Treating Obstructive Sleep Apnea with Continuous Positive Airway Pressure May Aid Weight Loss in Patients with Obesity on a Calorie Restriction Diet

Yuanjie Mao1,2*, Elena Ambrogini1, Irina Lendel1 and Peter Goulden1,3*
1Division of Endocrinology and Metabolism, University of Arkansas for Medical Sciences, Little Rock, Arkansas AR, USA
2Ohio University Diabetes Institute, Athens, OH, USA
3Division of Endocrinology and Metabolism, Mount Sinai St. Luke’s Hospital, New York, NY USA

Objective: To investigate if treating OSA with CPAP improves the efficacy of a 16-week calorie restriction weight loss program in patients with obesity.

Methods: We conducted a retrospective study from 1/1/2014 to 8/31/2017. Patients were eligible if they were 18-65 years old, BMI >= 30 and < 50, and underwent a weight loss program obtained by calorie restriction (800 Kcal/day) for the first 8 weeks and then 500 Kcal/day deficit diet for the second 8 weeks.

Results: Total 300 patients were divided into asymptomatic patients (OSA-A, n = 89), symptomatic OSA (OSA-S, n = 164), and OSA on CPAP treatment (OSA-T, n = 47) groups. At the end of 16 weeks, the absolute weight loss of the OSA-T group was significantly greater than that of the OSA-S and OSA-A groups (-12.1 ± 5.9 vs. -9.5 ± 5.5 vs. -8.7 ± 5.3 kg, P < 0.01). A correlation of CPAP treatment to the absolute weight loss (Spearman’s correlation coefficient -0.181, P = 0.013) was established after adjustment of body weight, age and gender.

Conclusions: Our results suggest that the combination of weight loss and CPAP treatment should be considered for patients with obesity and OSA.

Keywords
Obesity, Weight loss, OSA, CPAP

Introduction
Obesity has been defined by body mass index (BMI) and as abnormal or excessive fat accumulation that is associated with increased morbidity and mortality related to several conditions such as type 2 diabetes mellitus and cardiovascular diseases [1]. The prevalence of obesity has been recognized as a worldwide pandemic, which increased by 47.1% in children and by 27.5% in adults between 1980 and 2013 [2]. In 2016, according to the World Health Organization 39% of adults aged 18 years and over were overweight, and 13% (11% of men and 15% of women) were obese [1]. The first line treatment of obesity is weight loss via an energy restricted diet which typically involves restricting daily calorie intake by 15%–60% of baseline requirements [3]. Weight loss as low as 5% is associated with a significant improvement in type 2 diabetes mellitus and cardiovascular disease risk indicated by a reduction of serum total cholesterol, low-density lipoprotein cholesterol, triglycerides, glucose, insulin, C-reactive protein levels, and systolic and diastolic blood pressure [4–6].
Obstructive sleep apnea (OSA) affects approximately 2% of women and 4% of men aged 30 to 60 years [7]. Typical symptoms include loud snoring, restless sleep, and daytime sleepiness or fatigue. The most common cause of OSA in adults is obesity [7], and an estimated 70% of individuals with OSA are obese [8]. Moreover, OSA itself can cause weight gain [9, 10] by influencing energy consumption and energy intake in different ways, such as reduction of physical activity related to excessive daytime sleepiness and tiredness [11, 12], changes in eating behavior such as frequent eating and high caloric food intake [13] and neuroendocrine changes such as cortisol release, sympathetic activation, and leptin resistance [14, 15].

Treating OSA with continuous positive airway pressure (CPAP) is recommended widely in clinical practice as an adjunct therapy with weight loss in patients with obesity despite a lack of evidence to support this strategy. One study showed that some subjects lost weight after starting CPAP treatment [16]. Another study showed that both CPAP group and non–CPAP group lost significant body weight with respect to baseline, and this effect was independent of CPAP use [17]. More recently a study showed long-term treatment of OSA with CPAP is associated with a small but significant weight gain (a mean 0.3-kg weight gain over a 6-month period compared with non–CPAP treated patients, who lost a mean 0.7 kg of weight) [18]. However, the participants in the above studies were not on calorie restriction, and the impact of treating OSA with CPAP on the efficacy of intensive calorie restriction weight loss management remains unclear. This study is aimed to investigate if CPAP treatment for OSA facilitates weight loss in a 16-week calorie restriction weight loss program.

Material and Methods

We conducted a retrospective study in a cohort of patients seen in the University of Arkansas for Medical Sciences (UAMS) weight loss clinic from 1/1/2014 to 8/31/2017. Patients were eligible if they were 18-65 years old, had body mass index (BMI) ≥ 30 and < 50, and underwent a 16-week calorie restriction weight loss program. Patients who suffered from thyroid dysfunction, uncontrolled diabetes, acute or chronic active infection, active malignancy, required use of supplemental oxygen, end-organ damage, or serious medical or psychological conditions were excluded. The study was conducted in adherence to the Declaration of Helsinki and was approved by Institutional Review Board.

The 16-week calorie restriction weight loss program includes two stages. The first stage was obtained by five liquid meal replacement (OPTIFAST Ready to Drink Shakes, Nestle HealthCare Nutrition, Fremont, MI) a day with strict calorie restriction (800 kcal/day) for the first 8 weeks. It was then transitioned to the second stage obtained by a 500 kcal daily calorie deficit from their baseline energy intake (established using food diaries and dietary history) throughout the remainder 8 weeks. During the program, these patients were having weekly individual counseling and cognitive behavioral therapy regarding stress, dietary and physical activity. After the first 8 weeks, they were encouraged to exercise at least 150 minutes each week.

Participants underwent a standardized medical examination before the program and then every week in the program for 16 weeks. The laboratory tests were performed before the program and 16 weeks later. The patients’ history, physical examination, and laboratory results such as age, gender, body weight, height, blood pressure, complete blood count, basic metabolic profile, liver function test, lipid panel, and thyroid function tests were collected from medical records. They were divided into three groups based on self-reported OSA symptoms and CPAP treatment status: asymptomatic patient group (OSA-A, n = 89), symptomatic OSA group (OSA-S, n = 164), and OSA with CPAP treatment group (OSA-T, n = 47). Self-reported OSA symptoms are defined as having at least one of the following: a loud snoring, restless sleep, and/or daytime sleepiness.

The scale variables were expressed as mean ± SD. Paired t-test was performed to establish changes between baseline and follow-up evaluation for all the considered indices. ANOVA analysis with post hoc Tukey test or Fisher's exact test was performed to assess differences among the three groups. Pearson's or Spearman's test was used to assess correlation and partial correlation between any of weight loss, CPAP use, and other indices. All statistical tests were two-sided and P-values of less than 0.05 were considered statistically significant. Statistical analyses were done by using SPSS version 17.

Results

In the 501 patients screened, 201 were excluded in the study mainly due to lack of information in the sleep quality survey or not completing the 16 weeks program. Of 300 patients included, the average ages were 55 ± 10 years old and 236 (78.7%) were female. The clinical features and laboratory results at baseline and at the end of 16 weeks are summarized in the table 1. Compared to baseline, at the end of the 16 weeks program the participants had significant weight loss (98 ± 23 vs. 108 ± 24 kg; P < 0.05), elevation of white blood cell counts (7.4 ± 2.1 vs. 7.0 ± 2.1 K/microL; P < 0.05), serum urea nitrogen levels (15.5 ± 7.6 vs. 14.2 ± 5.1 mg/dL; P < 0.05), phosphorus levels, albumin levels, TSH levels, and reduction of serum chloride levels, HLD cholesterol levels (50.3 ± 12.8 vs. 54.1 ± 16.3 mg/dL; P < 0.05), and total cholesterol levels (177 ± 39 vs. 186 ± 41 mg/dL; P < 0.05) (Table 1).

At baseline, body weight was significantly higher in the OSA-T group than in the OSA-A group and OSA-S group (125 ± 28 vs. 104 ± 22 vs. 108 ± 25 kg, P < 0.01), as well as BMI (42.4 ± 8.3 vs. 37.3 ± 7.1 vs. 38.6 ± 7.5 kg/m², P < 0.01) (Table 2). In addition, there were more males in the OSA-T group than that in the OSA-A group and OSA-S group (42.6% vs. 11.2% vs. 20.7%, P < 0.05). There was no difference between the OSA-A and OSA-S groups in male gender ratio, baseline BMI, or baseline body weight (Table 2).

The absolute weight loss of the OSA-T group was significantly greater than those of the OSA-S and OSA-A groups at 4 weeks (-7.7 ± 5.1 vs. -4.4 ± 3.0 vs. -4.4 ± 2.5 kg,
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Figure 1: The absolute weight loss and percentage weight loss during the weight loss program. Values are the mean ± SE of body weight in the asymptomatic patient group (OSA-A, n = 89), the symptomatic OSA group (OSA-S, n = 164), and the OSA with CPAP treatment group (OSA-T, n = 47). *, P < 0.05 vs. OSA-A group; #, P < 0.05 vs. OSA-S group. OSA: obstructive sleep apnea.

Since there was significant difference in body weight and male gender ratio among the three groups at baseline, we further divided these patients based on BMI: mild obesity group with BMI > 30 but < 35 (n = 107); moderate obesity group with BMI > 35 but < 40 (n = 78), and severe obesity group with BMI ≥ 40 (n = 115). At the end of 16 weeks, there were no significant difference in the absolute weight loss among the three groups (~9.5 ± 5.3 kg in mild obesity group vs. -10.4 ± 5.5 kg in moderate obesity group vs. -10.1 ± 6.0 kg in severe obesity group, P > 0.05), whereas, the percentage weight loss of the severe obesity group was significantly lower

Table 1: Clinical features and laboratory results at baseline and at the end of 16 weeks in the weight loss program.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>16 weeks</th>
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<tbody>
<tr>
<td>Body weight, kg</td>
<td>108 ± 24</td>
<td>98 ± 23 *</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>133 ± 15</td>
<td>133 ± 16</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>82 ± 10</td>
<td>82 ± 11</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.6 ± 1.4</td>
<td>13.5 ± 1.5</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>41.1 ± 3.6</td>
<td>41.0 ± 3.9</td>
</tr>
<tr>
<td>White blood cells, K/microL</td>
<td>7.0 ± 2.1</td>
<td>7.4 ± 2.1 *</td>
</tr>
<tr>
<td>Platelets, K/microL</td>
<td>265 ± 70</td>
<td>268 ± 73</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.86 ± 0.23</td>
<td>0.88 ± 0.28</td>
</tr>
<tr>
<td>Blood urea nitrogen, mg/dL</td>
<td>14.2 ± 5.1</td>
<td>15.5 ± 7.6 *</td>
</tr>
<tr>
<td>Calcium, mg/dL</td>
<td>9.2 ± 0.3</td>
<td>9.2 ± 0.5</td>
</tr>
<tr>
<td>Phosphorus, mg/dL</td>
<td>3.60 ± 0.70</td>
<td>3.74 ± 0.60 *</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>4.0 ± 0.4</td>
<td>4.0 ± 0.4</td>
</tr>
<tr>
<td>Chloride, mmol/L</td>
<td>104 ± 3</td>
<td>103 ± 3 *</td>
</tr>
<tr>
<td>Bicarbonate, mmol/L</td>
<td>26.5 ± 2.3</td>
<td>26.6 ± 2.4</td>
</tr>
<tr>
<td>Uric acid, mg/dL</td>
<td>5.39 ± 1.30</td>
<td>5.38 ± 1.44</td>
</tr>
<tr>
<td>Total protein, g/dL</td>
<td>6.8 ± 0.4</td>
<td>6.8 ± 0.5</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.8 ± 0.4</td>
<td>3.9 ± 0.4 *</td>
</tr>
<tr>
<td>Alanine aminotransferase, IU/L</td>
<td>29.6 ± 18.9</td>
<td>28.7 ± 16.1</td>
</tr>
<tr>
<td>Aspartate aminotransferase, IU/L</td>
<td>27.2 ± 12.9</td>
<td>27.2 ± 13.1</td>
</tr>
<tr>
<td>Alkaline phosphatase, IU/L</td>
<td>70.7 ± 19.9</td>
<td>71.6 ± 20.6</td>
</tr>
<tr>
<td>Total bilirubin, mg/dL</td>
<td>0.62 ± 0.24</td>
<td>0.63 ± 0.27</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>110 ± 32</td>
<td>106 ± 33</td>
</tr>
<tr>
<td>Triglyceride, mg/dL</td>
<td>142 ± 86</td>
<td>138 ± 69</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>186 ± 41</td>
<td>177 ± 39 *</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>54.1 ± 16.3</td>
<td>50.3 ± 12.6 *</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>118 ± 34</td>
<td>113 ± 35</td>
</tr>
<tr>
<td>Thyroid stimulating hormone, uIU/ml</td>
<td>2.3 ± 1.4</td>
<td>4.0 ± 1.0 *</td>
</tr>
<tr>
<td>Free T4, ng/dL</td>
<td>0.89 ± 0.17</td>
<td>0.91 ± 0.18</td>
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</tbody>
</table>

Data are expressed by mean ± SD, *, P < 0.05 compared to baseline. HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2: Baseline clinical features in the three groups.

<table>
<thead>
<tr>
<th></th>
<th>OSA-A (n = 89)</th>
<th>OSA-S (n = 164)</th>
<th>OSA-T (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>55 ± 10</td>
<td>54 ± 9</td>
<td>54 ± 10</td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>79/10</td>
<td>130/34</td>
<td>27/20 *#</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>104 ± 22</td>
<td>108 ± 25</td>
<td>125 ± 28 #</td>
</tr>
<tr>
<td>BMI, kg/m2</td>
<td>37.3 ± 7.1</td>
<td>38.6 ± 7.5</td>
<td>42.4 ± 8.3 #</td>
</tr>
</tbody>
</table>

Data express by mean ± SD, *, P < 0.05 compared to OSA-A group; #, P < 0.05 compared to OSA-S group; BMI, body mass index; OSA-A, asymptomatic OSA; OSA-S, symptomatic OSA; OSA-T, OSA with CPAP treatment; CPAP: continuous positive airway pressure.

P < 0.01), at 8 weeks (-10.4 ± 5.6 vs. -6.6 ± 4.0 vs. -6.4 ± 3.3 kg, P < 0.01), at 12 weeks (-11.1 ± 5.7 vs. -8.4 ± 4.5 vs. -8.2 ± 3.7 kg, P < 0.01), and at 16 weeks (-12.1 ± 5.9 vs. -9.5 ± 5.5 vs. -8.7 ± 5.3 kg, P < 0.01). The absolute weight loss between OSA-A group and OSA-S group was not different (Figure 1). The percentage weight loss was also significantly greater in the OSA-T group compared to the OSA-A and OSA-S groups at 4 weeks (-6.03% ± 4.91 vs. -4.08 ± 2.45 vs. -4.32 ± 2.44 kg, P < 0.01) and 8 weeks (-8.25% ± 5.59 vs. -6.19 ± 3.41 vs. -6.30 ± 3.15 kg, P < 0.01), however, at the end of the 16 weeks the difference of percentage weight loss was not statistically significant in the 3 groups (-10.46 ± 5.63% vs. -9.14 ± 4.89% vs. -8.47 ± 4.97%, P = 0.065) (Figure 1).
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than those in the mild and moderate obesity groups (-7.69 ± 4.64% vs. -10.16 ± 4.91% vs. -9.97 ± 5.09%, P < 0.05). There were no differences in the percentage weight loss between the mild and moderate obesity groups (Figure 2).

We also divided these patients based on gender: male group (n = 64) and female groups (n = 236). At the end of 16 weeks, the absolute weight loss of the male group was significantly higher than that of the female group (-11.5 ± 7.0 vs. -9.2 ± 5.1 kg, P < 0.01), whereas, the percentage weight loss of the male group was not significantly higher than that of the female group (-9.90 ± 6.03% vs. -8.96 ± 4.76%, P > 0.05) (Figure 3).

In terms of similar impact of male gender to the absolute weight loss as CPAP use, we further studied the correlation of CPAP use to the absolute weight loss at the end of 16 weeks. Absolute weight loss was significantly correlated with male gender, baseline body weight, and CPAP use, but not to age and baseline BMI. After adjusting for baseline BMI and male gender, CPAP use still had a significant association with the absolute body weight loss (Spearman's correlation coefficient -0.181, P = 0.013). Notably, the association of male gender with the absolute body weight loss vanished after adjusting for CPAP use. Besides, we studied the correlation of CPAP use to the percentage weight loss at the 8 weeks. Percentage weight loss was significantly correlated with male gender, baseline BMI, and CPAP use, but not to age and baseline body weight. After adjusting for baseline BMI and male gender, CPAP use still had a significant association with the percentage body weight loss (Spearman's correlation coefficient -0.186, P = 0.003).

Discussion

Our results showed that patients with OSA who were treated with CPAP achieved a significantly greater absolute weight loss than non-CPAP treated patients in a 16-week calorie restriction weight loss program. The correlation of CPAP use to the absolute weight loss at the end of 16 weeks was independent of gender, age, and baseline body weight. In the first stage of intensive calorie restriction, patients with OSA who were treated with CPAP also achieved a significantly greater percentage weight loss than non-CPAP treated patients at 4 and 8 weeks.
The first-line treatment of patients with obesity is weight loss via a calorie restricted diet [3]. It has been shown that short-term weight loss (during the first 6 months of treatment) is a predictive factor for long-term weight loss maintenance [19], which supports the rationale of short-term intensive weight loss program. Two strategies, intensive low-calorie meal replacement diet and traditional balanced calorie deficit diet, are commonly used in the dietary weight loss program [20]. A 6-month pilot trial compared these two strategies for weight loss in older adults with BMI ≥ 35 kg/m² to assess weight loss response and safety. Intensive low-calorie meal replacement diet had greater weight loss and decreases in fat mass without increases in adverse events than traditional balanced calorie deficit diet [20]. In this study, a low caloric diet consisting of 800 kcal/d comprising five meal replacements for 8 weeks and then 500 Kcal/d calorie deficit for another 8 weeks led to successful weight reduction. These patients lost a mean 10 kg body weight which is comparable to a prior study (-10.5 kg loss) [21]. Besides, no remarkable side effects have been reported in our study.

Evidence from both laboratory and epidemiological studies has demonstrated that inadequate sleep caused by OSA is a novel risk factor associated with increased vulnerability to obesity and its complications [22, 23]. Treatment of OSA with CPAP should therefore prevent further weight gain or facilitate weight loss.

However, the available evidence is conflicting, with some studies demonstrating that CPAP users lost weight [16], while others observed either no change [24-26] or increases in weight [18, 27, 28]. Notably, the patients in the above studies were not on active dietary weight loss management and some even included non-obese CPAP users. A recent study investigated the effect of 24-week use of CPAP on CRP levels in patients with obesity, and the participants in study arms requiring weight loss received weekly counseling sessions with a caloric intake goal set at 1200-1500 kcal/day for those weighing <114 kg and 1500-1800 kcal/day for those weighing ≥114 kg. The results showed that the decline in body weight was similar (6.8 kg and 7.0 kg, respectively) in the weight-loss only group to the combined-intervention group with weight loss and CPAP therapy [21]. However, the primary focus of this study was not on weight changes, the caloric intake goals were not uniform, and all participants were pre-selected by baseline CRP >1.0 mg/dl, all of which could confound the results [21]. Another study showed that addition of CPAP treatment did not lead to greater weight loss when used as adjunctive therapy for a behavioral weight loss program in OSA patients (n = 17 in CPAP group and n = 14 in non-CRCP group). It also used a 4-week of very low-calorie restriction at the very beginning of behavioral program [17]. However, this study may be inadequately powered to detect a small weight change due to small sample sizes and very short term of dietary management.

Effective CPAP treatment may facilitate weight loss by several mechanisms, including but not limited to, increased physical activity at daytime and increased responsiveness to leptin. A few studies have previously suggested that increased severity of OSA [12, 29, 30] and excessive daytime sleepiness [11] are associated with decreased physical activity. Meanwhile, CPAP treatment can improve daytime sleepiness associated to OSA, as represented by a decrease in mean Epworth Sleepiness Scale scores [31]. Weight loss occurs when energy expenditure exceeds energy intake. Increased physical activity at daytime with CPAP use could change the balance between energy expenditure and energy intake in OSA patients. Moreover, studies in patients with OSA and similarly obese controls have showed that those with OSA had higher leptin levels than expected based on their percentage body fat [32-34] suggesting that OSA is associated with greater resistance to the weight-reducing effect of leptin than obesity alone. Surgical treatment of OSA leads to a decrease in leptin levels in the absence of weight change [35]. The decreases in leptin levels by treating with CPAP have also been demonstrated in multiple interventional studies [32, 36-38]. These hormonal changes may contribute to the weight loss in OSA patients with CPAP treatment.

Our results showed for the first time that patients who were treated with CPAP achieved a significantly greater absolute weight loss than non-CRCP treated patients in a 16-week calorie restriction weight loss program. Compared to the few available studies on this topic, the patients in our study were not pre-selected, and they were placed on a single goal of low-calorie meal replacement for the first 8 weeks. These may have contributed to the significant difference of the absolute and percentage weight loss in CRCP treated group to non-CRCP treated groups in the first 8 weeks in our study. A prior study [21] showed that the decline in body weight was similar (6.8 kg and 7.0 kg, respectively) in the weight-loss only group to the combined-intervention group with weight loss and CPAP therapy when they are not on intensive calorie restriction. Consistently, in our study when the patients were changed to a 500 Kcal daily calorie deficit diet instead of intensive calorie restriction after the first 8 weeks, the power of significance of percentage weight loss were lost at the end of 16 weeks.

This study has the limitations of lack of objective OSA diagnosis, measures of OSA severity and objective CPAP compliance data. We used a self-reported OSA symptoms for the classification of participants, and these symptoms are non-specific and could be from other sleep disorders. Nevertheless, the link between OSA and obesity has been clearly documented with weight change impacting the Apnea-Hypopnea Index (AHI), a measure of OSA severity [38-41]. In the Wisconsin Sleep Cohort Study, a 10% weight gain predicted a 32% increase in AHI score; conversely a 10% weight loss predicted a 26% decrease in AHI score over a 4-year period [38]. Although those self-reported OSA symptoms could be from other sleep disorders, when considering their high BMIs, most likely they have some extend of OSA. Limitations to this study also include the unblinded retrospective study design. This is a single-centered study and the result could be affected by the source of patients and the generalizability. Lastly, there is a possibility of the “healthy user effect”, i.e. patients who were using CPAP may have been more interested in their general health/well-being as opposed to patients who were symptomatic but not interested in CPAP. Therefore, they may be more adherent with the caloric restriction weight loss program.
Conclusions

Collectively, patients who were treated with CPAP achieved a greater absolute weight loss than non-CPAP treated patients in a 16-week calorie restriction weight loss program. This suggests the importance of sleep quality and possibly underlying neuroendocrine changes to the weight loss in patients with obesity. The combination of weight loss and CPAP treatment should be considered for patients with obesity and OSA [21].

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Disclosure statement

The authors have nothing to disclose.

Author contributions

Y.M. and P.G. designed the study and collected the data. Y.M. performed analysis and wrote the first draft with contributions from E.A., I.L., and P.G. All authors reviewed and commented on subsequent drafts of the manuscript.

References

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