

# Integrative Medicine

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## DEPRESSION

### ABSTRACT & COMMENTARY

# Prevention of Relapse in Depression: Antidepressants or Mindfulness-based Cognitive Therapy?

By *Ellen Feldman, MD*

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Dr. Feldman reports no financial relationships relevant to this field of study.

**SYNOPSIS:** Maintenance antidepressants or mindfulness-based cognitive therapy aimed at tapering or discontinuing antidepressants are both effective interventions for prevention of recurrent depression.

**SOURCE:** Kuyken W, et al. Effectiveness and cost-effectiveness of mindfulness-based cognitive therapy compared with maintenance antidepressant treatment in the prevention of depressive relapse or recurrence (PREVENT): A randomised controlled trial. *Lancet* 2015;386:63-73.

*“Good morning, Pooh Bear,” said Eeyore gloomily. “If it is a good morning,” he said. “Which I doubt,” said he.*

*“Why, what’s the matter?”*

*“Nothing, Pooh Bear, nothing. We can’t all, and some of us don’t. That’s all there is to it.”*

*“Can’t all what?” said Pooh, rubbing his nose.*

*“Gaiety. Song-and-dance. Here we go round the mulberry bush.”*

*From Winnie the Pooh by A.A. Milne*

Untreated depression has chronic health and wellness implications. Relapse risk following an episode of acute depression can approach 80%.<sup>1,2</sup> The current

recommendation for prevention of recurrent depression is to maintain antidepressant treatment for 2 years from symptom relief.<sup>3</sup> Recognizing that some patients prefer or require alternatives

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## Summary Points

- This study compared both clinical efficacy and cost-effectiveness of maintenance antidepressants and structured group therapy (aimed at reducing or discontinuing antidepressant use) in a population of U.K. adults at risk for recurrent depression.
- Both interventions reduce expected rates of remission in depression; there is no clear statistical evidence of superiority for either intervention.
- In this British study, mindfulness-based cognitive therapy (MBCT-TS) was not more cost-effective than maintenance antidepressants.
- MBCT-TS may show more effectiveness in patients with a history of childhood abuse (potential area of further study).

to conventional treatment and that adherence to antidepressant regimes tend to be problematic, this 2-year study compared efficacy and cost-effectiveness of antidepressant maintenance therapy with a structured non-pharmacologic alternative: group sessions of mindfulness-based cognitive therapy aimed at discontinuing or tapering antidepressants (MBCT-TS). The original aim of the study was to see if this psycho-social intervention would be more effective in preventing relapse than maintenance antidepressant medication.

Mindfulness-based cognitive therapy (MBCT) blends the teachings of cognitive-behavioral therapy with the meditative techniques of mindfulness-based stress reduction.<sup>4</sup> MBCT is typically a group intervention delivered in a standardized manner with a focus on recognizing and addressing specific thought patterns that impact recurrent depressive episodes. It is meant to be utilized during episodes of remission (not during actively depressed periods.)

Studies of MBCT have shown this technique has promise in reducing depression relapse rates in more chronically depressed and higher-risk patients.<sup>5,6,7</sup> This is the first study attempting a head-to-head comparison of MBCT-TS with maintenance antidepressants. In this study, MBCT-TS was delivered in the standard group format and combined with a medication-tapering regime delivered in conjunction with primary care.

Participants were recruited from general

practice populations across diverse areas of the United Kingdom. Eligibility criteria included adults with a diagnosis of major depressive disorder in full or partial remission, three or more past episodes of major depression, and currently taking a therapeutic dose of an antidepressant. Exclusion criteria included most comorbidities (medical and psychiatric), as well as persistent self-harm, current major depression, and current formal psychotherapy.

Of the initial 424 patients in the study, 212 were each assigned to one of two groups: maintenance antidepressant therapy via regular visits with a family physician over the 2-year period or MBCT-TS group therapy with one of four therapists (eight groups weekly for 8 weeks then four refresher sessions approximately every quarter over the 2-year period.) Participants in the MBCT-TS group also met regularly with their family physician over the study period to taper antidepressants and monitor response.

All patients were re-assessed for evidence of recurrence of depression at five set time intervals during the study period. A relapse was defined as symptoms that met DSM-IV criteria for major depression. The relapse rate for both groups was comparable and less than expected without intervention. The researchers also noted and studied the number of depression-free days, any residual depressive symptoms not meeting full criteria, any medical or psychiatric comorbidities, quality of life, and cost-effectiveness.

Of the 424 participants in this 2-year study, 366 remained active in the study at the last data collection point. Numbers were remarkably similar for each group at each time interval. In the maintenance antidepressant group, 162 remained on a therapeutic dose of antidepressants throughout the study period. In the MBCT-TS group, 176 completed four or more group MBCT sessions. Of these, 124 discontinued their medication entirely, 29 reduced the total dose (no specifics given), and 23 did not change their dose of antidepressant medication. (See Figures 1 and 2.)

There was no statistical significance between primary or secondary outcome results between the groups. Ninety-four patients (44%) in the original MBCT-TS group relapsed as did 100 patients (47%) in the original antidepressant maintenance group. None of the secondary measures showed a standardized mean difference of > 0.4 at any of the five follow-up time points.

There was a noted interaction involving the presence of childhood abuse. MBCT-TS patients with self-reported childhood abuse had a lower risk of relapse when compared to the maintenance antidepressant group (49 of 105 [47%] patients relapsed compared vs 65 of 111 [59%] patients relapse.) On the other hand, the patients with a low severity of childhood abuse in the MBCT-TS treatment group did not perform as well as their counterparts in the maintenance antidepressant group (44 of 105 [42%] relapse vs 35 of 101 [35%] relapse). (See Figure 3.)

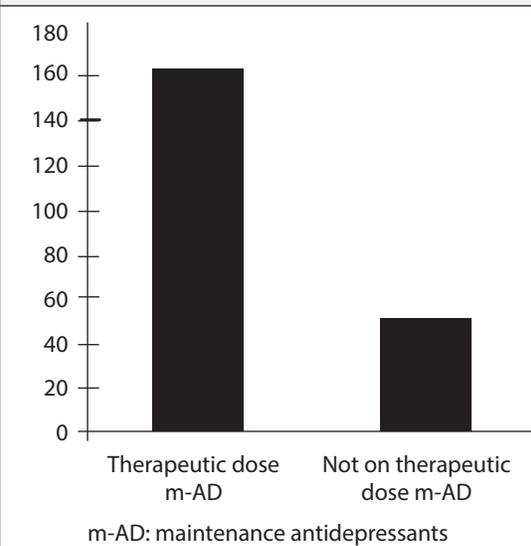
When determining cost effectiveness, these authors looked at several different measures, including total health care costs and societal costs, which included out-of-pocket and productivity costs for patients. *P* values ranging from 0.681 to 0.800 indicated the absence of statistical significance between these groups when looking at these designated parameters.

#### ■ COMMENTARY

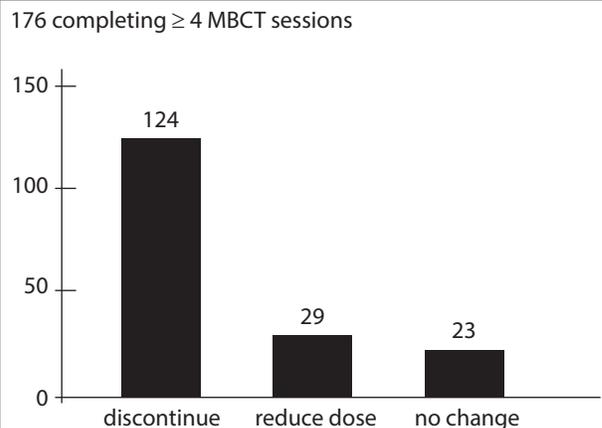
The results of this study are important on several levels and raise several questions, not the least of which revolves around the importance of considering an “exit strategy” when initiating antidepressant treatment.

A primary message appears fairly straightforward: There exists an effective alternative to maintenance antidepressants in the treatment of recurrent depression. Why is this important? In 2014, the

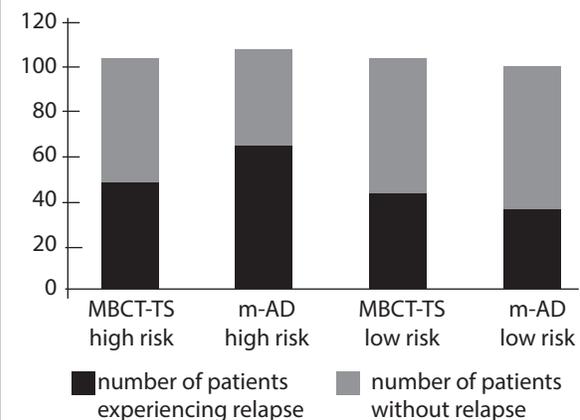
**Figure 1: Maintenance Antidepressant Group**



**Figure 2: MBCT-TS Group**



**Figure 3: Relapse in Specific Groups: High vs Low Risk Based on Childhood Abuse**



Rochester Epidemiology Project looked at several facets of antidepressant use. The researchers calculated the prevalence of use in their adult population (year 2011) at 14.4%, representing an increase from 10.8% in 2005.<sup>8</sup>

A different study in late 2013 looking at patterns and trends in adult antidepressant use found an overall significant increase in prevalence of antidepressant use in U.S. adults during the first decade of 2000.<sup>9</sup>

[The importance of this study lies in alerting practitioners to consider a role for mindfulness-based cognitive therapy aimed at discontinuing or tapering antidepressants as an alternative to maintenance antidepressants when treating patients to prevent recurrent depression.]

Most relevant today is that this increase was strongest for long-term use of antidepressants in adults treated by general medical providers, who currently prescribe the bulk of antidepressants in the United States.<sup>10</sup> It is not much of a stretch to extrapolate that this trend could be affected if clear alternatives to the use of long-term antidepressants are found effective. Chief among concerns for patients on long-term antidepressants is an emerging concern about the potential for weight gain and development of type 2 diabetes.<sup>11</sup>

However, before switching patients from maintenance antidepressants, physicians should consider several points. Recall that this study included two groups — one group met regularly with physicians to maintain antidepressant dosage and the other group engaged in MBCT but also met regularly with physicians to taper antidepressants. The design of the study failed to include a group of patients who attempted to taper or discontinue antidepressants without MBCT, but still with the assistance of their primary care practitioner. Thus, it is difficult to definitively state that the MBCT-TS is responsible for the success of this second group at reducing the rate of recurrent depression.

The cost-effectiveness analysis in this study may not be globally applicable. Health care costs, out-of-pocket costs, and medication costs in the

United Kingdom may differ from such costs in the United States and other countries. Regional availability of MBCT-TS or even of cognitive-behavioral therapists may differ not only across the United States, but globally as well. In the United States, out-of-pocket and societal costs will vary with specific health care plans. Nevertheless, the approach taken by this team of researchers to analyze costs bears merit as long it is understood in context.

The importance of this study lies in alerting practitioners to consider a role for specific group therapy (MBCT-TS) as an alternative to maintenance antidepressants when treating patients to prevent recurrent depression. The findings imply the most effective use of this therapy is found with patients who have had significant history of childhood abuse; this is consistent with other studies examining the use of MBCT in treating recurrent depression. The author's future goal to try to identify the specific mechanism(s) of action of MBCT should help bring more clarity to this point.

An in-depth review of the study leads to a consideration that a course of careful tapering of antidepressants in low-risk patients with recurrent depression may also have a role in the prevention of recurrent episodes of depression. As work is done in this area, more potential choices and definitive algorithms of treatment should emerge, allowing a more targeted approach to treating and preventing depression from a chronic and debilitating course. ■

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## COGNITIVE FUNCTION

### ABSTRACT & COMMENTARY

# Mediterranean Diet Increases Brain Volume

By David Kiefer, MD

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Dr. Kiefer reports he is a consultant for WebMD.

**SYNOPSIS:** Higher adherence to the Mediterranean diet led to measurable increases in brain volume in a multi-ethnic sampling of older adults.

**SOURCE:** Gu Y, et al. Mediterranean diet and brain structure in a multiethnic elderly cohort. *Neurology* 2015 Oct 21. pii: 10.1212/WNL.0000000000002121.

Can the Mediterranean diet, with its accumulating evidence for cardiovascular protection, cancer prevention, and anti-inflammatory effects, also benefit the human cerebrum? The authors of this analysis previously published research showing a decreased incidence of Alzheimer’s disease with adherence to a Mediterranean diet, but other results weren’t convincing, likely due to a variety of confounding variables. Here, the authors strived to clarify the brain effects of a Mediterranean diet through a prospective, cross-sectional study that utilized advance neuroimaging techniques sensitive for an aging brain’s changing structure.

This analysis was done on 2776 elderly (> 65 years of age) people without dementia receiving Medicare benefits in northern Manhattan. This cohort was an ongoing prospective study on aging and dementia, known by the acronym WHICAP. At baseline, physicians completed a physical exam and neurological history and assessed cognitive function using a “battery” of neuropsychological tests for each participant. These examinations were repeated every 18 months, at which time a diagnosis of dementia was made if criteria were met based on the DSM-III-R. Further criteria were used to determine the type of dementia, and the Clinical Dementia Rating scale was used to establish dementia severity.

Of this cohort, magnetic resonance imaging (MRI) data were available for 769 people, a subgroup that tended to be younger, African American, and male compared to the original cohort. Complete

### Summary Points

- The researchers analyzed the diet of a diverse elderly population without dementia.
- People consuming five or more Mediterranean diet foods had a greater brain volume than those consuming four or less Mediterranean diet foods, equivalent to about 5 years of brain aging.
- The brain volume benefits were most strongly associated with higher fish intake, lower meat intake, and moderate alcohol intake.

images were unavailable for 45 participants, 10 participants did not have dietary data available, and 40 participants were diagnosed with dementia at the time of the MRI scan, leaving 674 participants for analysis in this study. Table 1 describes the MRI information collected, including global brain measures, regional cortical volume analyses, and mean cortical thicknesses across 34 regions of interest.

At an average of 0.6 years before the MRI scan, the Willett’s semi-quantitative food frequency questionnaire was used to collect information about each participant’s average diet over the previous year. This diet information was then scored to determine adherence to a Mediterranean diet; one point was awarded for each of a variety of parameters (considered “beneficial food

components”) as delineated in Table 2 for a total score (9 points maximum). In addition, sub-group analyses were undertaken to determine the contribution of each of the nine different food groups to the observed MRI differences.

The total cohort (n = 674) had a mean age of 80.1 years, and was 67% female, 28% white, 35% black, and 36% Hispanic. The group was split into high adherence to the Mediterranean diet for scores 5-9 (n = 304) and low adherence to the Mediterranean diet for scores 0-4 (n = 370). The two Mediterranean diet adherence groups were statistically identical with respect to baseline demographics, past medical history (stroke, diabetes, hypertension, heart disease), body mass index, and cognitive scores on neuropsychiatric testing.

With respect to outcome variables, the two Mediterranean diet adherence groups were compared relative to MRI findings. The high vs low Mediterranean diet adherence group had similar cortical thicknesses (2.46 mm vs 2.45 mm, respectively,  $P = 0.44$ ), whereas the higher Mediterranean diet adherence group had larger brain volumes (total brain volume [TBV], total gray matter volume [TGMV], and total white matter volume [TWMV]), all statistically significant when adjusted for intracranial volume (ICV). (See Table 3.) The authors were able to calculate that one additional year of age corresponded to the loss of 2.62 mL of TBV ( $P < 0.0001$ ). From this calculation, the researchers were able to conclude that high Mediterranean diet adherence groups had about five years’ more brain volume than the low adherence group. Worded another way, a high adherence to an Mediterranean diet staved off brain aging by 5 years compared to a low adherence to an Mediterranean diet.

Furthermore, t-tests and chi-squared statistical analyses allowed the researchers to conclude that the individuals with higher TBV, TGMV, and TWMV tended to be younger, male, less likely to have diabetes, less likely to have dementia, and to have lower body mass index and better cognition.

With respect to specific foods, higher fish intake, lower meat intake, and moderate alcohol intake were associated with higher TBV, TGMV, and TWMV. Quantifiably, one could achieve protection from 3-4 years of brain atrophy but consuming at least 3-5 ounces of fish weekly or limiting meat consumption to 100 g weekly. Fish intake was also the one variable that affected cortical thickness and was associated with increased thickness;

Category of MRI Data	Examples
Global brain measures	<ul style="list-style-type: none"> <li>• Total brain volume (TBV)</li> <li>• Total gray matter volume (TGMV)</li> <li>• Total white matter volume (TWMV)</li> <li>• Intracranial volume (ICV), to account for variable head sizes</li> </ul>
Regional cortical volume analyses	<ul style="list-style-type: none"> <li>• Frontal</li> <li>• Parietal</li> <li>• Temporal</li> <li>• Occipital</li> <li>• Cingulate</li> </ul>
Mean cortical thickness	<ul style="list-style-type: none"> <li>• 34 regions of interest</li> <li>• 9 additional regions known to “reflect Alzheimer’s disease-associated neurodegeneration”</li> </ul>

<ul style="list-style-type: none"> <li>• Vegetables</li> <li>• Legumes</li> <li>• Cereals</li> <li>• Fish</li> <li>• Fruits or nuts (considered one “food component”)</li> <li>• Ratio of monounsaturated to saturated fatty acids greater than the sex-specific, caloric-adjusted population median</li> <li>• Meat consumption below population median</li> <li>• Dairy consumption below population median</li> <li>• Alcohol consumption &gt; 0 grams but &lt; 30 grams</li> </ul>
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other variables, including the Mediterranean diet as a whole, did not change cortical thickness. Regionally, the cingulate, parietal, temporal, and hippocampus volumes most accounted for the high vs low MEDDIET adherence differences.

■ **COMMENTARY**

This study lets the scientific and medical communities add a feather to the cap of the Mediterranean diet. The Mediterranean diet will protect you, among other things, from cardiovascular disease,<sup>1</sup> diabetes,<sup>2</sup> Alzheimer’s disease,<sup>3</sup> and, as we now learn from this

**Table 3: Brain Volumes for High vs Low Adherence to MEDDIET When Adjusted for ICV**

	Low MEDDIET Adherence	High MEDDIET Adherence	Low MEDDIET Adherence when Adjusted for ICV	High MEDDIET Adherence when Adjusted for ICV
<b>TBV (mL)</b>	865	878	-6.5	7.9 ( $P = 0.003$ )
<b>TGMV (mL)</b>	517	522	-2.9	3.6 ( $P = 0.017$ )
<b>TWMV (mL)</b>	372	379	-3.6	4.4 ( $P = 0.016$ )

TBV: total brain volume; TGMV: total gray matter volume; TWMV: total white matter volume; ICV: intracranial volume

study, will provide quantifiable changes to cerebral structure that have dementia correlates. Furthermore, some previous studies had limited demographic and ethnic diversity, limiting the generalizability of the results. In this case, with a relatively even split between Caucasian, African American, and Latino, many health care providers might see a direct relevancy to the patients in their clinical practice.

In some respects, these results are nothing new. Prior clinical trials have convincingly found associations between diet and cognitive function, even prevention of the ultimate ramification of cognitive decline, Alzheimer’s disease.<sup>3,4,5</sup> It’s the *how* that had been missing. I can imagine a day when we are discussing dietary change with our patients that we show before and after brain MRI images as a motivator: “Incorporate more vegetables and fish into your diet, and your brain will look like this in 5 years.” That’s hard to ignore.

A few minor points are lacking here, and leave clinicians wondering. It is difficult to ascertain how long someone needs to eat the Mediterranean diet foods to achieve the results here. The statistical associations were analyzed at different time points in this longitudinal cohort, so some clarification on the time course would have been helpful. Also, although these patients were dementia-free, and the study was organized in that way, it would have made sense to weave in the incidence of dementia as the trial progressed to then correlate brain volumes not only with Mediterranean diet adherence but subsequent development of dementia. Such a methodology would have created a more cohesive clinical story. Furthermore, the significance of the regional changes in brain volume is vague and went mostly unexplained, though it can be argued that such a deficit is more representative of the current state of our neurological knowledge than it is of the

researchers’ oversight. I would predict a honing of the specificity between diet and brain function/structure in the years to come.

Nonetheless, the breadth and depth of information collected was impressive and allowed for some interesting quantifications, the equivalent of “years of brain volume saved.” Overall, given the findings here, there is little reason to not recommend a Mediterranean diet to our patients that fall into this age group. Clinicians can confidently say such a dietary approach will have wide-ranging benefits, not the least of which is a clear-cut improvement in brain volume loss, mostly considered to be an inevitable result of the aging process. Not anymore! ■

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## ABSTRACT &amp; COMMENTARY

# High-intensity Intermittent Training for Type 2 Diabetes Mellitus

By William C. Haas III, MD, MBA

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Dr. Haas reports no financial relationships relevant to this field of study.

**SYNOPSIS:** High-intensity intermittent training improves cardiac structure and function in addition to reducing liver and visceral fat mass among non-insulin dependent type 2 diabetics.

**SOURCE:** Cassidy S, et al. High intensity intermittent exercise improves cardiac structure and function and reduces liver fat in patients with type 2 diabetes: A randomized controlled trial. *Diabetologia* 2015; [Epub ahead of print].

**T**ype 2 diabetes mellitus (T2DM) affects multiple organ systems within the body. The cardiovascular system is especially prone to damage as a result of elevated blood glucose levels. In fact, cardiac disease remains the leading cause of morbidity and mortality in patients with T2DM.<sup>1</sup>

Lifestyle modifications, including exercise, are among the foundational treatment strategies for both T2DM and heart disease. Traditionally, recommendations have centered on moderate levels of continuous aerobic exercise totaling 150 minutes per week. Recently, other exercise methods have generated attention, particularly high-intensity intermittent training (HIIT). HIIT involves brief intervals of vigorous activity interspersed with periods of low activity or rest. Variations of HIIT have been well studied in athletes with demonstrated improvements in cardiac function, carbohydrate and fat utilization, as well as mitochondrial efficiency.<sup>2-4</sup> On the other hand, less is known about the effect of HIIT on individuals with chronic disease.

Given that patients with T2DM have been shown to exhibit changes in left ventricular structure and function without overt cardiac disease, researchers in the United Kingdom set out to determine the cardiac benefits of HIIT on a small group of type 2 diabetics. Using advanced magnetic resonance imaging (MRI) techniques, researchers evaluated cardiac structure and function as well as regional fat deposition in response to HIIT.

Twenty-eight type 2 diabetics managed with diet and metformin were randomized to a HIIT intervention (n = 14) or a control group (n = 14). More than 200 patients were excluded during

## Summary Points

- High-intensity intermittent training (HIIT) is a form of exercise interspersing brief periods of vigorous exercise with periods of rest.
- HIIT improves cardiac structure and function in patients with type 2 diabetes.
- HIIT reduces liver fat and visceral adiposity.

initial screening based on the presence of overt cardiac disease, regular participation in exercise (> 60 min per week), contraindication to exercise stress testing, or use of a beta-blocker medication. The HIIT group performed three structured exercise sessions per week for 12 weeks. Each session consisted of five intervals of “very hard” cycling with a pedal cadence > 80 revolutions/minute; “very hard” was defined at 16-17 out of 20 on the Borg Rating of Perceived Exertion (RPE) scale. Intervals lasted 2 minutes during the first week and were extended by 10 seconds per week, reaching a final duration of 3 minutes and 50 seconds by the end of the study. Regardless of the duration, intervals were flanked by a 5-minute warm-up and a 3-minute cool-down with a 3-minute recovery period. The initial session was supervised and subsequent sessions were audio guided using voice-recorded instructions. Both the HIIT and control groups were instructed to continue their normal diabetic care without changing medication, physical activity, diet, or body weight.

The variables measured for both groups included

cardiac structure and function, liver and visceral fat, body composition, and glycemic control. Measurements were taken at baseline and again after the 12-week intervention. Cardiac variables (left ventricular wall mass, end-diastolic blood volume, systolic function) were evaluated using advanced MRI scanning technology and validated modeling algorithms. Similar technology was used to measure liver and visceral fat mass. Body composition was also measured using air displacement plethysmography. Glycemic control was evaluated using a fasting oral glucose tolerance test along with insulin resistance and beta-cell function calculations using HOMA2 and area under the glucose curve.

Twenty-three of the original 28 participants completed the study with no difference between the groups at baseline. Two patients in the control group declined to undergo MRI scanning and one patient cited time constraints. In the HIIT group, two patients withdrew for unrelated medical problems. No patients were excluded from analysis due to failed compliance with the treatment protocol, and no changes were noted in general daily activity levels during the intervention for either group.

With regards to cardiac structure and function, several key variables improved in the HIIT group and were statistically different from the control group. Among HIIT participants, left ventricular wall mass increased by 12% ( $P = 0.02$ ) without a corresponding change in myocardial wall thickness. This increased ventricular mass among HIIT participants was accompanied by improvements in their ejection fraction percentage ( $65.8 \pm 8\%$  pre-HIIT vs  $70.0 \pm 6\%$  post-HIIT;  $P = 0.02$ ). HIIT also improved end-diastolic volume, which increased by 4 mL ( $P = 0.01$ ), as well as early diastolic filling rate by 51 mL/s ( $P = 0.01$ ).

With regards to glycemic control, HIIT participants did not show improvement in any of the key variables after the intervention. Fasting glucose, fasting insulin, and hemoglobin A1c as well as insulin sensitivity and insulin resistance were all unchanged among HIIT participants. The same pattern was true among the control group. Interestingly, hemoglobin A1c and 2-hour glucose levels were the only variables different between the two groups after the intervention ( $P = 0.02$ ).

Finally, improvements were noted with regards to visceral adiposity in addition to liver fat. Visceral adipose tissue decreased among HIIT participants ( $201 \pm 80 \text{ cm}^2$  to  $181 \pm 72 \text{ cm}^2$ ,  $P = 0.04$ ); however,

no difference was noted between the groups. Aside from decreased visceral adiposity, HIIT elicited a 39% relative reduction in liver fat ( $6.9 \pm 6.9\%$  to  $4.2 \pm 3.6\%$ ,  $P < 0.05$ ) with a significant between-group effect ( $P < 0.05$ ). Researchers noted that the degree of liver fat reduction moved four patients into the normal range for liver fat. Of note, overall fat mass did not change within or between groups.

#### ■ COMMENTARY

The primary focus of this study was to determine the effect of HIIT to improve cardiac structure and function in type 2 diabetics without overt cardiac disease. Based on several findings, the authors

[... high-intensity intermittent training deserves consideration for use among type 2 diabetics, especially as it offers a solution to the commonly cited limitation of "not enough time." ]

concluded that HIIT was indeed an effective strategy to reverse cardiac dysfunction. First, HIIT participants experienced increased left ventricular mass without increased myocardial wall thickness. The precise mechanism of cardiac hypertrophy is important. Unlike with exercise, pathological damage to the heart leads to an increase in both left ventricular mass and wall thickness, thereby decreasing end-diastolic blood volume, the latter being an independent predictor of cardiovascular mortality.<sup>5</sup> Beyond improvements to cardiac structure, HIIT increased early diastolic filling rate. This change suggests that the myocardium HIIT participants became more compliant and quicker to relax, another predictor of decreased cardiac mortality.

Not only did HIIT improve cardiac parameters, it also reduced liver and visceral fat mass. Both liver and visceral fat deposition are proposed to play a key role in the underlying pathology of T2DM.<sup>6</sup> A reduction in these fat cells should theoretically improve glucose management. Interestingly, the study did not find significant improvements in glycemic control. The authors suggested that large individual variation in liver fat changes after HIIT might have accounted for lack of improvement in glycemic control. On the other hand, both fatty liver disease and visceral adiposity have been linked to cardiovascular disease.<sup>7</sup> The improvements in cardiac function in the present

study ultimately may be attributed to reductions in liver and visceral fat.

One of the biggest drawbacks of the study was the lack of comparison between HIIT and moderate continuous exercise. Moderate continuous exercise has been extensively studied and is known to have a beneficial effect on many chronic disease states. To best determine the place for HIIT when prescribing exercise, a direct comparison between the two forms of exercise would have been helpful. Although other studies have made comparisons, few have done so with a detailed focus on cardiac structure and function.

Ultimately, the present study is one of the first to demonstrate improvements in cardiac structure and function among type 2 diabetics engaging in HIIT. Moreover, the study raises speculation about the connection between regional fat deposition and the progression or resolution of T2DM and cardiovascular disease. Despite the lack of direct

comparison with moderate continuous exercise, HIIT deserves consideration for use among type 2 diabetics, especially as it offers a solution to the commonly cited limitation of “not enough time.” ■

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## OBESITY

### SHORT REPORT

# The Removal of Dietary Fructose Improves Pediatric Health

By David Kiefer, MD

**SYNOPSIS:** In 43 children with obesity and metabolic syndrome, 9 days of dietary sugar reduction (isocaloric with starch substitution) improved numerous metabolic parameters and led to more than 2 pounds of weight loss.

**SOURCE:** Lusting RH, et al. Isocaloric fructose restriction and metabolic improvement in children with obesity and metabolic syndrome. *Obesity* 2015 Oct 26. doi: 10.1002/oby.21371.

**F**ructose is probably the most maligned nutrient of late, and for good reason — the authors of this study reference unique aspects of its physiology that, combined with the fact that its inclusion in the diets of many children, could be related to the development of metabolic syndrome, obesity, and type 2 diabetes in younger and younger ages. In this study, the researchers recruited Latino (n = 27) and African American (n = 16) youth who were “high sugar consumers” (> 15% of calories from sugar, > 5% of which was fructose), and who were 8-18 years old, obese, and with one or more of the following: hypertension, hypertriglyceridemia, impaired fasting glucose, hyperinsulinemia, alanine aminotransferase > 40 U/L, or severe acanthosis nigricans.

The study started on day 0, with fasting labs and

### Summary Points

- From baseline diets, sugar was decreased to 10% from 28% and replaced with starch.
- After 9 days, diastolic blood pressure decreased 5 mmHg, triglycerides decreased 46%, LDL cholesterol decreased 0.3 mmol/L, weight decreased 0.9 kg, and fat mass decreased 0.6 kg.

an oral glucose tolerance test, parameters that were repeated at the end of the trial. The participants were then sent home with pre-prepared meals for 9 days meant to provide sufficient calories to maintain weight, but lower total sugar content to

10% (4% fructose) even though total carbohydrate percentage was maintained as per the baseline diet. After the 9 days, there were significant decreases in weight (0.9 kg,  $P = 0.001$ ), body mass index ( $0.4 \text{ kg/m}^2$ ,  $P < 0.001$ ), and fat-free mass (0.6 kg,  $P = 0.04$ ), but not fat mass (0.3 kg,  $P = 0.17$ ). Most of the weight change occurred in the first 4 days followed by a return to baseline, likely water loss, rather than insufficient caloric intake. Diastolic blood pressure was 4.9 mmHg less, but systolic blood pressure did not change. Other significant changes were decreased fasting

glucose, fasting insulin, alanine aminotransferase and fasting triglycerides, LDL cholesterol, and HDL cholesterol, though the latter decreased by only 0.1 mmol/L. Although this trial was a short-term intervention, it provides compelling evidence for cause-effect relationship between fructose intake and some important metabolic parameters. These results further strengthen the case against the consumption of this compound, especially in children at risk for metabolic diseases, and shows the efficacy of even short-term dietary changes for helping reverse dangerous physiologic trends. ■

## CANCER

### SHORT REPORT

# No More Bacon? Carcinogenicity of Meat

By David Kiefer, MD

SYNOPSIS: A review of published research by the World Health Organization concludes that processed meats are probably carcinogenic.

SOURCE: Bouvard V, et al. Carcinogenicity of consumption of red and processed meat. *Lancet Oncol* 2015 Oct 23. pii: S1470-2045(15)00444-1.

The cancer arm of the World Health Organization, the International Agency for Research on Cancer (IARC), classified red meat as probably carcinogenic (Group 2A category) to humans and processed meat as carcinogenic (Group 1 category) to humans.

A Group 1 classification indicates the scientists felt that there was sufficient evidence that an agent causes cancer; in the case of processed meat, there is causation for colorectal cancer and less so for stomach cancer. The processed meats studied included meats (usually beef and pork, but also other red meats, poultry, offal, and meat byproducts) that were salted, cured, fermented, smoked, or otherwise preserved in some way. Other Group 1 carcinogens are asbestos and tobacco smoking, but the IARC stressed that its report does not quantify carcinogenicity and that it is not saying that eating processed meats is as dangerous as those other carcinogens. A Group 2A carcinogen means there is limited epidemiological evidence for a cancer association but strong mechanistic evidence; in the case of red meat, there is some evidence of a connection with colorectal cancer, pancreatic cancer, and prostate cancer.

This was the result of a review of more than 800 scientific studies (700 studies commented on red meat and 400 commented on processed

### Summary Point

- The regular, high intake of processed meats more than red meat may have a connection to several types of cancer, especially colorectal cancer.

meat; there was some overlap) spanning 20 years, dozens of types of cancer, many countries, and a diversity of diets. For example, the report mentioned that eating the equivalent of three pieces of bacon (50 g) daily would increase the risk of colorectal cancer by 18%. With respect to red meat, eating the equivalent of ¼ pound (100 g) of hamburger daily could increase the risk of colon cancer by 17%. Other types of red meat that the researchers included, and should be a part of patient counseling, are veal, pork, lamb, mutton, horse (perhaps not a common part of the U.S. diet!), and goat. Further interpretation of the report's results have varied widely among media outlets and health experts; the extra risk from eating red and processed meats probably remains small for individuals, but it adds to other data steering people to minimize their red meat intake, and creates a compelling public health argument to address this consumption. ■

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## CME QUESTIONS

1. Which of the following statements is true when considering interventions to prevent recurrent depression?
  - a. Given the potential for side effects, antidepressants should be discontinued once remission from depression clearly is established.
  - b. A course of mindfulness based cognitive therapy (MBCT) combined with tapering support is superior to antidepressant maintenance therapy in reducing recurrent rates of depression.
  - c. MBCT with tapering support is equally as effective as maintenance antidepressants, but potentially most useful in lowering recurrent rates of depression in patients with higher risk.
  - d. MBCT is an effective and important adjunct treatment during acute depressive episodes.
2. Higher adherence to the Mediterranean diet can lead to which of the following?
  - a. No perceptible changes in brain structure
  - b. A loss of cortical thickness in all brain regions
  - c. Lower total brain volume, but higher white matter brain volume
  - d. Higher total brain volume, white matter brain volume, and gray matter brain volume
3. Based on the results of a recent study, high-intensity intermittent training may improve all of the following variables *except*:
  - a. end-diastolic volume.
  - b. visceral adiposity.
  - c. hemoglobin A1c.
  - d. left ventricular mass.
4. Which of the following is true about processed meats, according to the recent World Health Organization review?
  - a. Only smoked meats appear to have some risk of carcinogenicity.
  - b. Daily, "high intake" (50 grams or more) is carcinogenic.
  - c. The cancer with the most convincing association with processed meats is lung cancer.
  - d. The risk is comparable to that of smoking or asbestos exposure.
5. In the study on isocaloric fructose reduction, which of the following occurred after 9 days?
  - a. Increased diastolic blood pressure
  - b. Increased hyperinsulinemia
  - c. Loss of an average of 0.6 kilograms of fat-free mass
  - d. Increased LDL cholesterol

## CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- present evidence-based clinical analyses of commonly used alternative therapies;
- make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and;
- describe and critique the objectives, methods, results, and conclusions of useful, current, peer-reviewed, clinical studies in alternative medicine as published in the scientific literature.

## [IN FUTURE ISSUES]

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dietary supplements

Resveratrol and  
Alzheimer's disease

Echinacea for influenza

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behavioral interventions  
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