Reduction in consumption of sugar-sweetened beverages is associated with weight loss: the PREMIER trial1–3

Liwei Chen, Lawrence J Appel, Catherine Loria, Pao-Hwa Lin, Catherine M Champagne, Patricia J Elmer, Jamy D Ard, Diane Mitchell, Bryan C Batch, Laura P Svetkey, and Benjamin Caballero

ABSTRACT

Background: Consumption of liquid calories from beverages has increased in parallel with the obesity epidemic in the US population, but their causal relation remains unclear.

Objective: The objective of this study was to examine how changes in beverage consumption affect weight change among adults.

Design: This was a prospective study of 810 adults participating in the PREMIER trial, an 18-mo randomized, controlled, behavioral intervention trial. Measurements (weight, height, and 24-h dietary recall) were made at baseline, 6 mo, and 18 mo.

Results: Baseline mean intake of liquid calories was 356 kcal/d (19% of total energy intake). After potential confounders and intervention assignment were controlled for, a reduction in liquid calorie intake of 100 kcal/d was associated with a weight loss of 0.25 kg (95% CI: 0.11, 0.39; P = 0.001) at 6 mo and of 0.24 kg (95% CI: 0.11, 0.38; P = 0.008) at 18 mo. A reduction in liquid calorie intake had a stronger effect than did a reduction in solid calorie intake on weight loss. Of the individual beverages, only intake of sugar-sweetened beverages (SSBs) was significantly associated with weight change. A reduction in SSB intake of 1 serving/d was associated with a weight loss of 0.49 kg (95% CI: 0.11, 0.82; P = 0.006) at 6 mo and of 0.65 kg (95% CI: 0.22, 1.09; P = 0.003) at 18 mo.

Conclusions: These data support recommendations to limit liquid calorie intake among adults and to reduce SSB consumption as a means to accomplish weight loss or avoid excess weight gain. This trial was registered at clinicaltrials.gov as NCT00000616. Am J Clin Nutr 2009;89:1299–306.

INTRODUCTION

It has been projected that 75% of US adults will be overweight or obese by 2015 (1). One factor contributing to this obesity epidemic may be an increased dietary energy intake from beverages. Today, Americans consume 150–300 more calories per day than they did 30 y ago, and caloric beverages account for ≈50% of this increase (2, 3). Energy intake from beverages currently represents 21% of total daily energy intake in the general American population (4). Evidence from short-term human studies suggests that calories consumed in liquid form (ie, liquid calories) have weak satiety properties and elicit poor energy compensation compared with calories from solid foods (ie, solid calories) (5–8). These results suggest that an increase in consumption of liquid calories may result in weight gain, and, conversely, that a reduction in liquid calorie intake may lead to weight loss. However, there is a scarcity of strong scientific evidence supporting these hypotheses, particularly from long-term prospective studies. This paucity of evidence has impeded policymaking.

The type of beverage may also influence body weight. For sugar-sweetened beverages (SSBs), some longitudinal studies suggest a positive association between consumption and body weight (9–14). However, many of these studies either failed to control for important confounding factors, such as physical activity, or used unreliable dietary assessment methods. Likewise, recent reviews on the topic had reached different conclusions: 2 (15, 16) proposed that the consumption of SSBs was positively associated with body weight, whereas 6 others (17–20) concluded that there was insufficient evidence. Some studies suggest that milk intake may aid voluntary weight loss (21–24), whereas others found the opposite effect or no effect (25–30).

The objectives of the present study were to determine 1) how changes in liquid calorie intake affect body weight, 2) whether liquid calories are more obesogenic than are solid calories, and 3) how changes in consumption of specific beverages affect body weight among adults.

1 From the Center for Human Nutrition, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD (LC and BC); the Department of Internal Medicine, Johns Hopkins School of Medicine, Baltimore, MD (LJA); the Division of Prevention and Population Sciences, National Heart, Lung, and Blood Institute, Bethesda, MD (CL); the Department of Medicine, Duke University Medical Center, Durham, NC (P-HL); the Pennington Biomedical Research Center, Baton Rouge, LA (CMC); the Kaiser Permanente Center for Health Research, Portland, OR (PJF); the Division of Clinical Nutrition & Dietetics, University of Alabama at Birmingham, Birmingham, AL (JDA); the Diet Assessment Center, Pennsylvania State University, University Park, PA (DM); and the Duke Hypertension Center, Duke University, Durham, NC (BCB and LPS).

2 Supported by the National Heart, Lung, and Blood Institute; NIH grants U01 HL60570, U01 HL60571, U01 HL60573, U01 HL60574, and U01 HL62828; the Center for Human Nutrition, Johns Hopkins Bloomberg School of Public Health; and the Eunice Kennedy Shriver National Institute of Child Health & Human Development.

3 Reprints not available. Address correspondence to B Caballero, Johns Hopkins Bloomberg School of Public Health, 615 North Wolfe Street, Room 2041, Baltimore, MD 21205. E-mail: caballero@jhu.edu.

Received November 15, 2008. Accepted for publication February 21, 2009. First published online April 1, 2009; doi: 10.3945/ajcn.2008.27240.
SUBJECTS AND METHODS

Study population

PREMIER is a completed, 18-mo multicenter randomized trial designed to test the blood pressure–lowering effects of 2 multicomponent behavioral interventions in adults with prehypertension or stage 1 hypertension (a systolic blood pressure of 120–159 mm Hg and a diastolic blood pressure of 80–95 mm Hg). The cohort consisted of 810 men and women aged 25–79 y, recruited from 4 study centers (Baltimore, MD, Baton Rouge, LA, Durham, NC, and Portland, OR). Individuals who used antihypertensive medications, weight-loss medications, or oral steroids routinely were excluded. Other exclusion criteria included diabetes, a history of a cardiovascular event, congestive heart failure, current symptoms of angina or peripheral vascular disease by Rose Questionnaire, cancer diagnosis or treatment in past 2 y (except for nonmelanoma skin cancer), renal insufficiency, or a psychiatric hospitalization within the past 2 y. Detailed information regarding the study methods and main results can be found in our previous publications (31, 32). Eligible participants were randomly assigned to 1 of 3 groups: (A) an “Advice Only” comparison group that received information but no behavioral counseling on weight loss, increased physical activity, sodium reduction, and the DASH (Dietary Approaches to Stop Hypertension) dietary pattern (33); (B) a behavioral intervention group, termed “Established,” that received counseling on how to lose weight, increase physical activity, and reduce sodium intake; or (C) a behavioral intervention group, termed “Established Plus DASH,” that received counseling on the same lifestyle goals as the Established group along with counseling on the DASH dietary pattern. The weight-loss approaches in the Established group focused on increased physical activity and reduced energy intake. In contrast, the weight-loss approach in the Established Plus DASH group focused on increased physical activity, reduced energy intake, and substitution of fruit and vegetables for high-fat, high-calorie foods. Except for the advice to increase the intake of low-fat dairy products in the Established Plus DASH group, no other advice regarding beverage consumption was given to any of the groups. Regarding the contact pattern, participants in the Advice Only group received two 30-min individual advice sessions, one at randomization and the other after the 6-mo data collection.Both the Established and Established Plus DASH groups received behavioral interventions derived from the social cognitive theory. The intervention format and contact pattern of the 2 groups were identical: 14 group meetings were conducted weekly in the initial 14 wk; 6 group meetings were conducted every other week plus a single individual session in the next 14 wk; monthly group meetings and 3 quarterly individual counseling sessions were conducted in the last 48 wk. The PREMIER study was conducted from January 2000 through November 2002. All 810 study participants enrolled at baseline were included in this analysis.

Measurement of dietary and beverage intake

Dietary intake was measured by unannounced 24-h dietary recall conducted by telephone interviews. Two recalls (one on a weekday and the other on a weekend day) per participant were obtained at baseline and at 6 and 18 mo. A multiple-pass technique and portion size estimation aids were used. Intakes of nutrients and food groups were calculated by using the Nutrition Data System for Research, version NDS-R 1998 (University of Minnesota, Minneapolis, MN).

We divided beverages into 7 categories based on calorie content and nutritional composition: 1) SSBs (regular soft drinks, fruit drinks, fruit punch, or any other high-calorie beverage sweetened with sugar), 2) diet drinks (diet soda and other “diet” drinks sweetened with artificial sweeteners), 3) milk (whole milk, 2% reduced-fat milk, 1% low-fat milk, and skim milk), 4) 100% juice (100% fruit and vegetable juice), 5) coffee and tea with sugar (CTS: coffee and tea sweetened with sugar), 6) coffee and tea without sugar (CT: unsweetened coffee and tea or coffee and tea sweetened with artificial sweeteners), and 7) alcoholic beverages (beer, wine, spirits, and other alcoholic drinks). Each participant’s daily nutrient, energy, and beverage intakes were calculated by taking the average of 2 recalls per time point. Liquid calorie intake was calculated as the sum of calories from the 7 beverage categories. Solid calorie intake was calculated by subtracting liquid calories from total calories.

Statistical analysis

All statistical analyses were performed by using STATA version 9.0 (Stata Corp, College Station, TX). Statistical significance was set at $P \leq 0.05$ (2-tailed). The analyses were conducted by combining all participants and adding intervention assignment as a covariate in all models.

TABLE 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>$n$ = 810</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline characteristics of the PREMIER participants</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>50.0 ± 8.9$^d$</td>
</tr>
<tr>
<td>Female (%)</td>
<td>61.7</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>34.4</td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>64.2</td>
</tr>
<tr>
<td>All others</td>
<td>1.4</td>
</tr>
<tr>
<td>Education, college degree or above (%)</td>
<td>57.2</td>
</tr>
<tr>
<td>Household income $&gt;$45,000 y (%)</td>
<td>70.0</td>
</tr>
<tr>
<td>Marital status, married (%)</td>
<td>65.2</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>4.8</td>
</tr>
<tr>
<td>Fitness (heart rate/min)</td>
<td>130.5 ± 14.5</td>
</tr>
<tr>
<td>Physical activity (kcal · kg$^{-1}$ · d$^{-1}$)</td>
<td>33.7 ± 2.9</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>95.2 ± 18.8</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>33.1 ± 5.8</td>
</tr>
<tr>
<td>BMI classification (%)</td>
<td></td>
</tr>
<tr>
<td>Normal weight, BMI &lt; 25 kg/m$^2$</td>
<td>5.4</td>
</tr>
<tr>
<td>Obese, BMI $\geq$ 30 kg/m$^2$</td>
<td>65.2</td>
</tr>
</tbody>
</table>

$^d$ Mean ± SD (all such values).
The 2 main exposures of interest were 1) changes in consumption of liquid calories and 2) changes in consumption of individual types of beverages, each assessed from baseline to 6 and 18 mo separately. Key outcome variables were weight changes from baseline to 6 and 18 mo. For the primary analysis, exposure and outcome variables were modeled as continuous variables. Additional analyses with exposures modeled as categorical variables were carried out to assess the patterns of dose response. In model 1, changes in consumption of solid and liquid calories were simultaneously included with adjustments for baseline age, sex, race, income, education, marital and employment status, body mass index (BMI; in kg/m²) status, intervention allocation, and concurrent changes in fitness and physical activity. In model 2 the primary exposure variable was individual types of beverages, each assessed from baseline to 6 and 18 mo separately.
percentage of liquid calories, and the model was adjusted for the same covariates as in model 1. In model 3, we assessed the role of individual beverages by including each type of beverage; in this model, we adjusted for total energy intake and the covariates included in model 1. Additional adjustment for smoking status (never, past, or current) and dietary factors such as fat and carbohydrate intakes and energy density did not change the results. Therefore, these variables were not included in the final models. Missing values were not imputed in primary analyses. In sensitivity analyses, we used the baseline observation carried forward method to assess the effect of missing values on study results. The study protocol was approved by the institutional review boards of each of the participating centers and was monitored by an external data safety committee.

RESULTS

Baseline characteristics and retention to follow-up

The baseline characteristics of the participants are shown in Table 1. There were 62% women and 34% African Americans, with an average age of 50 y. Fifty-seven percent of participants had college degrees or above, 65% were married, and 70% had a household income >$45,000/y. Most of the participants were current nonsmokers (95%), 29% were overweight (BMI: 25–29.9), and 65% were obese (BMI ≥ 30). At 18 mo, 94% of the participants had a weight measurement, and 90% had at least one dietary recall.

**Table 4**

Longitudinal associations between changes from baseline (Δ) in beverage consumption (exposure) and in body weight (exposure) by race, sex, baseline BMI status, and age group among participants in the PREMIER study.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Race</th>
<th>Sex</th>
<th>Baseline BMI status</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White</td>
<td>Black</td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>ΔLiquid calorie intake (100 kcal/d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mo</td>
<td>0.21&lt;sup&gt;6&lt;/sup&gt;</td>
<td>0.37&lt;sup&gt;6&lt;/sup&gt;</td>
<td>0.22&lt;sup&gt;6&lt;/sup&gt;</td>
<td>0.30&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>18 mo</td>
<td>0.19</td>
<td>0.53&lt;sup&gt;6&lt;/sup&gt;</td>
<td>0.22</td>
<td>0.29&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>ΔSolid calorie intake (100 kcal/d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mo</td>
<td>0.07</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>18 mo</td>
<td>0.11&lt;sup&gt;6&lt;/sup&gt;</td>
<td>0.05</td>
<td>0.05</td>
<td>0.12&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>ΔSSBs (servings/d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mo</td>
<td>0.38&lt;sup&gt;6&lt;/sup&gt;</td>
<td>0.59&lt;sup&gt;6&lt;/sup&gt;</td>
<td>0.27</td>
<td>0.70&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>18 mo</td>
<td>0.81&lt;sup&gt;6&lt;/sup&gt;</td>
<td>0.54</td>
<td>0.38</td>
<td>1.08&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup> SSBs, sugar-sweetened beverages. A likelihood ratio test was used to test for interactions.
<sup>2</sup> Test for interaction between race and liquid calories was not significant (P = 0.6 at 6 mo and 0.2 at 18 mo).
<sup>3</sup> Test for interaction between sex and SSB intake was not significant (P = 0.2 at 6 mo and 0.2 at 18 mo).
<sup>4</sup> Test for interaction between BMI and SSB intake was not significant (P = 0.08 at 6 mo and 0.06 at 18 mo).
<sup>5</sup> Test for interaction between age and BMI was not significant (P = 0.3 at 6 mo and 0.9 at 18 mo).
<sup>6</sup> P < 0.05.
<sup>7</sup> Changes in liquid and solid calories were simultaneously included in the model, adjusted for baseline sex, race, age, income, education, marital and employment status, BMI status, intervention group, and change in fitness and physical activity. Change in all beverages were simultaneously included in the model, adjusting for baseline sex, race, age, income, education, marital and employment status, BMI status, intervention group, and change in fitness, physical activity and total calorie intake. One serving = 12 fl oz, or 355 mL.
CTS, and CT decreased with time, whereas the consumption of diet drinks increased.

**Association between beverage consumption and weight loss**

The longitudinal associations between changes in body weight and in intakes of liquid calories, solid calories, and individual beverages are shown in Table 3. We also examined these associations in cross-sectional analyses and found them similar to those in the longitudinal analyses (data not shown).

**Change in consumption of liquid and solid calories and change in body weight**

When both liquid and solid calories were included in the analysis (model 1), changes in these variables were significantly and positively associated with weight change. A reduction of 100 kcal/d in liquid calorie intake was associated with 0.3 kg of weight loss (95% CI: 0.1, 0.4; P < 0.001) at 6 mo and of 0.2 kg (95% CI: 0.06, 0.4; P = 0.008) at 18 mo. A reduction in solid calorie intake by 100 kcal/d was associated with a 0.06-kg weight loss (95% CI: 0.002, 0.14; P = 0.04) at 6 mo and of 0.09 kg (95% CI: 0.005, 0.16; P = 0.003) at 18 mo. A reduction in liquid calorie intake had a stronger effect on weight loss than did a reduction in solid calorie intake, but the difference was statistically significant only at 6 mo (P value for the test of \( \beta_{\text{liquid}} - \beta_{\text{solid}} \geq 0 \) was 0.006 at 6 mo and 0.09 at 18 mo). This finding was also supported by the results from model 2 (Table 3). A reduction in the percentage of liquid calories from total calories by 1% was associated with a weight loss of 0.04 kg (95% CI: 0.01, 0.06; P = 0.005) at 6 mo and of 0.02 kg (95% CI: −0.01, 0.06; P = 0.2) at 18 mo. We further conducted a stratified analyses based on participants’ race (white or black), sex (male or female), baseline BMI (<30 or ≥30), or age group (<50 or ≥50 y). The results are shown in Table 4. Liquid calories apparently had a stronger effect on weight loss in blacks than in whites; however, there was no evidence to suggest that the difference was statistically significant (P for interaction = 0.6 at 6 mo and 0.8 at 18 mo).

**Consumption of individual beverages and change in body weight**

In another model (model 3), in which the exposures were individual beverages, only the change in consumption of SSBs was significantly associated with weight change at both 6 and 18 mo. A reduction in SSBs by 1 serving/d (355 mL, or 12 fl oz) was associated with a weight loss of 0.5 kg (95% CI: 0.1, 0.8; P = 0.006) at 6 mo and of 0.7 kg (95% CI: 0.2, 1.1; P = 0.003) at 18 mo. Changes in the consumption of diet drinks and alcoholic beverages were inversely associated with weight loss, both at 6 and 18 mo, but were not statistically significant. None of the other beverage types was significantly associated with weight change at follow-up (Table 3). In the stratified analyses, the positive association between SSB consumption and weight loss

![FIGURE 1. Model-adjusted mean weight change and 95% CIs (6 mo – baseline) by tertile of 6-mo liquid calorie intake change and 18-mo weight change (18 mo – baseline) by tertile of 18-mo liquid calorie intake change. At 6 mo, the median change in liquid calorie intake was −271 kcal/d in the first tertile, −47 kcal/d in the second tertile, and 169 kcal/d in the third tertile. At 18 mo, the corresponding change in liquid calorie intake in each tertile was −267, −48, and 138 kcal/d, respectively. Models were adjusted for baseline age, sex, race, education, income, BMI status, intervention groups, concurrent change in fitness, physical activity, and solid calorie intake (test for trend was conducted by Wilcoxon’s rank-sum test).](image)
was also consistent across each strata. No test for interaction was statistically significant (Table 4).

Change in body weight and change in consumption of liquid calories and SSBs

We examined dose-response patterns for body weight and changes in consumption of liquid calories and SSBs by dividing participants into tertiles based on their 6- or 18-mo change in consumption of liquid calories or SSBs (persons in the first tertile had the greatest reduction). We calculated the model-adjusted mean change and 95% CIs in body weight for participants in each tertile.

Liquid calories

At both 6 and 18 mo, participants in the first tertile had a greater mean weight loss (6-mo change: 0.8 kg; \( P = 0.006 \); 18-mo change: 1.5 kg; \( P < 0.001 \)) than did those in the third tertile (Figure 1). A significant dose-response trend between change in body weight and change in liquid calorie intake was observed for both the 6-mo change (\( P = 0.01 \)) and the 18-mo change (\( P < 0.001 \)).

SSBs

At both 6 and 18 mo, participants in the first tertile had a greater mean weight loss than did those in the second (6-mo change: 0.7 kg; \( P = 0.006 \); 18-mo change: 1.6 kg; \( P < 0.001 \)) and third (6-mo change: 2.4 kg; \( P < 0.001 \); 18-mo change: 3.6 kg; \( P < 0.001 \)) tertiles (Figure 2). A significant dose-response trend between change in body weight and change in SSB intake was observed at both 6 mo (\( P < 0.001 \)) and 18 mo (\( P < 0.001 \)).

Sensitivity analysis

During the follow-up, 1 participant began antihypertensive drug treatment between 3 and 6 mo, 4 participants began antihypertensive drug treatment between 12 and 18 mo, and 6 and 9 participants began insulin/hypoglycemic drug treatment by the 6 and 18 mo visits, respectively. Exclusion of these individuals from our analyses did not change the results. We also applied the baseline observation carried forward method to check the potential influence of missing values. The differences between estimates with and without imputation were very small. For example, the \( \beta \) regression coefficient for change in one serving of SSB consumption at 6 mo was 0.489 (kg/d) without imputation and 0.485 (kg/d) with imputation.

DISCUSSION

Four principal findings emerged from our study. First, a reduction in liquid calorie intake was significantly associated with weight loss at both 6 and 18 mo. Second, the weight-loss effect of a reduction in liquid calorie intake was stronger than that of a reduction in solid calorie intake. Third, a reduction in SSB intake was significantly associated with weight loss at both 6 and 18 mo. Fourth, no other beverage type was associated with weight change. On average, a reduction in liquid calorie intake of

![Figure 2](image-url)
100 kcal/d was associated with a 0.3-kg weight loss at 6 mo and a 0.2-kg weight loss at 18 mo. A reduction in SSB intake of 1 serving/d was associated with a 0.5-kg weight loss at 6 mo and a 0.7-kg weight loss at 18 mo.

To our knowledge, our study was the first to document the relative effects of calories from liquids compared with those of calories from solid food on weight loss in free-living adults over an extended period, 18 mo. Previously, evidence on this topic came primarily from animal studies (35–37). The only trial in humans was a 4-wk crossover study of 15 individuals, in which weight gain occurred during the liquid load period, but not during the solid load period (38).

Our study was also one of the few prospective studies to evaluate the effects of a reduction in SSB consumption on weight loss. Two trials investigated the effects of a reduction in SSB intake on weight change in children. Neither reported significant results, but methodologic issues, including inadequate power, may hinder their interpretation.

One explanation for the different satiating effects of beverages and solid foods is the absence of mastication when beverages are consumed (39). The absence of chewing and swallowing when ingesting beverages might result in decreased pancreatic exocrine and endocrine responses compared with the ingestion of solid foods. Second, beverages are also emptied from the stomach at a higher rate than are solids and may induce weaker signals in the gastrointestinal tract that would lead to inhibition of further food intake (40).

Another proposed link between SSB consumption and body weight is related to the high fructose content of SSBs. Long-term consumption of a large amount of fructose can promote fat storage and excessive food intake through an increase in de novo lipogenesis (41) and changes in postprandial hormonal patterns (42).

There are several possible explanations for why the consumption of other caloric beverages was not associated with body weight. First, beverages can differ in their effects on satiety and energy intake (43). It has been proposed that the addition of protein, fat, or fiber to a beverage enhances satiety, perhaps by slowing stomach emptying. Milk, for example, might be expected to have more satiating effects than soft drinks because it contains protein and fat in addition to sugar. Second, beverages are also emptied from the stomach at a higher rate than are solids and may induce weaker signals in the gastrointestinal tract that would lead to inhibition of further food intake (40).

In conclusion, our study supports policy recommendations and public health efforts to reduce intakes of liquid calories, particularly from SSBs, in the general population.

We thank the PREMIER participants and staff for their contributions to the study. The authors’ responsibilities were as follows—LC: conducted the analyses and the first draft of the manuscript. All authors: conceived of and designed the study, interpreted the analyses, and revised the manuscript. None of the authors reported any personal or financial conflict of interests.

**REFERENCES**


