand, have demonstrated proportional increases in liver fat through DNL simulation. PUFA, on the other hand, appear to reduce lipolysis and may—outside of an overfeeding context—help reverse NAFLD.

Metabolic diseases such as insulin resistance, chronic inflammation, and NAFLD are so intricately intertwined that it is often difficult to distinguish cause and effect. NAFLD is regarded as a potent predictor for type 2 diabetes and cardiovascular disease, independent of obesity. The existence of a weight-independent link between NAFLD and T2DM is further supported by the observation that people with T2DM have 80% greater liver fat content when compared to people without diabetes, matched for age, sex, and bodyweight. Which one causes which, or whether they are both caused by a common factor, is hard to say.

It has been suggested that liver fat levels are a marker, and not a cause, of IR. Corresponding evidence comes from gene studies showing that certain genotypes are associated with NAFLD but not IR. After all, the study under review did not demonstrate convincing measures for IR. Keep in mind that just because something is deemed a significant difference, it may not be clinically meaningful. IR diagnosis values for HOMA-IR vary across populations (1.55 to 3.8) meaning it may not be the most sensitive measurement, especially when, in the study at hand, baseline values ranged from 1.3 to 5.0.

Ceramides are types of sphingolipids that have demonstrated influence on glucose homeostasis and insulin signaling. Previous studies have shown that the prevention of ceramide accumulation or inhibition of its signaling appears to improve IR. Corresponding models seem to confirm this connection. Few studies link increased ceramide levels to IR in humans. One study reported reduced ceramide accumulation with exercise, as exercise has been shown to improve insulin sensitivity. While there is a probable connection, more human research is necessary to confirm the causal link between ceramides and IR in humans.

Macronutrient compositions aside, overfeeding will not only lead to obesity, but will likely be accompanied by NAFLD. Beyond reduced caloric intake, reductions in saturated fat and simple sugars and increases in PUFA can lead to positive changes in liver fat content and other NAFLD-related markers. It is uncertain whether dietary based changes related to NAFLD are causally linked to increases in IR in humans.

Frequently asked questions

What are some of the dietary recommendations for people with NAFLD?

Since there are no approved medicines to treat NAFLD, lifestyle and dietary recommendations are the staple. Recommendations include reducing bodyweight by 7-10%, reducing saturated fat to less than 7% of total

calories, minimizing trans-fatty acid intake, maintaining cholesterol intake below 200 milligrams per day, and keeping fat intake to 25-35% of caloric intake. A simpler guideline is a Mediterranean-type diet with emphasis on legumes, fruits, vegetables, fish, nuts, whole grains, with or without caloric restriction.

How do saturated fats affect cardiovascular disease risk? Saturated fats are not inherently harmful. Research has suggested that there is no significant association between saturated fat consumption and the risk of heart disease. Moreover, many of the long-term interventions on this topic were flawed in ways that prevent drawing conclusions about saturated fat per se. When discussing the cardiovascular risks associated with saturated fat, the type of macronutrient that is replacing it in the diet plays a large role.

Still, saturated fats do increase several heart disease risk factors compared to unsaturated fats and carbohydrates, which may be reason enough to limit its consumption in favor of these other nutrients. It's also important to be mindful of the effects of whatever food is supplying the saturated fat, since the food matrix can mediate effects.

What should I know?

This three-week parallel randomized clinical trial comparing the metabolic responses to overfeeding with saturated fats, unsaturated fats, and simple sugars demonstrated increases in liver fat content for all macronutrients, implying that overfeeding is a main driver. However, liver fat content increased more from saturated fat overfeeding than unsaturated fat overfeeding, likely through inflammation-induced increases in lipolysis, while simple sugars appear to have increased overweight participants' liver fat content through stimulation of *de novo* lipogenesis. Whether dietary macronutrient composition has an impact on insulin resistance in the context of NAFLD is uncertain. ◆

Discuss how great it would be to overfeed yourself, in the name of science, on the ERD Facebook forum!

ERD Mini: Expert consensus statements on multivitamin and multimineral supplement use

In November of 2016, an international group of 14 nutritional experts were gathered to create a set of statements concerning multivitamin and multimineral supplement use. While Pfizer sponsored the event, the company had no role in the process or in crafting the article reporting the results of this panel discussion, which was published earlier this year.

The experts discussed the evidence and used what's called a modified Delphi process to agree upon a set of nine statements about this issue. After a draft of nine statements was made, the experts used a Likert-type scale to rate the level of agreement or disagreement with the statement. Over several months, they remotely discussed the evidence and modified the statements, and ultimately met in June 2017 in person for a final vote, where they reached consensus. "Consensus" was pre-defined as 80% or more of the panelists either "agreeing strongly" or "agreeing with reservation" with the statement.

Here are the nine statements about multivitamins and multiminerals that the panel came to a consensus on:

1	For the purpose of broad-spectrum micronutrient supplementation for a general population, multivitamin and multimineral supplements (MVMS) should contain at least the micronutrients that are commonly underconsumed relative to their recommended intakes within that country/region. Most of these vitamins and nutritionally essential minerals should be present in amounts approximating recommended intakes. Within this context, MVMS may be safely formulated for large subgroups according to age, sex, and/or life-cycle–specific micronutrient needs.
2	Several factors are associated with deficient, inadequate, or adequate micronutrient intake: biological functions; cellular, metabolic, or physiological states; and health outcomes. For some micronutrients, higher intakes might provide added health benefits.
3	Achieving micronutrient intake levels on a population-wide and individual basis that are consistent with established reference values should be an explicit public health goal.
4	Using a daily MVMS is one way to help provide the recommended intake levels of many micronutrients that are necessary for maintaining health through supporting the function of specific metabolic pathways, cells, organs, or other physiological systems.
5	On a population basis, use of daily MVMS reduces the prevalence of inadequate intakes of the micronutrients they contain.
6	Based on current knowledge, the long-term use of MVMS with an amount not exceeding the upper limit is safe in healthy adults.
7	The evidence that long-term use of MVMS contributes to a reduction in the risk of some chronic diseases is insufficient to support the use of MVMS in the primary prevention of these diseases.
8	MVMS use in populations with inadequate intakes or increased needs of micronutrients can provide benefits to apparently healthy individuals, including children, pregnant women, and older adults.
9	Some individuals with chronic medical conditions experience nutritional deficiencies and/or inadequacies that can be prevented and treated with adequate dietary management and/or the use of MVMS.

Do you find these consensus statements to be useful, clear, and actionable, or not? Why? Share your thoughts around these consensus statements on the ERD Facebook forum.

DASHing toward lower blood pressure

Comparative effects of different dietary approaches on blood pressure in hypertensive and pre-hypertensive patients: A systematic review and network meta-analysis

Introduction

Over one billion adults suffer from high blood pressure, or hypertension, worldwide. It affects one in four men and one in five women. Heart disease is the number one cause of death in the world, and hypertension is one of its leading risk factors. The global direct medical costs of hypertension are estimated at $370 billion per year, while savings from effective management of blood pressure are projected at about $100 billion per year.

Current management and treatment for hypertension commonly involves medication, supplements, and/or lifestyle changes. The average reductions in systolic and diastolic blood pressure for antihypertensive drugs, supplements, diets, and exercise have been reported to be 9/5 mmHg, 4/2 mmHg, 6/4 mmHg, and 5/3 mmHg, respectively. While drugs are generally the most effective way to reduce blood pressure, adherence can be surprisingly low, reported at 18.8% of participants in one study.

On the other hand, dietary approaches to reduce blood pressure (BP) are effective and have reported adherence levels of up to 95%. But, which dietary approach is best? Unfortunately, guidelines sometimes emphasize different aspects of diet, and are occasionally inconsistent with one another. For instance, the American Heart Association's guidelines suggest that hypertensive and prehypertensive people should consume less alcohol and sodium and more fruits, vegetables, and low-fat dairy products. The European Society of Hypertension and European Society of Cardiology guidelines, on the other hand, includes extra emphasis on reductions in saturated fat and cholesterol, accompanied by increases in fiber and plant protein.

These inconsistencies become all the more obvious when considering all the different dietary approaches that exist in the context of blood pressure reduction. To list a few, the Dietary Approaches to Stop Hypertension (DASH) diet, the Mediterranean diet, and a simple low-sodium diet all have evidence suggesting they have some impact on BP. Are all of these equally effective? The study under review sought to answer this question by performing a network meta-analysis of randomized controlled trials (RCTs) comparing anti-hypertensive diets.

The prevalence of hypertension is high and increasing, impacting global mortality and health costs. A variety of diets are recommended for and have demonstrated efficiency at lowering blood pressure. The study under review was designed to compare these diets, so as to establish a clinically meaningful hierarchy of antihypertensive dietary patterns.

Who and what was studied?

This systematic review and network meta-analysis compared the effect of different dietary interventions on systolic (SBP) and diastolic blood pressure (DBP) in hypertensive and pre-hypertensive participants. The study was preregistered, the protocol was published before the results were obtained, and it followed the PRISMA guidelines and its extension for network meta-analysis.

The authors searched for randomized controlled trials comparing different dietary interventions or comparing diets to a control group. The studies had to last at least three months and include adults with hypertension (SBP equal to or greater than 140 mmHg or DBP equal to or greater than 90 mmHg) or prehypertension (SBP 130-139 mmHg or DBP 85-89 mmHg). Studies that included pregnant women or children, were based on a single food, used supplementation, exercise or medication as co-interventions added to the diet, and involved very low-energy diets (less than 600 kcal per day) were excluded.

In the end, 67 studies, spanning 13 dietary interventions recruiting 17,230 participants, met the eligibility criteria. The studies lasted between three and 48 months, had

participants with an age average between 23.6 and 71 years, a BMI between 23.6 and 45.4, and were primarily conducted in Europe (n=29), North America (n=18), and Australia and New Zealand (n=15). The primary outcomes were changes in SBP and DBP.

A random effects network meta-analysis was performed to quantify the relative effect of each dietary intervention against every other dietary intervention. The network meta-analysis method allows for simultaneous comparisons of multiple interventions, even if the studies it synthesizes compare them two at a time. For more on the basics of what a random effects network meta-analysis is, see the sidebar.

In addition, various assessments were performed to

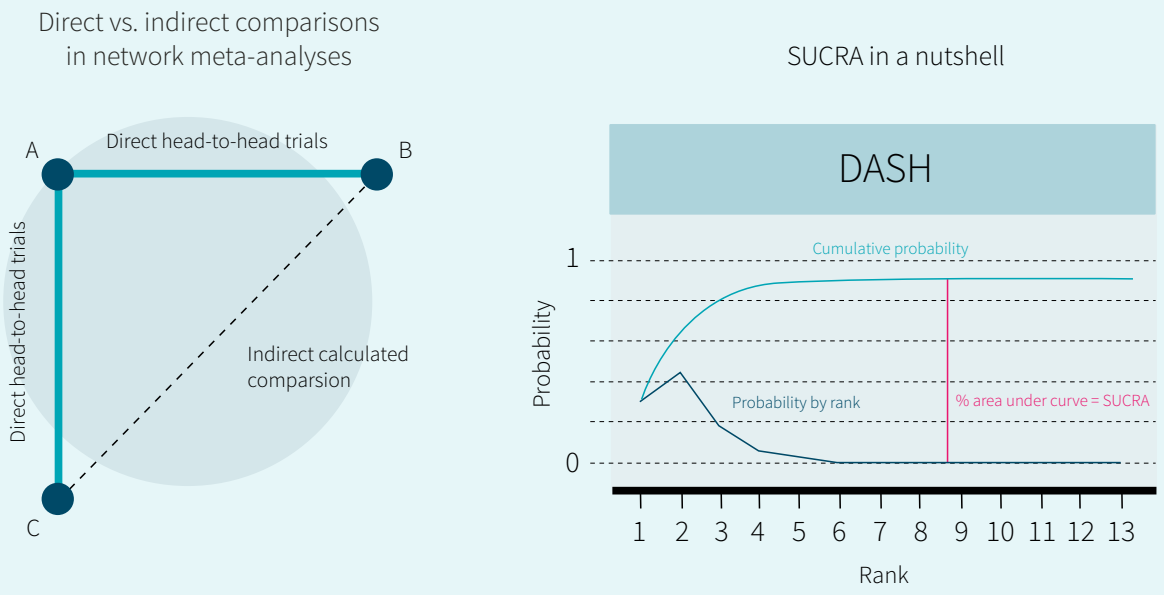
Network meta-analysis 101

When there are many studies comparing just a couple of interventions or a single intervention to a control, how does a researcher choose the best out of all available interventions? A network meta-analysis helps to generate practical evidence-based answers to these questions.

Clinical trials typically consist of a direct comparison between two interventions (or an intervention compared to a control). A traditional meta-analysis can synthesize these trials only if the interventions and controls are similar. A network meta-analysis extends this concept by integrating direct comparisons (ones where clinical trials have been done), while also using statistical modelling to yield indirect comparisons (comparisons where no trial has actually been performed). As an oversimplified example, if trials comparing A to B exist, and there are other trials comparing A to C exist, network meta-analysis can calculate how B compares to C even though there aren't trials that directly compare B to C.

One valuable number that can be obtained from network meta-analyses (and was calculated in the study under review) is called the surface under the cumulative ranking curve (SUCRA). Each treatment in a network meta-analysis can have a SUCRA associated with it. It indicates the relative ranking of the treatment—in other words, how good it is compared to the others. It ranges from 0% to 100%, and can be roughly thought of as the probability that the treatment is among the best of the bunch. The higher an intervention's SUCRA value, the more likely it is that it ranks near the top of all treatments considered in the network-meta-analysis. If a treatment is definitely the best of those considered, it would have a SUCRA of 100%. The ideas of indirect comparisons and SUCRA are illustrated in Figure 1.

Figure 1: Some basic ideas in network meta-analysis, illustrated



evaluate quality of the results, including assessment of transitivity and statistical inconsistency (assumptions necessary to properly perform this type of network-meta-analysis), subgroup and sensitivity analyses, influence of small studies and overall publication bias, and credibility of the evidence.

The study under review is a systematic review and network meta-analysis of 67 studies comparing 13 dietary interventions for their effects on blood pressure. Studies included had to be of randomized or controlled design, longer than three months, and recruit hypertensive and prehypertensive adults.

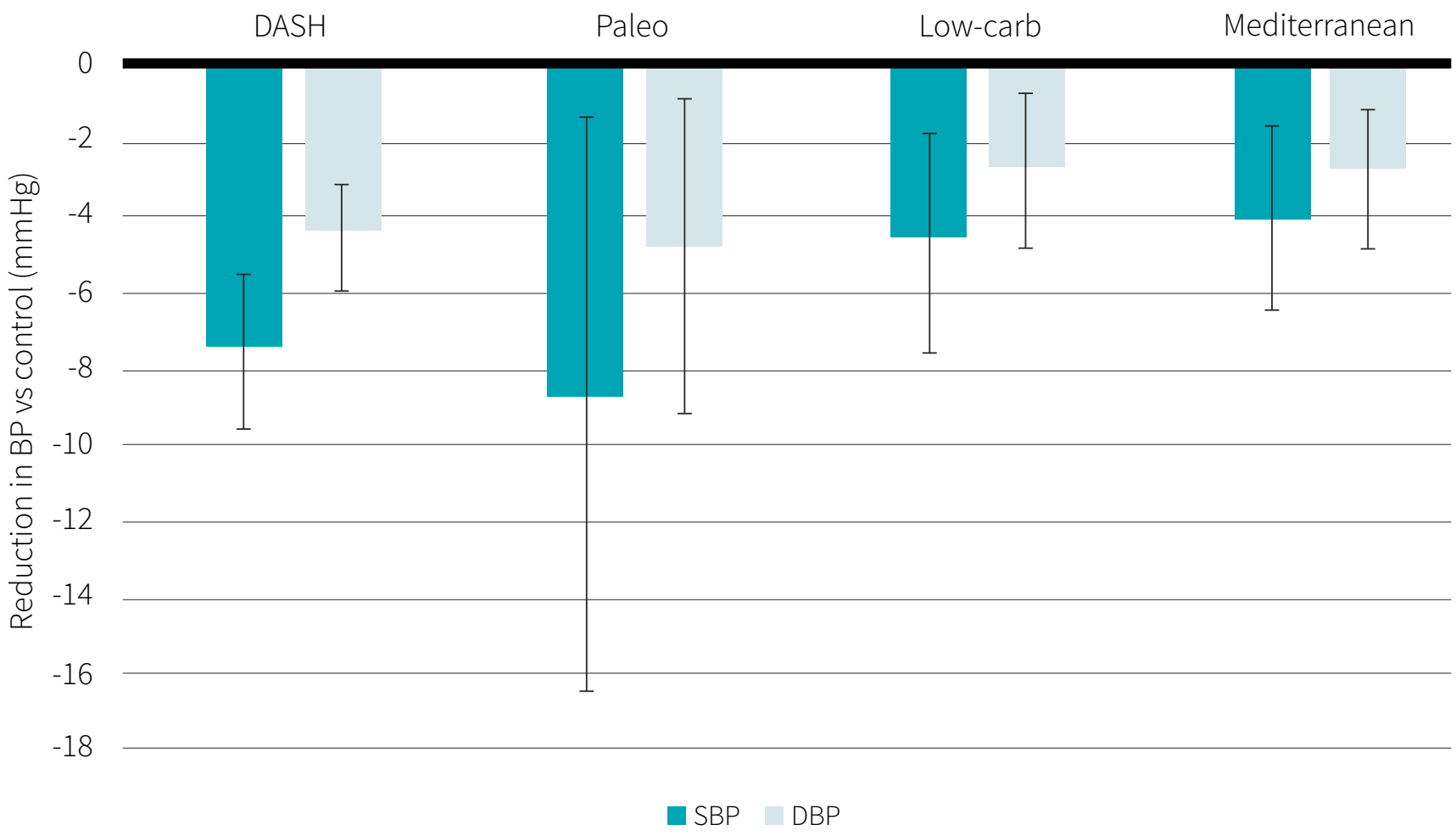
What were the findings?

The DASH, Mediterranean, low-carbohydrate, Palaeolithic, high-protein, low-glycemic index, low-sodium, and low-fat dietary approaches were significantly more effective in reducing SBP (-8.73 to -2.32 mmHg) and DBP (-4.85 to -1.27 mmHg) compared to a control diet. Of these, the DASH diet was the most effective (SUCRA of 90% for SBP and 91% for DBP), followed by the Paleolithic diet, the low-carbohydrate diet, and the Mediterranean diet. The BP reductions for these top four diets are shown in Figure 2. Most of the comparisons between diets exhibited a low-to-moderate credibility (meaning the certainty of these comparisons isn't high), while DASH vs. low fat was rated with high credibility.

The comparisons with the largest number of trials (direct comparisons) included high protein vs. low fat (n=12), low sodium vs. control (n=10), low fat vs. control (n=9), and low carbohydrate vs. low fat (n=8). However, most of the contribution to the study results came from indirect comparisons.

In terms of risk of bias, 23 trials were of low risk, five of high risk, and 39 were of moderate or unclear risk, with the dominant reason being blinding practices. This isn't too surprising, though, since blinding participants to a

Figure 2: BP reductions for the top four diets with 95% CIs



dietary intervention is difficult. Inconsistency among results within the same dietary approaches from different trials was only identified among comparisons of dietary approaches that differed greatly in total fat and carbohydrate intake ratio (for example, Mediterranean, low fat, low carbohydrate, etc.).

Subgroup analysis by study duration suggested that studies lasting more than 12 months resulted in different outcomes than the primary analysis. Specifically, the Paleolithic diet became the most effective for reducing SBP, followed by the Mediterranean and low-carbohydrate diets. Similarly, the Paleolithic diet was superior for reducing DBP, followed by the Mediterranean and high-protein diets. It is not clear how DASH would have fared in this comparison, since the longest DASH study included in this analysis was six months. A separate subgroup analysis by sample size suggested that studies with smaller sample sizes (less than 100) yielded more significant results when compared to studies with larger samples (greater than 100). In a third subgroup analysis only looking at trials with a low risk of bias, the DASH diet was the only diet found to effectively reduce BP. No other dietary interventions had significant effects.

Univariate meta-regression analysis demonstrated larger reductions in SBP and DBP for shorter trials with younger participants and also showed a stronger impact in studies with large changes in participant bodyweight. Small studies did appear to favor dietary interventions when compared to control diets.

The DASH diet was the most reliably effective diet for lowering SBP and DBP, followed by the paleolithic, low-carbohydrate, and Mediterranean diets. About one-third of the studies had a low risk of bias and shorter-term studies of smaller sample sizes reported more significant results and were more likely to favor dietary interventions as opposed to control diets.

What does the study really tell us?

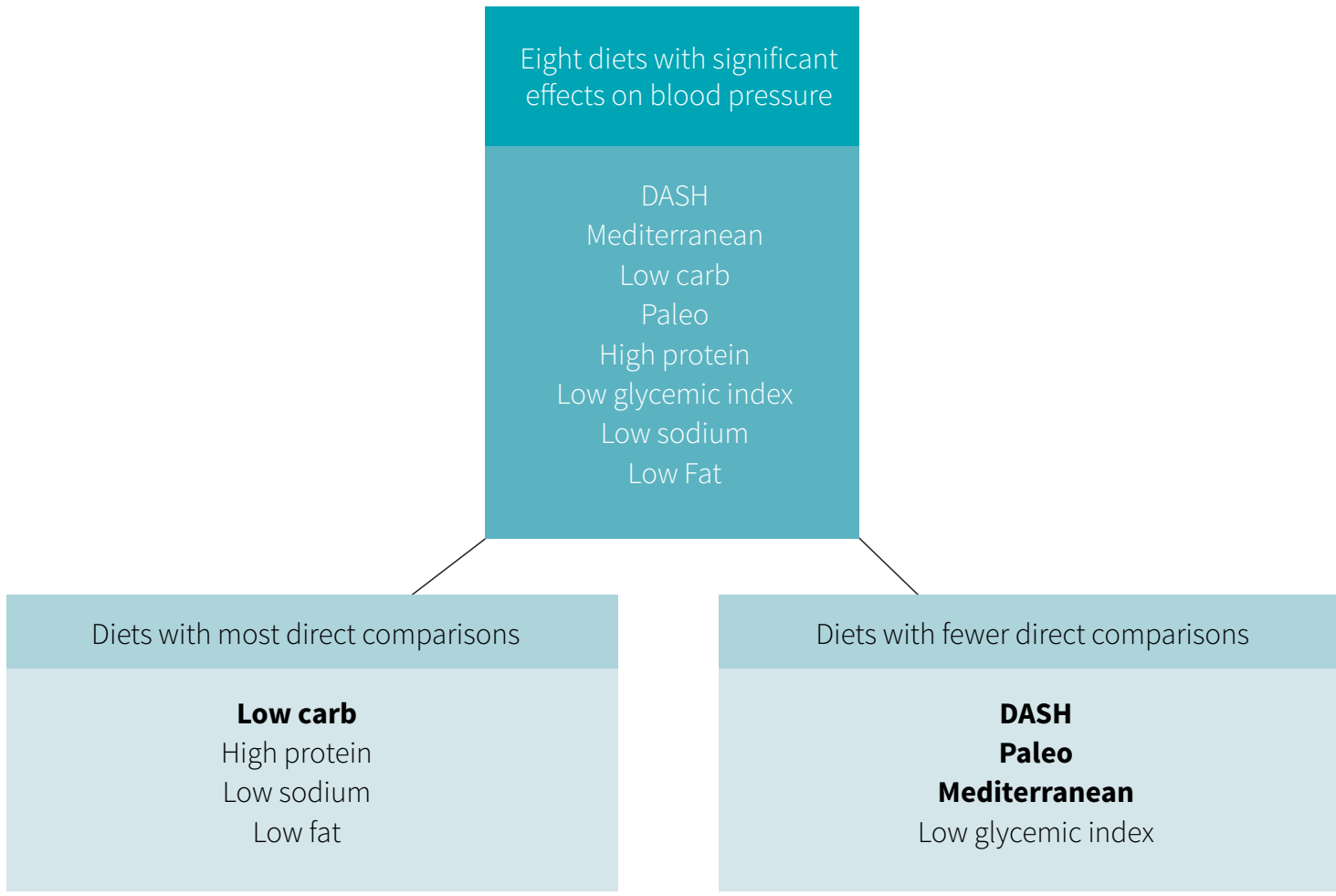
This study suggests that a variety of popular diets effectively reduce blood pressure in people with hypertension or on the verge of developing it, but that the DASH diet may be the best. However, a meta-analysis can only be as good as the studies included and methods of analysis. This is especially important for the study at hand, where most of the data feeding the results came from indirect, calculated comparisons.

Several problems can present themselves when making such comparisons. For instance, many of the measures taken to control potential confounders within a specific trial may not be the same across studies, making the comparisons more heterogeneous. Heterogeneity also rears its head when intensity and type of dietary approach, diet prescription, details of participant adherence, fat intake, age, sex, and sample size are heterogeneous across studies with the same diet.

Studies have demonstrated how these subtle differences in intervention set-up can alter results, such as group-based interventions' increased effectiveness in combating obesity when compared to individual-based interventions. Nonetheless, there were four dietary approaches, beyond the four with the highest number of direct comparisons, that were found to be significantly effective for decreasing SBP and DBP. As illustrated in Figure 3, only one of the approaches with the greater amount of direct comparisons (low-carbohydrate diet) made it to the top four in the overall ranking. This suggests that the trials were controlled enough to create robust indirect comparisons, and demonstrates the utility of the network meta-analytic approach.

The authors of the study at hand conducted some quality control to ensure the validity of their primary analysis. The fact that a sensitivity analysis, which analyzed the comparisons of only the 23 trials that were

Figure 3: Most of the top-ranked diets had relatively fewer direct comparisons



Bold = top four in effectiveness

rated with a low risk of bias, confirmed that the DASH diet comes out on top partially addresses concerns of bias. However, the fact that other subgroup analyses did not confirm this (possibly because no DASH diet trial was included that lasted longer than six months) shows that there's uncertainty in the ranking of the other diets. Also, the inconsistency among comparisons of dietary approaches with different fat-to-carbohydrate ratios introduces doubt within the third-place rankings of the Mediterranean and low-carbohydrate approaches. The authors explicitly accounted for doubt between comparisons by assessing the credibility of the rankings, which was low or moderate for most comparisons. This implies that there's room for more evidence, since many of the rankings aren't set in stone.

As previously pointed out, the scientists found a small bias, with short-term studies being more likely to favor dietary approaches, in comparison to a control. Accordingly, results of dietary approaches with trials of small participant pools should be considered cautiously. In this context, it is interesting to note that of the three top ranked dietary approaches, only the Paleolithic approach had trials with small participant pools, and had two studies (direct comparisons) included in this study. The small study bias may explain why the Paleolithic approach demonstrated greater average decreases for SBP and DBP than the DASH diet, while the existence of only two direct comparisons might explain the large ranges for estimated values. In the end, the only primary result confirmed was the efficacy of the DASH diet approach.

It would have been a good idea to exclude dietary approaches that didn't have many trials backing them up to see how this would have altered the results. For example, the Paleolithic, vegetarian, Tibetan, and Nordic diets had a maximum of 2 studies each for this

review. While the authors didn't perform this additional analysis, they did suggest that results concerning these diets should be interpreted with caution.

Furthermore, extrapolating the the primary results from this study across longer time periods may not be warranted. The subgroup analysis of longer term trials could not confirm the results of the primary analysis and trials with larger sample sizes yielded less strong results, when compared to shorter term and smaller sample-sized trials, respectively. One potential explanation for the difference between short- and long-term trials is a decrease in compliance over time. The univariate meta-regression analysis supports this, but also adds that large changes in participant bodyweight was related to greater improvements in SBP and DBP.

This study suggests that the DASH diet is the best dietary approach to improve blood pressure in hypertensive and prehypertensive people. It implemented measures of quality control to confirm the primary result despite a high heterogeneity among studies included. Although the results concerning the DASH diet are somewhat certain, the extrapolation of all the dietary approaches' impact across longer time periods may not be warranted, given the preponderance of shorter studies.

The big picture

A dose-response meta-analysis of prospective cohort studies indicates that consumption of whole grains, fruits, nuts, legumes and dairy products is associated with a reduction in hypertension risk, while intake of red and processed meat and sugar-sweetened beverages is associated with an increase in risk. Another study reviewing dietary patterns and BP in adults reported that diets rich in fruit, vegetables, whole grains, legumes, seeds, nuts, fish, and dairy but low in meat, sweets, and alcohol are associated with reduced BP. While these are just observational studies, the results do concord with those of the study under review to some degree. These food groups are the same as those emphasized in the DASH diet, overlap with various guidelines, and appear to steer clear of energy dense and nutrient poor processed foods, which are associated with obesity.

A systematic review and meta-analysis of the DASH diet reported significant reductions in SBP (-6.74 mm Hg) and DBP (-3.54 mm Hg) and reported a greater decrease in BP accompanied by energy restriction. This supports the data of the study under review, as similar SBP (-6.88 mm Hg) and DBP (-3.79 mm Hg) reductions for the analysis of trials with a low risk of bias comparing the DASH diet to a control diet were reported. Even assuming slightly lower effects than what general analysis in the study at hand reported, its results align pretty well with existing data.

Another systematic review and meta-analysis of dietary approaches also reported the largest net effect on SBP and DBP from the DASH diet, while low-sodium; low-sodium, high-potassium; low-sodium, low-calorie; and low-calorie diets demonstrated significant reductions. A low-sodium diet is effective, but focusing on only one nutrient restricts the possible benefits. The same can be said for other dietary approaches that were ranked lower than the DASH diet in the study under review (low-carbohydrate, high protein, low-fat, etc.). The benefits of these other approaches appear to rely more on calorie restriction and reduced bodyweight than on nutrient quality and content, as dietary weight loss appears to to be a main driver of the diet-related decreases in BP.

The advantage of the DASH diet is likely attributable to the variety and content of nutrients. The DASH diet is high in various phytochemicals, protein, vitamins, and minerals such as carotenoids, flavonoids, fiber, calcium, magnesium, potassium, zinc, and vitamins A, C, and E, most of which are associated with improvements in BP.

The food groups and the associated variety and content of nutrients recommended by various guidelines and associated with reduced BP in observational studies overlap with the DASH diet approach. Although several dietary approaches have demonstrated considerable effectiveness for BP reduction, the DASH diet consistently demonstrates a high efficacy slightly beyond most other dietary approaches. Other dietary approaches that focus on one specific nutrient or completely disregard a food group appear to miss out on benefits beyond weight loss or monitoring sodium and potassium.

Frequently asked questions

This study found that lower blood pressure was associated with weight loss. How big of an impact does weight loss make on blood pressure?

One meta-analysis has found that both systolic and diastolic BP drops about 1 mmHg per kilogram of weight lost on average.

How does lowering blood pressure cash out in terms of actual outcomes?

Lowering systolic BP by 10 mmHg results in a 13% lower risk of death from any cause, and a 20% lower risk of cardiovascular disease. Lowering diastolic BP by 5 mmHg reduces stroke risk by 34% and coronary heart disease by 21%.

What should I know?

This systematic review and network meta-analysis of 67 studies suggests that the DASH diet is probably the most effective dietary approach to improve both systolic and diastolic blood pressure (BP), compared to 12 other dietary approaches. However, Mediterranean, low-carbohydrate, Paleolithic, high-protein, low-glycemic index, low-sodium, and low-fat diets were also effective.

While most of the results came from indirect comparisons, the study implemented various methods of quality control, such as assessment of credibility and risk of bias, to eliminate weak connections. The food groups and associated variety and content of nutrients consumed as a part of the DASH diet appear to contribute to the high level of efficacy for BP improvement beyond those that are triggered by weight loss alone. However, weight loss was strongly associated with BP reductions. ◆

DASH on over to the ERD Facebook forum to discuss this study!

Is melatonin useful for more than just sleep?

Melatonin and health: an umbrella review of health outcomes and biological mechanisms of action.

Introduction

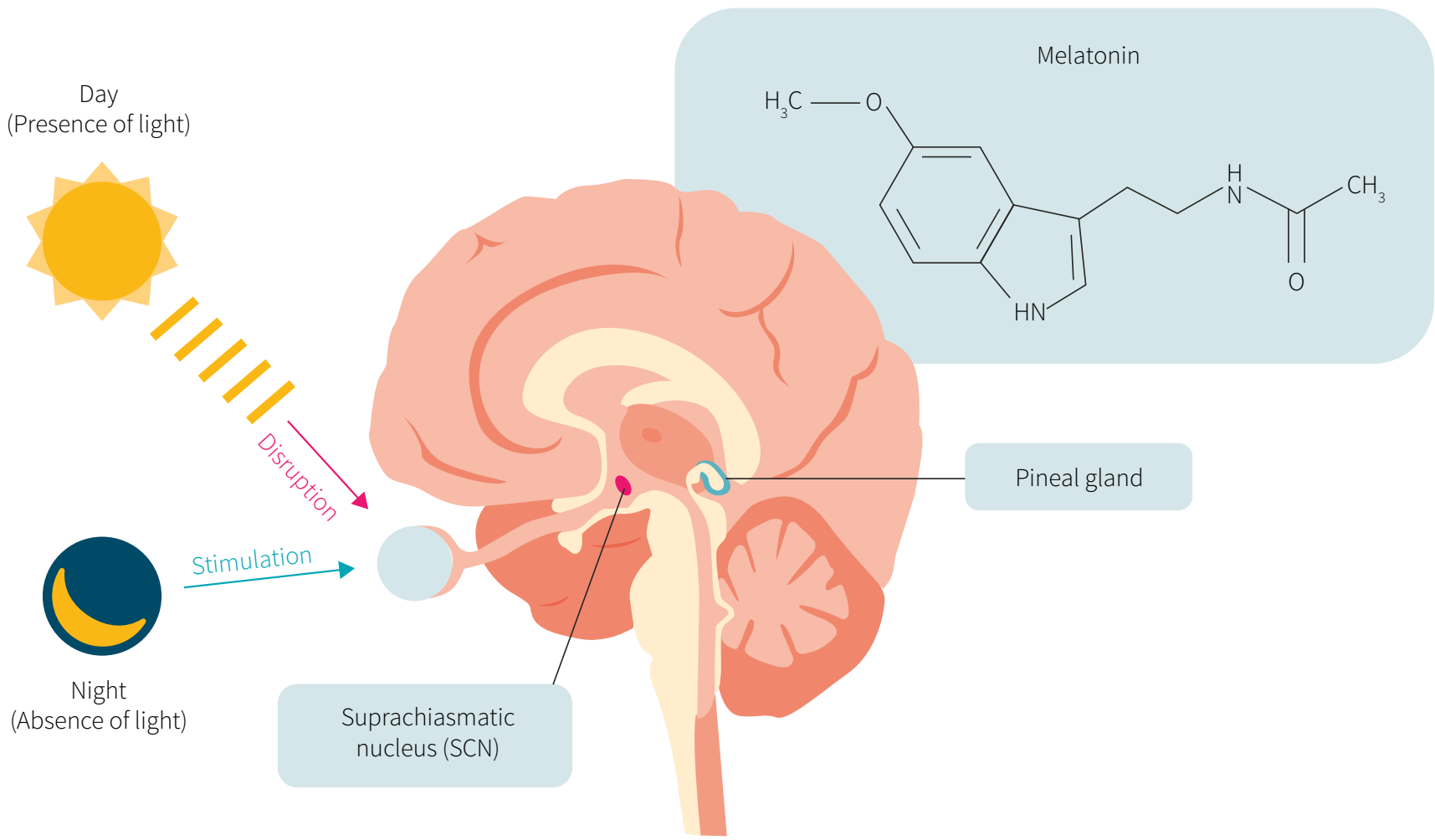
Some aspects of our behavior (like sleep), cognition, and physical feelings follow a 24-hour rhythmic cycle known as circadian rhythm. It's produced by our biological clocks and controls many processes in the body. But it doesn't exist in a vacuum — it's influenced by external cues, which are referred to as zeitgebers (German for "time givers"). Light is one of these zeitgebers. It impacts our circadian rhythm through its interaction with blue light receptors in the retina and the neural pathways that they influence.

One of the hormones that light influences is melatonin. Melatonin is one of the primary controllers of our body's circadian rhythm and is produced in the brain, specifically in the pineal gland in the absence of blue-wavelength light (shown in Figure 1). Therefore, production of melatonin can be disrupted by exposure to artificial light after sunset. It follows that if melatonin is one of the primary controllers of the circadian rhythm, disruptions to its function may also lead to disruptions in our circadian rhythms.

Several studies in the past few decades have linked circadian rhythm disruptions to negative health outcomes, such as insulin resistance, inflammation, neurological disorders, and cancer. Many of these disruptions are also linked to exposure to artificial light. As a result, some organizations that conduct research on sleep and circadian rhythms recommend avoiding blue light before sleep.

In addition to avoiding bright light, melatonin supplementation has been explored as a way to entrain circadian rhythms. Randomized trials have found that supplementation was able to help manage delayed-sleep phase disorder and jet lag, conditions believed to be a result of disrupted circadian rhythms. In addition to melatonin regularizing circadian rhythms, it is a potent antioxidant and seems to have anti-cancer activity, which has been documented in over a decade's worth of research, making it a molecule of interest for oncology researchers.

Figure 1: The effect of light on melatonin production



Although several studies and reviews have been done on melatonin supplementation, few have compiled all the evidence to determine the utility of melatonin for several health outcomes, and few have summarized its mechanisms of action. The study under review is an umbrella review (a review of reviews) that aimed to look at the evidence in favor of the use of melatonin supplements for various health outcomes.

Circadian rhythm abnormalities have been associated with several negative health outcomes. Large cross-sectional and cohort studies have linked artificial light exposure to both negative health outcomes and circadian rhythm abnormalities. Melatonin supplementation has been explored for use in many circadian rhythm disorders and for several other health outcomes. The study under review looked to compile all the evidence on melatonin and assess its impact on various health outcomes.

Who and what was studied?

This umbrella review, which was preregistered on PROSPERO (a major repository for preregistering systematic reviews) included both systematic reviews and narrative reviews of melatonin from 1996 to 2017. Reviews were included if they focused on endogenous/exogenous melatonin use in humans, animal models, or *in vitro* models. The authors excluded reviews dealing with the use of melatonin in plants, as well as papers where an English-language full-text was not available.

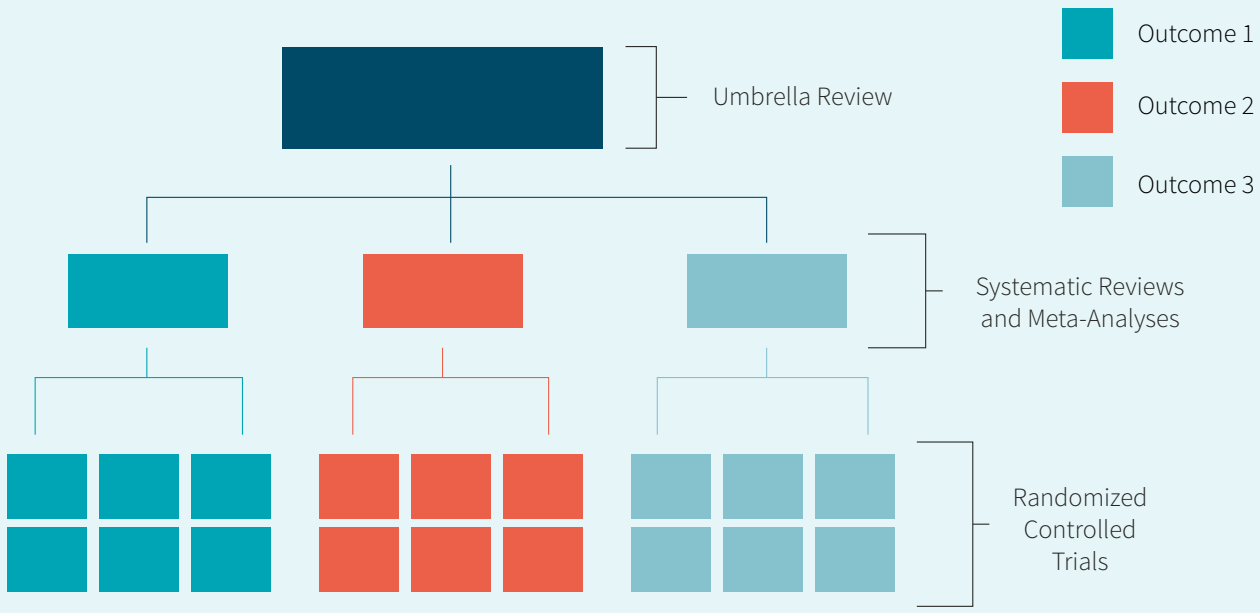
A total of 195 review articles were included. Several of the review articles (n=164) did not quantitatively pool data and were assessed qualitatively by the authors, while the quantitative data from the rest of the reviews was reconstructed by the authors and summarized. The authors also assessed the quality of the systematic reviews and the studies included in those reviews.

Reviews of 27 health outcomes were evaluated in this

What is an umbrella review?

Umbrella reviews differ from narrative reviews or systematic reviews in that they generally try to compile other reviews on a topic (shown in Figure 2), whereas systematic reviews and narrative reviews are synthesizing and analyzing primary research studies with a very specific question in mind for a particular intervention and population. Umbrella reviews may be particularly useful for assessing what the overall scientific body of evidence says about several effects of a single intervention.

Figure 2: What is an umbrella review



study. Some of these outcomes included effects on cancer, sleep outcomes, the nervous system, psychiatric conditions, obesity, pregnancy, and inflammation.

Less than half (n=84) of the reviews included in this study were exclusively on humans, while the majority of the reviews (n=99) included animal and/or *in vitro* studies. Many of the reviews included primary studies that overlapped with the other reviews found. Thus, it was difficult to estimate the total number of participants overall.

This umbrella review summarized the evidence from 195 systematic and narrative reviews on the effects of melatonin on various health outcomes. The reviews included studies on in vitro models, animals, and humans. Reviews dealing with plants and those that lacked an English-language full text were excluded.

What were the findings?

Most of the systematic reviews were graded as poor quality. A large portion (n=154) of the reviews did not evaluate the validity of the primary studies they included, while those that did (n=41) often found that these studies were of moderate quality, with several primary studies ranging from poor quality to high quality.

When looking at health outcomes, the authors reported that several of the meta-analyses found that melatonin supplementation resulted in a significant reduction of the risk of breast cancer and that supplementation resulted in significant reductions in both preoperative and postoperative anxiety, along with postoperative pain and agitation. Melatonin was also found to have statistically significant effects on nocturnal hypertension and reduced both systolic and diastolic blood pressure. A list of the statistically significant and insignificant effects of melatonin for health outcomes that were quantitatively analyzed is shown in Figure 3.

One meta-analysis investigating the effects of exogenous melatonin on sleep quality for participants with insomnia found a small overall improvement and met the authors' criteria for a high-quality review. Melatonin was also found in several other meta-analyses to have large, statistically significant effects on sleep latency and sleep quality for participants with sleep disorders.

Figure 3: Effect of Melatonin on Various Health Outcomes

✓ Significant effect ✗ No Significant effect

✓ Reducing the risk of breast cancer	✗ Withdrawal symptoms from addiction
✓ Increasing remission of breast cancer	✗ Incidence of delirium
✓ Reducing pre- and post-operative anxiety	✗ Mood and cognition in people with dementia
✓ Preventing agitation	✗ Pregnancy rates related to infertility
✓ Reducing post-operative pain	✗ Mood disorders
✓ Sleep latency and sleep quality	

While melatonin did have significant effects on several health outcomes, it had no discernible effect on others. For example, when it came to mood disorders, specifically depression, a meta-analysis with 3,862 participants found no significant effect on response to treatment or remission.

Melatonin supplementation also had no effect on dementia-related outcomes such as cognition or mood and behavior. Similarly, meta-analyses did not find significant fertility-promoting effects. It also had no effect on withdrawal symptoms in the context of addiction and no effect on the incidence of delirium.

Many of the systematic reviews were of poor quality. However, the primary studies they included were, on average, of moderate quality. Meta-analyses included in this review found that melatonin supplementation significantly reduced the risk of breast cancer and had significant effects on several other outcomes, such as pre- and postoperative anxiety, nocturnal systolic and diastolic blood pressure, and sleep quality. Melatonin was found to have no effect on depression, fertility, drug withdrawal symptoms, incidence of delirium, and cognition for people diagnosed with dementia.

What does the study really tell us?

The authors found that some of the most commonly discussed mechanisms of melatonin in these reviews were in the context of its anti-inflammatory, antioxidative, and immunomodulatory effects. Many of these purported mechanistic effects may be useful for people suffering from diseases like cancer, and the data from a few systematic reviews in this study seem to suggest this.

For example, one of the included meta-analyses found that melatonin resulted in a large increase in the rates of partial or complete tumor remission for breast cancer. These results contrast with the data from studies of other antioxidant supplements, which often find that supplementation actually increases the risk of cancer because some antioxidants could fuel the growth of cancerous cells.

Moreover, the evidence from this review seems to suggest that melatonin can be used for treating primary sleep disorders, which are often linked to disruptions in circadian rhythms. More specifically, several of the meta-analyses found that melatonin supplementation had significant effects on total sleep time, sleep latency, and sleep quality. These effects may be a result of melatonin's entrainment of the circadian rhythm to the suprachiasmatic nuclei and its reduction of the core body temperature.

Although melatonin could affect many health outcomes in theory, things were different in practice—several of the meta-analyses in this umbrella review found no effects on outcomes such as depression and dementia. These results contrast with some of the mechanistic data from animal studies, which suggest that melatonin regulates several behavioral and cognitive processes, which are often impaired in people suffering from mood disorders.

Due to the small sample size of studies, it is quite possible that these meta-analyses had low probabilities to detect a significant effect. Some of the confidence intervals that the meta-analyses produced were very wide, and as such, indicate a large amount of uncertainty. This uncertainty leaves room for the possibility that melatonin does indeed have an effect in some of these areas, although a small and possibly trivial one. Ruling out whether a clinically meaningful effect exists can be done with larger meta-analyses to increase precision and statistical power.

This review had several strengths. It was preregistered and transparent in what it would include in the analy-

ses. Furthermore, the umbrella review included a large number of systematic reviews and meta-analyses, which are often more objective than other types of reviews.

The latter is not necessarily the case for narrative reviews. Accordingly, the inclusion of narrative reviews, which are not necessarily reproducible and can suffer from selection bias, is one of the putative weaknesses of the study under review. Furthermore, the inclusion of narrative reviews and several animal studies could potentially skew the prevalence of mechanistic effects, which may not, and often don't, translate to humans. The authors also did not attempt to assess the quality of the included animal studies.

Several of the meta-analyses also included primary studies with high amounts of methodological heterogeneity and several of the average treatment effects also had high amounts of statistical heterogeneity, which can be described as true differences between studies not attributed to random error. It is very possible that melatonin has different effects at different dosages and in different populations. So, pooling the results of studies with such differences can result in summary effects with high heterogeneity, making it difficult to find a statistically significant effect.

This review found that melatonin had significant effects on several outcomes, such as sleep quality and risk of cancer, which aligns with the previously documented effects of melatonin at the cellular and molecular level. For other outcomes, however, the review didn't find significant effects—in spite of evidence of corresponding mechanisms. However, this may also be due to the studies having small sample sizes and having a low probability to detect a significant effect. The results of this review were strengthened by the inclusion of several systematic reviews and meta-analyses, but it was also limited by the inclusion of narrative reviews, which are prone to selection bias.

The big picture

Melatonin supplementation is often associated with sleep and, as such, is primarily marketed toward individuals who suffer from sleep disorders. This review confirmed melatonin's effectiveness for this use. The review also presents evidence in favor of significant benefits in people with surgical-related anxiety, hypertension or generally increased cardiovascular disease risk.

As a potent antioxidant, melatonin is also considered a possible intervention for cancer prevention and treatment. Although several observational studies find that plant and antioxidant consumption is typically associated with a lower risk of cancer, large human studies show no benefit from supplementing antioxidants. Mechanistic studies also seem to show that antioxidant supplementation could actually fuel the growth of cancerous cells.

Melatonin, on the other hand, seems to have unique and fairly robust anti-tumor effects in *in vitro* and *in vivo* studies in animals and humans. While more and higher-quality research on the use of melatonin in cancer prevention and treatment is necessary, the existing evidence clearly indicates that melatonin is much more than a simple sleep supplement.

Melatonin is primarily used for sleep-related conditions and this umbrella review has shown it to be effective for this and several other outcomes. Most notably, its effects on breast cancer seem promising and there appears to be both mechanistic and human evidence to support its utility. This suggests melatonin may be more than just a supplement to aid sleep.

Frequently asked questions

Is melatonin supplementation safe?

In this umbrella review, only 5.6% of the included reviews reported adverse effects and most of these effects were mild symptoms, such as dizziness, nausea,

headaches, and fatigue. In some studies, pharmacological doses as high as 75 milligrams have been used without any serious adverse events being reported. It is worth noting, however, that there aren't many long-term studies that have been conducted on melatonin.

There are, however, two things that should be kept in mind: First, a recent study found that many melatonin supplements do not meet the label claims. Second, some of the supplements that were tested in this study were contaminated with serotonin, a neurotransmitter.

Will supplementing melatonin affect my own production of melatonin?

It seems unlikely with low doses. Studies that have administered melatonin at doses of 0.5 milligrams, 2.0 milligrams, 5.0 milligrams, and 50 milligrams have found no significant effect on basal endogenous secretions of melatonin.

What should I know?

Melatonin plays a large role in regulating our circadian rhythms. A large body of evidence suggests that supplementing it is effective for managing sleep. However, melatonin has some other properties that may be useful for other aspects of health beyond sleep. The goal of this preregistered umbrella review was to collect and synthesize reviews of melatonin's various effects.

Fewer than half of the articles found explored melatonin's effects in humans. Also, a minority of the reviews quantitatively synthesized the evidence using meta-analyses. Those that did found that melatonin was effective in reducing risk and increasing remission rates in breast cancer, reducing anxiety before and after medical operations as well as decreasing postoperative pain, preventing agitation, and improving sleep. However, no discernible effects were found in other areas, including mood disorders, improving cognition in people with dementia, and helping with fertility. Given the poor quality of many of the reviews found and the small sample sizes in many primary research studies, there's still room for more evidence concerning many of melatonin's putative effects. ◆

Turn on your blue light filter and head on over the the ERD Facebook forum to discuss this umbrella review.

Credits

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