

1 **Improvement in Patient-Reported Sleep in Type 2 Diabetes and Prediabetes Participants**  
2 **Receiving a Continuous Care Intervention with Nutritional Ketosis**

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39 J.S.D edited the manuscript. W.W.C. proposed measuring subjective sleep quality as part of the

40 parent Continuous Care Intervention clinical trial. All authors approved the final version of the

41 manuscript.

42

43 **Abbreviations:**

44 CCI, continuous care intervention; UC, usual care; T2D, type 2 diabetes; BMI, body mass index;

45 PSQI, Pittsburgh Sleep Quality Index; OSA, obstructive sleep apnea; HbA1c, hemoglobin A1c;

46 CPAP, continuous positive airway pressure; AHI, apnea and hypopnea indices; KD, ketogenic

47 diet; REM, rapid eye movement; SWS, slow wave sleep; BHB, beta-hydroxybutyrate; HOMA-

48 IR, homeostatic model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive

49 protein

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54 **Abstract**

55 **Objective:** Sleep disruption is frequently associated with type 2 diabetes (T2D) and  
56 hyperglycemia. We recently reported the effectiveness of a continuous care intervention (CCI)  
57 emphasizing nutritional ketosis for improving HbA1c, body weight and cardiovascular risk  
58 factors in T2D patients. The present study assessed the effect of this CCI approach on sleep  
59 quality using a subjective patient-reported sleep questionnaire.

60 **Methods:** A non-randomized, controlled longitudinal study; 262 T2D and 116 prediabetes  
61 patients enrolled in the CCI and 87 separately recruited T2D patients continued usual care (UC)  
62 treatment. Patients completed the Pittsburgh Sleep Quality Index (PSQI) questionnaire. A PSQI  
63 score of >5 (scale 0 to 21) was used to identify poor sleepers.

64 **Results:** Global sleep quality improved in the CCI T2D ( $p < 0.001$ ) and prediabetes ( $p < 0.001$ )  
65 patients after one year of intervention. Subjective sleep quality (component 1), sleep  
66 disturbance (component 5) and daytime dysfunction (component 7), also showed improvements  
67 in the CCI T2D ( $p < 0.01$  for sleep quality and sleep disturbance; and  $p < 0.001$  for daytime  
68 dysfunction) and prediabetes patients ( $p < 0.001$  for all three components); compared to the UC  
69 T2D group after one year. The proportion of patients with poor sleep quality was significantly  
70 reduced after one year of CCI (T2D; from 68.3% at baseline to 56.5% at one year,  $p = 0.001$  and  
71 prediabetes; from 77.9% at baseline to 48.7% at one year,  $p < 0.001$ ).

72 **Conclusion:** This study demonstrates improved sleep quality as assessed by PSQI in patients  
73 with T2D and prediabetes undergoing CCI including nutritional ketosis but not in T2D patients  
74 receiving UC. The dietary intervention benefited both sleep quality and the severity of T2D  
75 symptoms suggesting that nutritional ketosis improves overall health via multiple mechanisms.

76 **Keywords:** Type 2 diabetes, prediabetes, ketogenic diet, PSQI, nutritional ketosis

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## Introduction

Sleep **disruption** is associated with obesity and type 2 diabetes (T2D), yet the bidirectional relationship between sleep and glucose metabolism is not fully understood. It is linked to increased diabetes prevalence in both experimental<sup>1-4</sup> and epidemiological studies<sup>5-7</sup>. In addition, the severity of hyperglycemia in individuals with diabetes is associated with poor sleep quality<sup>8,9,10,11</sup>, short sleep duration<sup>8,9,12,13</sup> and a greater tendency to develop sleep disorders including obstructive sleep apnea (OSA)<sup>14,15</sup>. **Both the International Diabetes Federation (IDF) and American Diabetes Association (ADA) recommend evaluating T2D patients for sleep breathing problems especially OSA and strongly encourage treatment when found<sup>16,17</sup>.**

**Weight loss is one of the most effective ways to improve sleep quality, quantity [Yannakoulia, 2017 and Xanthopoulos 2018] and to treat OSA in obese patients.** Lifestyle intervention induced weight loss showed significant reduction in the apnea and hypopnea indices (AHI) in conjunction with a decrease in hemoglobin A1c (HbA1c) levels in a randomized controlled trial of obese OSA patients with comorbid diabetes<sup>18</sup>. Further, weight loss following bariatric surgery is effective at improving glycemic control and improving AHI in OSA patients<sup>19</sup>. Intervention studies specifically targeting sleep disruption in OSA patients without any effect on weight, such as continuous positive airway pressure (CPAP) treatment, have shown contradictory results for glycemic control. Most CPAP intervention studies in T2D reported no glycemic benefit from the treatment<sup>20,21</sup>, but one study demonstrated a slight reduction in HbA1c<sup>22</sup>. In contrast, CPAP studies on prediabetic OSA patients showed improvements in insulin sensitivity and glucose tolerance<sup>23,24</sup>. It is not clear from these studies whether improvement of glycemic control in conjunction with weight loss improves sleep quality or vice-versa.

106           A few studies have investigated the impact of dietary macronutrient composition on  
107 sleep duration and quality. Two studies reported reduction of slow wave sleep (SWS) and  
108 elevation of rapid eye movement (REM) sleep in individuals consuming higher carbohydrates  
109 (600g carbohydrate or 80% energy from carbohydrate)<sup>25,26</sup>. Another study reported the effect of  
110 a high carbohydrate (56% energy from carbohydrate) diet in reducing sleep onset latency when  
111 compared to a control diet<sup>27</sup>. Studies investigating low carbohydrate diets showed the opposite  
112 effect; reduced REM<sup>28</sup>, increased REM onset latency<sup>29</sup> and increased SWS<sup>28</sup>, even after 4  
113 hours of administering a very low carbohydrate meal<sup>28</sup>. Collectively, these findings signify  
114 dietary carbohydrate content as an important factor in modulating sleep architecture, but  
115 extrapolation from these studies is limited since they were conducted in experimentally  
116 controlled conditions with small numbers of healthy individuals in a short time-span and with  
117 diets administered at specific time points.

118           Population and intervention-based studies on the overall impact of carbohydrate intake  
119 on sleep indices or sleep quality are very limited. Katagiri et al. showed reduced sleep quality in  
120 individuals consuming more carbohydrates as measured by a subjective sleep measure, the  
121 Pittsburgh Sleep Quality Index (PSQI)<sup>30</sup>. Studies investigating the effect of ketogenic diet (KD)  
122 in children with sleep problems showed improvement in daytime sleepiness<sup>31,32</sup> as well as  
123 positive changes in sleep architecture<sup>32,33</sup>. However, in one of these studies, sleep  
124 improvements were suggested to be due to weight loss rather than the KD<sup>33</sup>. Despite restricted  
125 carbohydrate intake concurrent with sleep improvement in these children, SWS decreased<sup>33</sup>  
126 and REM increased<sup>32,33</sup> which contradicts studies on carbohydrate intake and sleep  
127 architecture in adults<sup>25,26,28</sup>. Carbohydrate restriction and ketogenic diets are widely used in the  
128 clinical management of obesity and diabetes, but studies assessing the effect of this diet on  
129 sleep are currently limited. We recently demonstrated a continuous remote care treatment for  
130 T2D including nutritional ketosis significantly improved glycemic control, weight, and  
131 cardiovascular disease risk factors and reduced diabetes medication use at one year<sup>34-36</sup>.

132 The purpose of this study was to assess the effect of the intervention by time-interval on the  
133 global PSQI and its seven component scores as well as compared its changes with different  
134 intervention and disease categories. We also assessed the relationship between changes in the  
135 sleep parameters versus key biochemical parameters, and also investigated the correlation of  
136 pain, circadian rhythm disruption and CPAP usage versus patient-perceived sleep status. We  
137 hypothesized that the global sleep indexes would improve analogously, as improvement in other  
138 key biochemical parameters observed in the intervention.

## 139 **Materials and Methods**

### 140 ***Study participants and design***

141 This study is part of a clinical trial (*Clinical trials.gov identifier: NCT02519309*) that was  
142 approved by the Franciscan Health Lafayette Institutional Review Board. Patients between age  
143 21 and 65 years with either a diagnosis of T2D and a BMI > 25 kg/m<sup>2</sup> or prediabetes and a BMI  
144 > 30 kg/m<sup>2</sup> were included in this study. Detailed study design including the inclusion and  
145 exclusion criteria were previously reported<sup>34,35</sup>. Briefly, the trial was an open-label, non-  
146 randomized, controlled, longitudinal study with patients divided into three groups. The T2D and  
147 pre-diabetes patients in the continuous care intervention (CCI) regimen self-selected either on-  
148 site (CCI-onsite) or web-based (CCI-web) education delivery. Educational content and medical  
149 treatment was the same for both CCI-onsite and CCI-web. As there were no significant  
150 differences in outcomes including PSQI scores, between educational groups, they are combined  
151 for further analysis<sup>34,35</sup>. Both T2D and prediabetes CCI patients had access to a mobile health  
152 application (app) that enabled them to communicate and be continuously monitored by a team  
153 of healthcare professionals including a personal health coach and physician or nurse  
154 practitioner. Patients received individualized guidance in achieving nutritional ketosis, typically  
155 including restriction of daily dietary carbohydrates to less than 30 grams. Patients were  
156 encouraged to measure and input weight, blood glucose and blood beta-hydroxybutyrate (BHB)  
157 concentrations daily in the app. These measurements were used by the health care team for

158 monitoring the patient's condition (weight and glucose) and assessing carbohydrate restriction  
159 (BHB).

160 Separately recruited usual care (UC) T2D patients were participants in a local diabetes  
161 education program including care by their primary care physician or endocrinologist and  
162 counseling by registered dietitians; no modification to their care was made for the study. This  
163 group was observed at baseline and one year as reference for typical disease treatment and  
164 progression within the same geography and health system. (UC patients were informed that the  
165 trial had an intervention arm and could participate in that group if they chose to do so).

### 166 ***Demographic and clinical variables***

167 Patient demographic and clinical data were collected at baseline, 70 days and one year.  
168 Laboratory measures were assessed at a Clinical Laboratory Improvement (CLIA) certified  
169 laboratory. These data were initially analyzed to evaluate the safety and effectiveness of the  
170 CCI in improving diabetes status (glycemic control and medication use), weight and other  
171 metabolic factors in T2D<sup>34,35</sup> and prediabetes patients<sup>36</sup> (unpublished data, manuscript in  
172 preparation). Some of the clinical variables - weight, fasting blood glucose, HbA1c, homeostatic  
173 model assessment of insulin resistance (HOMA-IR), BHB and high sensitivity C-reactive protein  
174 (hsCRP) - were included for further analyses in this study. Usual care T2D patients were not  
175 continuously monitored for weight, blood glucose, or BHB; clinical and laboratory measures  
176 were obtained for this group only at baseline and one year.

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### 178 ***Pittsburgh Sleep Quality Index (PSQI)***

179 CCI patients were administered a set of questionnaires, including the PSQI, during visits  
180 at baseline, 70 days and one year; UC participants completed questionnaires at baseline and  
181 one year. The PSQI consists of 19 validated questions assessing sleep quality and efficiency<sup>37</sup>.  
182 The global PSQI score is calculated from seven component scores on subjective sleep quality  
183 (component 1), sleep latency (component 2), sleep duration (component 3), habitual sleep

184 efficiency (component 4), sleep disturbances (component 5), use of sleep medication  
185 (component 6) and daytime dysfunction (component 7). Each question within the component is  
186 scored on a 4-point Likert scale of 0 to 3, with 3 indicating worse outcomes and the mean was  
187 calculated for each component score. The sum of the component score means generates the  
188 global PSQI score that ranges from 0 to 21. Higher global PSQI scores indicate poorer sleep. A  
189 patient with a global PSQI score  $\leq 5$  is considered a “good sleeper” and  $> 5$  is categorized as a  
190 “poor sleeper”<sup>38</sup>. Change in the PSQI score over time was calculated using the formula below:

$$191 \quad \text{Delta PSQI} = \frac{(\text{Post-intervention PSQI} - \text{Baseline PSQI})}{\text{Baseline PSQI}}$$

### 193 **Pain, *shifted sleep chronotype* and CPAP usage**

194 Patients were classified into “pain” and “non-pain” groups based on their response to  
195 pain-related questions in both the PSQI (question 5i) and a separate questionnaire used to  
196 calculate the knee injury and osteoarthritis outcome score (KOOS). Overall KOOS results will be  
197 reported in a separate publication. Classification of patients under circadian rhythm “disrupted”  
198 and “non-disrupted” groups was based on the wake time and bedtime responses for PSQI  
199 questions 1 and 3 for compilation of component 4 (sleep efficiency). Patients were classified as  
200 having a shifted wake-up time if they reported typically waking between 11am and 2am, while  
201 those with bedtimes between 12am to 6pm were bedtime shifted. These arbitrary bedtime and  
202 wake time cut-off ranges were selected based on evening and night shift workers schedule (2nd  
203 shift - 3pm to 11pm and 3rd shift- 11pm to 7am); which causes these workers to have sleep  
204 patterns that deviate from a normal chronotype. Patients were also surveyed regarding CPAP  
205 usage and discontinuation, however detailed usage information such as CPAP pressure  
206 settings and usage compliance were not obtained making it difficult to interpret the patients OSA  
207 treatment status.

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## 210 **Statistical Analyses**

211           The questionnaires were administered by research personal and completed by patients  
212 on paper. Paper questionnaires were scanned and responses were transcribed in duplicate by  
213 an independent contract data entry firm. The patterns of missing data were assessed using  
214 Little's MCAR test<sup>39</sup> and were found to be missing at random (MAR). Missing data were  
215 imputed by Multivariate Imputation by Chained Equations (MICE)<sup>40</sup>, and Intent to treat (ITT)  
216 analyses were performed. Normality of the global PSQI and component scores was evaluated  
217 using Lilliefors test. Even after transformation, the data failed the normality test (i.e. there was a  
218 skew toward lower PSQI scores and a long tail of higher scores) (Supplemental figures 1A-C);  
219 therefore, nonparametric tests were used for analyses of PSQI scores. Results from continuous  
220 variables were expressed as mean  $\pm$  standard deviation. Comparisons between groups were  
221 performed using the Kruskal-Wallis test, and comparisons within groups were performed using  
222 the Wilcoxon Sign Rank test. Tukey's honest significant difference test was used to analyze  
223 pairwise differences among significant results from omnibus tests. McNemar's test was used for  
224 assessing statistical significance of transitioning between 'good' and 'poor' sleeper among the  
225 CCI and UC cohorts.

226           Adjusted Pearson's and Spearman correlations were calculated between changes from  
227 baseline in global PSQI and changes in metabolic-parameters. Adjusted correlations were  
228 performed while controlling for age, gender and BMI at baseline. All participants in the CCI  
229 group were stratified by sleep improvement status based on their baseline and one year global  
230 PSQI scores. Patients that were initially considered "poor sleepers" with a baseline PSQI > 5  
231 but whose score after one year decreased to at or below the threshold of 5 were classified as  
232 *improved*. Those patients who were considered "good sleepers" at both baseline and one year  
233 were classified as *maintained*. Finally, those patients whose 1 year PSQI score was >5  
234 (regardless of their baseline score) were classified as *not improved*. Stepwise analyses of  
235 covariance (ANCOVA) were performed between the three different CCI sleep status groups at

236 one year with the change of the glucose-related, ketone and inflammatory markers, while  
237 controlling by age, gender and years living with diabetes. Statistical tests were performed with  
238 MATLAB R2017b using the Statistics and Machine Learning Toolbox<sup>41</sup> and the R statistical  
239 program version 3.5.0.<sup>42</sup>

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## 242 **Results**

### 243 ***Baseline participant characteristics***

244 Details on the recruitment and extensive baseline characteristics of the CCI and UC T2D  
245 patients were previously published<sup>34,35</sup>. The demographic, glycemic, inflammatory and sleep  
246 baseline characteristics of the participants that were included for assessments of sleep are  
247 presented in Table 1. One-hundred forty-three (54.6%) CCI T2D, 61(54%) CCI prediabetes, and  
248 53 (62.3%) UC T2D patients completed the PSQI at all expected time points. **The patients who**  
249 **completed the trial at one year were slightly higher than those who completed the PSQI**  
250 **questionnaires. Some of the patients completed the study period and laboratory analysis but**  
251 **were unable to attend the clinic for their 70-days and one-year follow-up visits, where they are**  
252 **required to complete their corresponding questionnaires. The proportion of missing PSQI data**  
253 **were similar across the three groups with 77.61% of CCI T2D, 79.06% of CCI prediabetes and**  
254 **79.24% of UC T2D completed the PSQI in all expected time points. There were no significant**  
255 **differences between completers and non-completers on baseline characteristics for either group**  
256 **at one year of the intervention (supplemental Table 1).** The global PSQI and component scores  
257 did not differ significantly among the groups (CCI T2D, CCI prediabetes and UC T2D) at  
258 baseline. The proportion of participants with overall poor sleep quality was higher in the CCI  
259 prediabetes group (77.9%) compared to the CCI T2D (68.3%) and UC T2D (68.2%) groups.

### 260 ***Effect of intervention on sleep***

#### 261 ***Global PSQI and component scores***

262 Overall sleep quality as assessed by the global PSQI score, improved in CCI T2D  
263 (median change from 7 to 6;  $p<0.001$ ) and prediabetes (median change from 7 to 5;  $p<0.001$ )  
264 groups after one year of the intervention (Figure 1). No significant change in the global PSQI  
265 score was observed in UC T2D (median change from 7 to 8,  $p=0.245$ ). At one year, global PSQI  
266 scores in the CCI T2D ( $p<0.001$ ) and prediabetes ( $p<0.01$ ) were significantly lower than in the  
267 UC T2D, whereas no differences were observed at baseline (Figure 2A). Among patients  
268 characterized as poor sleepers at baseline (global PSQI  $>5$ ), one year global PSQI score was  
269 lower in the CCI T2D ( $p<0.001$ ) and prediabetes ( $p<0.001$ ) than in the UC T2D (Figure 2B).  
270 Greater reduction in the global PSQI score was observed in CCI T2D (median change of -1,  
271  $p<0.01$ ) and CCI prediabetes groups (median change of -2,  $p<0.001$ ) compared to the UC T2D  
272 group (Figure 3). Further assessment of the PSQI component scores revealed three of the  
273 seven components showed significant change at one year for CCI T2D and prediabetes groups.  
274 Subjective sleep quality ( $p<0.01$  CCI T2D;  $p<0.001$  CCI prediabetes), sleep disturbance ( $p<0.01$   
275 CCI T2D;  $p<0.001$  CCI prediabetes) and daytime dysfunction ( $p<0.001$  CCI T2D;  $p<0.001$  CCI  
276 prediabetes) score were lower in the CCI T2D and prediabetes patients compared to the UC  
277 T2D group at one year (Figure 4 A-C).

### 278 ***Resolution of poor sleep quality***

279 There were 179 (68.3%) T2D and 88 (77.9%) prediabetes patients categorized as “poor  
280 sleepers” in the CCI at baseline. The proportions of “poor sleepers” in the CCI were reduced  
281 after one year of the intervention, with 56.5% of T2D ( $p=0.001$ ) and 48.7% ( $p<0.001$ ) of  
282 prediabetes patients categorized as “poor sleepers” at one year. In the UC cohort, the  
283 proportion of patients categorized as “poor sleepers” did not change after one year (68.2% at  
284 baseline to 69.4% at one year).

### 285 ***Association within the CCI group between changes in global PSQI with metabolic and*** 286 ***inflammatory markers***

287 Table 2 shows correlations between changes in the global PSQI score with changes in  
288 glucose-related, ketone and inflammatory markers in the CCI. In the prediabetes group,  
289 changes in fasting glucose ( $r= 0.23$ ,  $p=0.02$ ) and HOMA-IR ( $r= 0.32$ ,  $p<0.001$ ) were correlated  
290 to changes in PSQI scores after controlling for baseline age, sex and weight. Increased ketone  
291 concentrations in the prediabetes participants were also associated with reduction of global  
292 PSQI scores ( $r= -0.242$ ,  $p=0.01$ ). These correlations observed in the prediabetes group were  
293 not present in the CCI T2D group and changes in the HbA1c and hsCRP did not correlate with  
294 changes in global PSQI scores in either group. Change in mean weight ( $p=0.04$ ) and HOMA-IR  
295 ( $p=0.01$ ) were the only variables independently and significantly associated between the three  
296 different sleep status (improved, maintained and not improved sleep status) at one year of the  
297 intervention. No statistically significant differences were found in weight loss changes between  
298 patients with improved, maintained and not improved sleep status. Patients who maintained  
299 sleep showed highest reductions of HOMA-IR ( $-6.94 \pm 0.86$ ), with statistically significant  
300 difference than those who did not improve sleep, after one year of the intervention ( $p = 0.02$ ).  
301 Improvements in HOMA-IR among patients in the improved sleep ( $-4.17 \pm 0.86$ ) and not  
302 improved sleep status ( $-4.24 \pm 0.55$ ) did not differ significantly.

### 303 ***Effect of persistent pain on sleep improvement***

304 We further assessed the effect of pain on sleep improvement in the CCI by classifying  
305 the patient's pain status using response retrieved from questions specifically related to pain in  
306 the sleep and knee (KOOS) questionnaires. As illustrated in supplementary figure 2, patients  
307 with pain had higher global PSQI scores, indicating poorer sleep, compared to those  
308 categorized under "non-pain" group at all three time points. Both patients in the "non-pain"  
309 (Supplementary figure 3A,  $p<0.001$ ). and "pain" group (Supplementary figure 3B,  $p<0.01$ ) had  
310 reductions in their global PSQI score at 70 days and one year.

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313 **Effect of *shifted sleep chronotype* on sleep improvement**

314 We also assessed the effect of *shifted sleep chronotype* on the global PSQI score  
315 improvement. Patients were classified as having *shifted sleep chronotype* based on their self-  
316 reported wake-up times and bedtimes as defined in the methods. There were 18, 27, and 96  
317 patients in the CCI cohort classified as both wake-up time and bedtime shifted, wake-up time  
318 shifted only or bedtime shifted only respectively. Patients with shifted bedtimes, had reduced  
319 global PSQI scores ( $p < 0.01$ ), as did those with normal chronotype ( $p < 0.001$ ) (Supplementary  
320 figures 4A and B). However, those patients with shifted wake-up times (Supplementary figures  
321 4C) did not show a change in their global PSQI score after one year of the intervention. Those  
322 with both shifted wake-up times and bedtimes also did not show a change in their global PSQI  
323 score after one year of the intervention.

324 **Effect of CPAP usage on sleep improvement**

325 At baseline, there were a total of 140 participants in both CCI and UC treatment groups  
326 with CPAP equipment prescribed for sleep. Among CPAP users, 91 were in the CCI T2D group,  
327 31 in the CCI prediabetes and 18 in the UC T2D group. Fifteen (13 CCI T2D and 2 UC T2D) of  
328 the 140 participants discontinued using CPAP at one year. Only 6 (46%) of the 13 CCI T2D  
329 participants discontinued due to patient-reported improvement in sleep quality from the CCI and  
330 reduction of weight; the remaining 7 reported dis-continuation due to discomfort or personal  
331 choice. Global PSQI scores among the CPAP users at baseline and one year did not show a  
332 significantly different distribution pattern than what was observed in the full cohort of  
333 participants.

334 **Discussion**

335 This study is one of the first designed to assess the effect of carbohydrate restriction and  
336 nutritional ketosis on sleep quality in individuals with hyperglycemia and insulin resistance.  
337 Improved patient-reported sleep quality as assessed by global PSQI suggests that CCI  
338 including nutritional ketosis benefited sleep quality in both patients with T2D and prediabetes.

339 The proportion of patients categorized as “poor sleepers” at one year was significantly reduced  
340 in the CCI groups but not in the UC group. Furthermore, these results demonstrate that the  
341 sleep quality improvement observed in the whole intervention population was due in part to 17%  
342 of baseline “poor sleepers” being reclassified as “good sleepers” at one year. Our results are  
343 consistent with previous findings that showed improved overall sleep quality in children  
344 consuming ketogenic diets <sup>31, 32</sup>.

345 Improvement in the global PSQI score of patients undergoing the CCI was mainly  
346 due to significant changes in three PSQI components: subjective sleep quality, sleep  
347 disturbance and daytime dysfunction. Both objective and subjective sleep quality impairment are  
348 frequently reported in diabetes patients and positively associated with severity of hyperglycemia  
349 <sup>8-11</sup>. Likewise, correlation between poor sleep quality and increased carbohydrate intake <sup>30</sup> is  
350 also previously reported. These observed patterns of association between sleep quality with  
351 hyperglycemia and carbohydrate intake may explain why this carbohydrate restriction  
352 intervention improved subjective sleep quality. The sleep disturbance component of the global  
353 PSQI score is associated with poor glycemic control among T2D patients <sup>43</sup>. One study reported  
354 a significant correlation between sleep disturbance and HbA1c level <sup>44</sup>. Night time sleep  
355 disturbance in T2D patients can be related to a wide range of conditions such as nocturnal  
356 polyuria, pain, and breathing problems, especially in those with OSA. In our study, we also  
357 showed that patients encountering persistent pain, including knee pain, had a higher median  
358 global PSQI score, while one year of the intervention effectively improved global PSQI scores in  
359 these patients despite the persistence of reported pain in some patients. It is possible that  
360 improvement in the sleep disturbance of the CCI patients contributed to the glycemic control  
361 improvement in these patients. The effectiveness of the intervention in improving sleep in those  
362 with pain, further emphasizes its’ applicability in alleviating sleep disturbance.

363 Furthermore, there was a significant improvement in the daytime dysfunction component  
364 of the global PSQI score in the CCI group. Excessive daytime sleepiness and dysfunction are

365 reported commonly in T2D <sup>45,46</sup>, and weight loss through bariatric surgery has a positive  
366 resolving effect on daytime dysfunction and sleepiness <sup>47,48</sup>. In the present investigation, the  
367 majority of CCI patients achieved weight loss of  $\geq 10\%$ , which could have contributed to the  
368 significant improvement observed in daytime function. In addition, we also evaluated the effect  
369 of the intervention on a subcohort of patients with a self-reported pattern of shifted non-standard  
370 bedtimes and wake-up times that were not aligned to the light dark cycle, which likely affects  
371 daytime functioning. Circadian rhythm disruption is frequently associated with metabolic  
372 alterations, especially in an insulin resistant state <sup>49,50</sup>. While patients with a normal sleep  
373 chronotype benefited the most, the intervention also improved the sleep of patients with time  
374 shifted bedtimes. A similar advantage of the intervention was not observed in patients with  
375 shifted wake-up times, though this may be due to the limited number of patients in this subgroup  
376 (n=27).

377 The improvement in the global PSQI score observed in CCI patients occurred  
378 concurrently with weight reduction and glycemic control improvement <sup>34,35</sup>. Martin et al <sup>51</sup>  
379 reported a direct correlation between degree of weight loss and global PSQI score improvement  
380 in healthy nonobese adults receiving an energy restricted diet, while Chaput et al <sup>52</sup> reported an  
381 improvement in global PSQI score following the initial 5-kg weight loss, but no additional  
382 improvement with subsequent weight loss. A study using a ketogenic diet in children alleviated  
383 abnormal sleep architecture; however, weight loss was suggested as the main determinant of  
384 improved sleep <sup>33</sup>. These studies collectively imply a direct association between weight loss and  
385 improved PSQI score. **Likewise, long-term maintenance of weight loss was associated with**  
386 **better sleep quality and quantity (); while the degree of weight loss reduction is directly**  
387 **correlated with OSA improvement().** However, some studies also demonstrate the efficacy of  
388 anti-glycemic medications for improving PSQI score concurrent with improved glycemic control  
389 <sup>53</sup>. This study identified associations between HOMA-IR and weight reductions with stratification

390 of patients' sleep status in the full CCI cohort even though there were no significant differences  
391 in weight loss and insulin resistance reduction levels between those who had improved sleep  
392 and those who did not. Patients with good sleep quality at the beginning of the intervention  
393 benefited the most in reducing insulin resistance. Improvement in fasting glucose and HOMA-IR  
394 were only positively associated with improved PSQI score in prediabetes patients.

395 It is not clear if nutritional ketosis achieved by substantial carbohydrate restriction  
396 augmented the effect of the intervention on sleep or if weight loss and/or improved glycemic  
397 control generated from the intervention contributed to sleep quality improvements. We showed  
398 a significant correlation between blood beta-hydroxybutyrate (BHB) levels and PSQI  
399 improvement in the prediabetes cohort. While the effect of and mechanism of BHB in sleep are  
400 not clear, a positive correlation between blood BHB levels and carbon dioxide (CO<sub>2</sub>) response  
401 was previously reported in patients with obesity related hypoventilation syndrome that had  
402 reduced CO<sub>2</sub> response<sup>54</sup>. A continuous state of ketosis through carbohydrate restriction and fat  
403 intake also induces the postprandial release of a satiety hormone, cholecystokinin (CCK)<sup>28,55,56</sup>.  
404 When administered in rats, CCK was shown to promote slow wave activity and NREM sleep<sup>57</sup>.  
405 CCK was also shown to induce sleep when administered in diabetic rats<sup>58</sup>. Therefore, it is  
406 possible that one mechanism of improved sleep with a ketogenic diet that increases BHB levels  
407 is through CCK induction.

408 There are several limitations of our study. The study was designed mainly to assess the  
409 impact of the CCI on glycemic control, medication use, weight, and cardiovascular disease risk  
410 factors. Patient-reported outcomes for quality of life measures including sleep were included as  
411 secondary endpoints. It is difficult to determine the causality among the intervention,  
412 improvement in primary outcomes and improvement in sleep from this study. A major limitation  
413 of this study is the use of subjective sleep measures as self-reported sleep assessment is  
414 subject to limited self-knowledge of sleep behavior and inconsistency in reporting. Therefore,  
415 future studies that use randomized controlled trial designs and objective sleep measures are

416 needed to confirm our results. In addition, patients with an established diagnosis of a sleep  
417 disorder such as OSA were not separated in the analysis since complete records of their CPAP  
418 usage were not collected in the questionnaire. Patient compliance with CPAP usage is essential  
419 for making interpretations about the status of their OSA treatment and its effect on sleep and  
420 glycemic control. **The study also lacked recruitment of prediabetes patients in the UC group for**  
421 **direct comparison of the treatment effect between UC and CCI on sleep in these patients.**

422 In conclusion, these results demonstrate that overall sleep quality significantly improved  
423 in T2D and prediabetes patients undergoing remote CCI including nutritional ketosis but not in  
424 T2D patients in the UC group. The sleep improvement was concurrent with weight reduction  
425 and glycemic control improvement. The PSQI components that improved were sleep quality,  
426 sleep disturbance and daytime dysfunction. These results suggest that nutritional ketosis  
427 benefits overall health through improved glycemic control as well as improved sleep quality.

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## e Legends

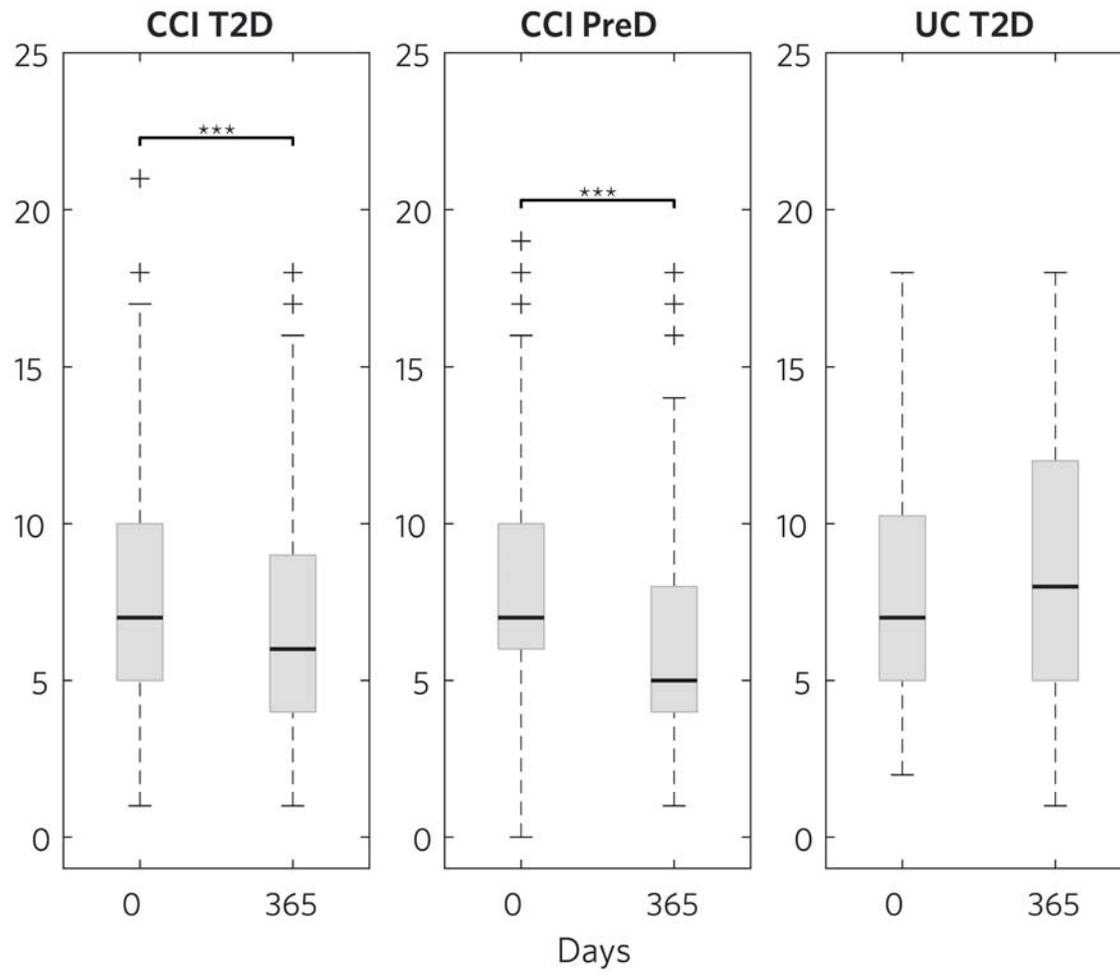
**e 1.** Distribution of global PSQI scores at baseline and 365 days in CCI T2D, CCI PreD and UC T2D. Global PSQI score significantly reduced in the CCI T2D and CCI PreD groups but not in the UC T2D group after 365 days.

**e 2.** Distribution of PSQI components subjective sleep quality, sleep disturbances and daytime dysfunction in CCI T2D and UC T2D groups at three different timepoints (0, 70 and 365 days). Subjective sleep quality (A), sleep disturbances (B) and daytime dysfunction (C) were significantly lower in the CCI T2D and CCI PreD groups when compared to UC T2D group at 365 days.

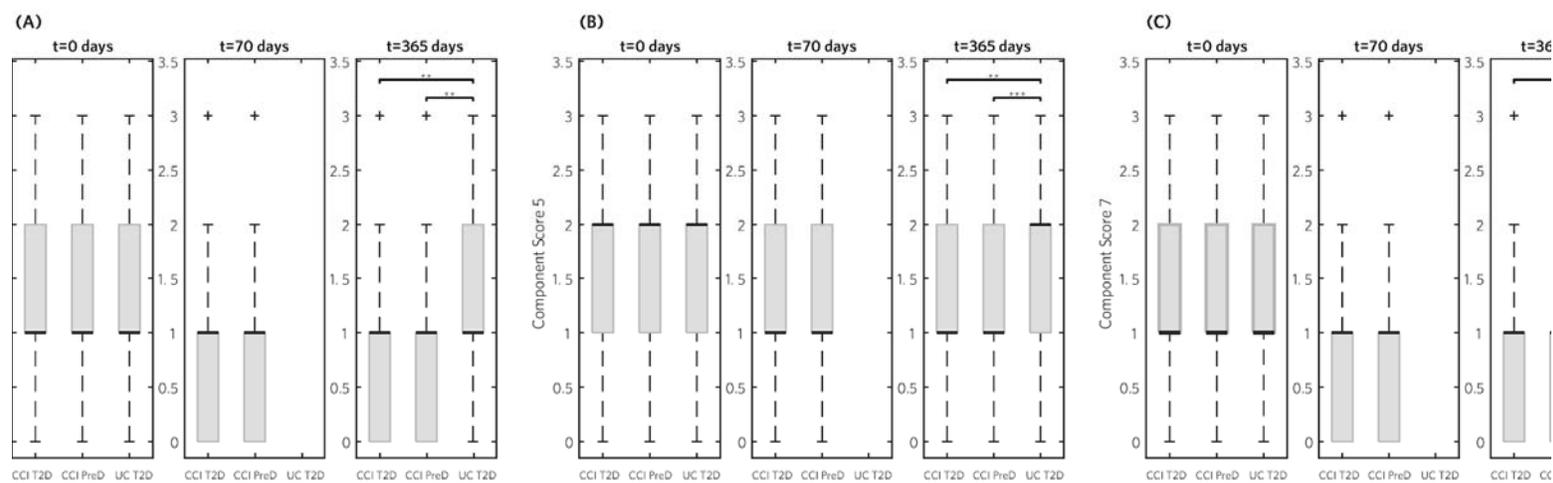
*Box plot descriptors (Figures 1-4) Horizontal line within the box indicates median; upper and lower boundaries of the box represent 25<sup>th</sup> and 75<sup>th</sup> percentiles; whiskers of the box represent the highest and lowest values and “+++” signs represent outlier values.*

*\* p-value <0.05; \*\* p-value <0.01; \*\*\* p-value <0.001*

e 1.



e 2.



1. Baseline characteristics of participants included in the study. Baseline data were calculated using intent-to-treat (ITT)

| Int Cohorts                             | CCI Type 2 Diabetes | CCI Prediabetes    | UC Type 2 Diabe  |
|---|---------------------|--------------------|------------------|
| ers, Completers, PSQI Available (n)     | 262, 218, 143       | 116, 113, 61       | 87, 78, 53       |
|   | mean (S.D.)         |                    |                  |
| years)                                  | 53.8 (± 8.4)        | 51.9 (± 9.4)       | 52.7 (± 9.3)     |
| /female (ratio)                         | 87/175 (1:2)        | 29/84 (1:3)        | 35/50 (2:3)      |
| weight (kg)                             | 116.4 (± 26.1)      | 109.9(± 23.6)      | 108.3 (± 25.1)   |
| kg/m <sup>2</sup> )                     | 40.4 (± 8.9)        | 38.8 (± 7.1)       | 38.2 (± 9.1)     |
| mg glucose (mg/dL)                      | 160.78 (± 61.32)    | 109.58 (± 15.20) * | 157.08 (± 72.48) |
| c (%)                                   | 7.60 (± 1.50)       | 5.91 (± 0.24) *    | 7.67 (± 1.77)    |
| A-IR                                    | 11.8 (± 13.1)       | 7.1 (± 7.4) *      | 13.7 (± 17.8)    |
| sensitivity C-reactive protein (nmol/L) | 9.31 (± 19.31)      | 7.46 (± 7.51)      | 9.34 (± 9.10)    |
| hydroxybutyrate (mmol/L)                | 0.17 (± 0.15)       | 0.14 (± 0.13)      | 0.15 (± 0.12)    |
| il PSQI Score                           | 7.72 (± 3.72)       | 7.96(± 3.43)       | 7.92 (± 3.85)    |
| ctive sleep quality                     | 1.18 (± 0.75)       | 1.22 (± 0.73)      | 1.25 (± 0.79)    |

|                                |                    |                     |                    |
|--------------------------------|--------------------|---------------------|--------------------|
| <b>latency</b>                 | 1.09 ( $\pm$ 0.93) | 1.33 ( $\pm$ 0.958) | 1.05 ( $\pm$ 0.89) |
| <b>duration</b>                | 1.23 ( $\pm$ 0.92) | 1.27 ( $\pm$ 0.96)  | 1.14 ( $\pm$ 0.94) |
| <b>usual sleep efficiency</b>  | 0.68 ( $\pm$ 0.99) | 0.61 ( $\pm$ 0.89)  | 0.71 ( $\pm$ 1.04) |
| <b>disturbances</b>            | 1.64 ( $\pm$ 0.63) | 1.66 ( $\pm$ 0.68)  | 1.75 ( $\pm$ 0.74) |
| <b>use of sleep medication</b> | 0.69 ( $\pm$ 1.16) | 0.66 ( $\pm$ 1.11)  | 0.85 ( $\pm$ 1.26) |
| <b>daytime dysfunction</b>     | 1.22 ( $\pm$ 0.77) | 1.21 ( $\pm$ 0.76)  | 1.17 ( $\pm$ 0.86) |
| <b>total sleepers N (%)</b>    | 179 (68.3)         | 88 (77.9)           | 58 (68.2)          |
| <b>total sleepers N (%)</b>    | 83 (31.7)          | 25 (22.1)           | 27 (31.8)          |

Subjective sleep quality, component 1; sleep latency, component 2; sleep duration, component 3; habitual sleep efficiency, component 4; sleep disturbances, component 5; use of sleep medication, component 6, and daytime dysfunction, component 7

all p-values <0.001

2. Correlation analyses between change in the global PSQI score and change in metabolic parameters after one year of

|                 | <i>CCI T2D Cohort</i> |                 |                   |                            | <i>CCI Prediabetes Cohort</i> |                 |                   |                            |
|-----------------|-----------------------|-----------------|-------------------|----------------------------|-------------------------------|-----------------|-------------------|----------------------------|
|                 | <i>N=262</i>          |                 |                   |                            | <i>N=113</i>                  |                 |                   |                            |
|                 | <i>rho</i>            | <i>P value*</i> | <i>Adjusted r</i> | <i>P value<sup>†</sup></i> | <i>rho</i>                    | <i>P value*</i> | <i>Adjusted r</i> | <i>P value<sup>†</sup></i> |
| glucose (mg/dl) | 0.032                 | 0.60            | 0.008             | 0.90                       | 0.240                         | 0.01            | 0.226             | 0.018                      |
| %)              | -0.037                | 0.55            | -0.049            | 0.44                       | -0.024                        | 0.80            | -0.032            | 0.74                       |
| R               | -0.060                | 0.34            | -0.069            | 0.27                       | 0.314                         | 0.0008          | 0.323             | 0.0006                     |
|                 | -0.003                | 0.96            | -0.044            | 0.49                       | -0.297                        | 0.002           | -0.242            | 0.011                      |
|                 | -0.067                | 0.29            | -0.008            | 0.90                       | -0.022                        | 0.82            | -0.032            | 0.74                       |

rman and <sup>†</sup>adjusted Pearson's correlations. Adjustments while controlling for age, sex and baseline weight