

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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19 **Word Count:** 4000

20 **Tables:** 2

21 **Figures:** 4

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30 **Conflicts of Interest:** SJA, SJH, ALM, NHB, JPM, and SDP are employed by Virta Health Corp

31 and were offered company's stock options. SDP and JSV are founders of Virta Health Corp.

32 CJV, MJS and WWC have no conflict of interest to declare.

33

34 **Financial support:** Virta Health

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36 **Author contributions:** S.J.A, M.S, C.J.V and J.P.M drafted the manuscript. A.L.M, N.H.B,

37 S.J.H and S.J.A participated in data acquisition and compiling. M.S and S.J.A analyzed the

38 data. C.J.V supervised this particular analysis, J.P.M, A.L.M, S.J.H, N.H.B, W.W.C, S.D.P and

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 disturbance is associated with obesity and type 2 diabetes (T2D), yet the bidirectional relationship between sleep and glucose metabolism is not fully understood. Sleep disruption is linked to increased diabetes prevalence in both experimental¹⁻⁴ and epidemiological studies⁵⁻⁷. In addition, the severity of hyperglycemia in individuals with diabetes is associated with poor sleep quality^{8,9, 10, 11}, short sleep duration^{8,9, 12,13} and a greater tendency to develop sleep disorders including obstructive sleep apnea (OSA)^{14,15}. Both the International Diabetes Federation (IDF) and American Diabetes Association (ADA) recommend evaluating T2D patients for disrupted sleep and strongly encourage treatment when found^{16,17}.

Weight loss is one of the most effective ways of treating sleep disruption and 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 diabetes¹⁸. Further, weight loss following bariatric surgery is effective at improving glycemic control and improving AHI in OSA patients¹⁹. 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^{20,21}, but one study demonstrated a slight reduction in HbA1c²². In contrast, CPAP studies on prediabetic OSA patients showed improvements in insulin sensitivity and glucose tolerance^{23,24}. It is not clear from these studies whether improvement of glycemic control in conjunction with weight loss improves sleep quality or vice-versa.

A few studies have investigated the impact of dietary macronutrient composition on sleep duration and quality. Two studies reported reduction of slow wave sleep (SWS) and

106 elevation of rapid eye movement (REM) sleep in individuals consuming higher carbohydrates
107 (600g carbohydrate or 80% energy from carbohydrate)^{25,26}. Another study reported the effect of
108 a high carbohydrate (56% energy from carbohydrate) diet in reducing sleep onset latency when
109 compared to a control diet²⁷. Studies investigating low carbohydrate diets showed the opposite
110 effect; reduced REM²⁸, increased REM onset latency²⁹ and increased SWS²⁸, even after 4
111 hours of administering a very low carbohydrate meal²⁸. Collectively, these findings signify
112 dietary carbohydrate content as an important factor in modulating sleep architecture, but
113 extrapolation from these studies is limited since they were conducted in experimentally
114 controlled conditions with small numbers of healthy individuals in a short time-span and with
115 diets administered at specific time points.

116 Population and intervention-based studies on the overall impact of carbohydrate intake
117 on sleep indices or sleep quality are very limited. Katagiri et al. showed reduced sleep quality in
118 individuals consuming more carbohydrates as measured by a subjective sleep measure, the
119 Pittsburgh Sleep Quality Index (PSQI)³⁰. Studies investigating the effect of ketogenic diet (KD)
120 in children with sleep problems showed improvement in daytime sleepiness^{31,32} as well as
121 positive changes in sleep architecture^{32,33}. However, in one of these studies, sleep
122 improvements were suggested to be due to weight loss rather than the KD³³. Despite restricted
123 carbohydrate intake concurrent with sleep improvement in these children, SWS decreased³³
124 and REM increased^{32,33} which contradicts studies on carbohydrate intake and sleep
125 architecture in adults^{25,26,28}. Carbohydrate restriction and ketogenic diets are widely used in the
126 clinical management of obesity and diabetes, but studies assessing the effect of this diet on
127 sleep are currently limited. We recently demonstrated a continuous remote care treatment for
128 T2D including nutritional ketosis significantly improved glycemic control, weight, and
129 cardiovascular disease risk factors and reduced diabetes medication use at one year³⁴⁻³⁶.
130 The purpose of this study was to assess the effect of the intervention by time-interval on the
131 global PSQI and its seven component scores as well as compared its changes with different

132 intervention and disease categories. We also assessed the relationship between changes in the
133 sleep parameters versus key biochemical parameters, and also investigated the correlation of
134 pain, circadian rhythm disruption and CPAP usage versus patient-perceived sleep status. We
135 hypothesized that the global sleep indexes would improve analogously, as improvement in other
136 key biochemical parameters observed in the intervention.

137 **Materials and Methods**

138 ***Study participants and design***

139 This study is part of a clinical trial (*Clinical trials.gov identifier: NCT02519309*) that was
140 approved by the Franciscan Health Lafayette Institutional Review Board. Patients between age
141 21 and 65 years with either a diagnosis of T2D and a BMI > 25 kg/m² or prediabetes and a BMI
142 > 30 kg/m² were included in this study. Detailed study design including the inclusion and
143 exclusion criteria were previously reported^{34,35}. Briefly, the trial was an open-label, non-
144 randomized, controlled, longitudinal study with patients divided into three groups. The T2D and
145 pre-diabetes patients in the continuous care intervention (CCI) regimen self-selected either on-
146 site (CCI-onsite) or web-based (CCI-web) education delivery. Educational content and medical
147 treatment was the same for both CCI-onsite and CCI-web. As there were no significant
148 differences in outcomes including PSQI scores, between educational groups, they are combined
149 for further analysis^{34,35}. Both T2D and prediabetes CCI patients had access to a mobile health
150 application (app) that enabled them to communicate and be continuously monitored by a team
151 of healthcare professionals including a personal health coach and physician or nurse
152 practitioner. Patients received individualized guidance in achieving nutritional ketosis, typically
153 including restriction of daily dietary carbohydrates to less than 30 grams. Patients were
154 encouraged to measure and input weight, blood glucose and blood beta-hydroxybutyrate (BHB)
155 concentrations daily in the app. These measurements were used by the health care team for
156 monitoring the patient's condition (weight and glucose) and assessing carbohydrate restriction
157 (BHB).

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

164 ***Demographic and clinical variables***

165 Patient demographic and clinical data were collected at baseline, 70 days and one year.
166 Laboratory measures were assessed at a Clinical Laboratory Improvement (CLIA) certified
167 laboratory. These data were initially analyzed to evaluate the safety and effectiveness of the
168 CCI in improving diabetes status (glycemic control and medication use), weight and other
169 metabolic factors in T2D^{34,35} and prediabetes patients³⁶(unpublished data, manuscript in
170 preparation). Some of the clinical variables - weight, fasting blood glucose, HbA1c, homeostatic
171 model assessment of insulin resistance (HOMA-IR), BHB and high sensitivity C-reactive protein
172 (hsCRP) - were included for further analyses in this study. Usual care T2D patients were not
173 continuously monitored for weight, blood glucose, or BHB; clinical and laboratory measures
174 were obtained for this group only at baseline and one year.

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176 ***Pittsburgh Sleep Quality Index (PSQI)***

177 CCI patients were administered a set of questionnaires, including the PSQI, during visits
178 at baseline, 70 days and one year; UC participants completed questionnaires at baseline and
179 one year. The PSQI consists of 19 validated questions assessing sleep quality and efficiency³⁷.
180 The global PSQI score is calculated from seven component scores on subjective sleep quality
181 (component 1), sleep latency (component 2), sleep duration (component 3), habitual sleep
182 efficiency (component 4), sleep disturbances (component 5), use of sleep medication
183 (component 6) and daytime dysfunction (component 7). Each question within the component is

184 scored on a 4-point Likert scale of 0 to 3, with 3 indicating worse outcomes and the mean was
185 calculated for each component score. The sum of the component score means generates the
186 global PSQI score that ranges from 0 to 21. Higher global PSQI scores indicate poorer sleep. A
187 patient with a global PSQI score ≤ 5 is considered a “good sleeper” and > 5 is categorized as a
188 “poor sleeper”³⁸. Change in the PSQI score over time was calculated using the formula below:

$$189 \quad \text{Delta PSQI} = \frac{(\text{Post-intervention PSQI} - \text{Baseline PSQI})}{\text{Baseline PSQI}}$$

191 ***Pain, circadian rhythm disruption classification and CPAP usage***

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

206

207 ***Statistical Analyses***

208 The questionnaires were administered by research personal and completed by patients
209 on paper. Paper questionnaires were scanned and responses were transcribed in duplicate by

210 an independent contract data entry firm. The patterns of missing data were assessed using
211 Little's MCAR test³⁹ and were found to be missing at random (MAR). Missing data were
212 imputed by Multivariate Imputation by Chained Equations (MICE)⁴⁰, and Intent to treat (ITT)
213 analyses were performed. Normality of the global PSQI and component scores was evaluated
214 using Lilliefors test. Even after transformation, the data failed the normality test (i.e. there was a
215 skew toward lower PSQI scores and a long tail of higher scores) (Supplemental figures 1A-C);
216 therefore, nonparametric tests were used for analyses of PSQI scores. Results from continuous
217 variables were expressed as mean \pm standard deviation. Comparisons between groups were
218 performed using the Kruskal-Wallis test, and comparisons within groups were performed using
219 the Wilcoxon Sign Rank test. Tukey's honest significant difference test was used to analyze
220 pairwise differences among significant results from omnibus tests. McNemar's test was used for
221 assessing statistical significance of transitioning between 'good' and 'poor' sleeper among the
222 CCI and UC cohorts.

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

235 MATLAB R2017b using the Statistics and Machine Learning Toolbox⁴¹ and the R statistical
236 program version 3.5.0.⁴²

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238

239 **Results**

240 ***Baseline participant characteristics***

241 Details on the recruitment and extensive baseline characteristics of the CCI and UC T2D
242 patients were previously published^{34,35}. The demographic, glycemc, inflammatory and sleep
243 baseline characteristics of the participants that were included for assessments of sleep are
244 presented in Table 1. One-hundred forty-three (54.6%) CCI T2D, 61(54%) CCI prediabetes, and
245 53 (62.3%) UC T2D patients completed the PSQI at all expected time points. The global PSQI
246 and component scores did not differ significantly among the groups (CCI T2D, CCI prediabetes
247 and UC T2D) at baseline. The proportion of participants with overall poor sleep quality was
248 higher in the CCI prediabetes group (77.9%) compared to the CCI T2D (68.3%) and UC T2D
249 (68.2%) groups.

250 ***Effect of intervention on sleep***

251 ***Global PSQI and component scores***

252 Overall sleep quality as assessed by the global PSQI score, improved in CCI T2D
253 (median change from 7 to 6; $p<0.001$) and prediabetes (median change from 7 to 5; $p<0.001$)
254 groups after one year of the intervention (Figure 1). No significant change in the global PSQI
255 score was observed in UC T2D (median change from 7 to 8, $p=0.245$). At one year, global PSQI
256 scores in the CCI T2D ($p<0.001$) and prediabetes ($p<0.01$) were significantly lower than in the
257 UC T2D, whereas no differences were observed at baseline (Figure 2A). Among patients
258 characterized as poor sleepers at baseline (global PSQI >5), one year global PSQI score was
259 lower in the CCI T2D ($p<0.001$) and prediabetes ($p<0.001$) than in the UC T2D (Figure 2B).
260 Greater reduction in the global PSQI score was observed in CCI T2D (median change of -1,

261 p<0.01) and CCI prediabetes groups (median change of -2, p<0.001) compared to the UC T2D
262 group (Figure 3). Further assessment of the PSQI component scores revealed three of the
263 seven components showed significant change at one year for CCI T2D and prediabetes groups.
264 Subjective sleep quality (p<0.01 CCI T2D; p<0.001 CCI prediabetes), sleep disturbance (p<0.01
265 CCI T2D; p<0.001 CCI prediabetes) and daytime dysfunction (p<0.001 CCI T2D; p<0.001 CCI
266 prediabetes) score were lower in the CCI T2D and prediabetes patients compared to the UC
267 T2D group at one year (Figure 4 A-C).

268 ***Resolution of poor sleep quality***

269 There were 179 (68.3%) T2D and 88 (77.9%) prediabetes patients categorized as “poor
270 sleepers” in the CCI at baseline. The proportions of “poor sleepers” in the CCI were reduced
271 after one year of the intervention, with 56.5% of T2D (p=0.001) and 48.7% (p<0.001) of
272 prediabetes patients categorized as “poor sleepers” at one year. In the UC cohort, the
273 proportion of patients categorized as “poor sleepers” did not change after one year (68.2% at
274 baseline to 69.4% at one year).

275 ***Association within the CCI group between changes in global PSQI with metabolic and*** 276 ***inflammatory markers***

277 Table 2 shows correlations between changes in the global PSQI score with changes in
278 glucose-related, ketone and inflammatory markers in the CCI. In the prediabetes group,
279 changes in fasting glucose (r= 0.23, p=0.02) and HOMA-IR (r= 0.32, p<0.001) were correlated
280 to changes in PSQI scores after controlling for baseline age, sex and weight. Increased ketone
281 concentrations in the prediabetes participants were also associated with reduction of global
282 PSQI scores (r= -0.242, p=0.01). These correlations observed in the prediabetes group were
283 not present in the CCI T2D group and changes in the HbA1c and hsCRP did not correlate with
284 changes in global PSQI scores in either group. Change in mean weight (p=0.04) and HOMA-IR
285 (p=0.01) were the only variables independently and significantly associated between the three
286 different sleep status (improved, maintained and not improved sleep status) at one year of the

287 intervention. No statistically significant differences were found in weight loss changes between
288 patients with improved, maintained and not improved sleep status. Patients who maintained
289 sleep showed highest reductions of HOMA-IR (-6.94 ± 0.86), with statistically significant
290 difference than those who did not improve sleep, after one year of the intervention ($p = 0.02$).
291 Improvements in HOMA-IR among patients in the improved sleep (-4.17 ± 0.86) and not
292 improved sleep status (-4.24 ± 0.55) did not differ significantly.

293 ***Effect of persistent pain on sleep improvement***

294 We further assessed the effect of pain on sleep improvement in the CCI by classifying
295 the patient's pain status using response retrieved from questions specifically related to pain in
296 the sleep and knee (KOOS) questionnaires. As illustrated in supplementary figure 2, patients
297 with pain had higher global PSQI scores, indicating poorer sleep, compared to those
298 categorized under "non-pain" group at all three time points. Despite having a higher PSQI score,
299 the patients in the "pain" group (Supplementary figure 3B, $p < 0.01$) also showed no difference in
300 reduction of the global PSQI score at 70 days and one year, relative to baseline as observed in
301 the "non-pain" patients (Supplementary figure 3A, $p < 0.001$).

302 ***Effect of circadian rhythm disruption on sleep improvement***

303 We also assessed the effect of circadian rhythm disruption on the global PSQI score
304 improvement. Patients were classified as having circadian rhythm disruption based on their self-
305 reported wake-up times and bedtimes as defined in the methods. There were 18, 27, and 96
306 patients in the CCI cohort classified as both wake-up time and bedtime shifted, wake-up time
307 shifted only or bedtime shifted only respectively. Patients with shifted bedtimes, had reduced
308 global PSQI scores ($p < 0.01$), as did those without any circadian rhythm disruption ($p < 0.001$)
309 (Supplementary figures 4A and B). However, those patients with shifted wake-up times
310 (Supplementary figures 4C) did not show a change in their global PSQI score after one year of
311 the intervention. Those with both shifted wake-up times and bedtimes also did not show a
312 change in their global PSQI score after one year of the intervention.

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

314 At baseline, there were a total of 140 participants in both CCI and UC treatment groups
315 with CPAP equipment prescribed for sleep. Among CPAP users, 91 were in the CCI T2D group,
316 31 in the CCI prediabetes and 18 in the UC T2D group. Fifteen (13 CCI T2D and 2 UC T2D) of
317 the 140 participants discontinued using CPAP at one year. Only 6 (46%) of the 13 CCI T2D
318 participants discontinued due to patient-reported improvement in sleep quality from the CCI and
319 reduction of weight; the remaining 7 reported dis-continuation due to discomfort or personal
320 choice. Global PSQI scores among the CPAP users at baseline and one year did not show a
321 significantly different distribution pattern than what was observed in the full cohort of
322 participants.

323 **Discussion**

324 This study is one of the first designed to assess the effect of carbohydrate restriction and
325 nutritional ketosis on sleep quality in individuals with hyperglycemia and insulin resistance.
326 Improved patient-reported sleep quality as assessed by global PSQI suggests that CCI
327 including nutritional ketosis benefited sleep quality in both patients with T2D and prediabetes.
328 The proportion of patients categorized as “poor sleepers” at one year was significantly reduced
329 in the CCI groups but not in the UC group. Furthermore, these results demonstrate that the
330 sleep quality improvement observed in the whole intervention population was due in part to 17%
331 of baseline “poor sleepers” being reclassified as “good sleepers” at one year. Our results are
332 consistent with previous findings that showed improved overall sleep quality in children
333 consuming ketogenic diets ^{31, 32}.

334 Improvement in the global PSQI score of patients undergoing the CCI was mainly
335 due to significant changes in three PSQI components: subjective sleep quality, sleep
336 disturbance and daytime dysfunction. Both objective and subjective sleep quality impairment are
337 frequently reported in diabetes patients and positively associated with severity of hyperglycemia
338 ⁸⁻¹¹. Likewise, correlation between poor sleep quality and increased carbohydrate intake ³⁰ is

339 also previously reported. These observed patterns of association between sleep quality with
340 hyperglycemia and carbohydrate intake may explain why this carbohydrate restriction
341 intervention improved subjective sleep quality. The sleep disturbance component of the global
342 PSQI score is associated with poor glycemic control among T2D patients⁴³. One study reported
343 a significant correlation between sleep disturbance and HbA1c level⁴⁴. Night time sleep
344 disturbance in T2D patients can be related to a wide range of conditions such as nocturnal
345 polyuria, pain, and breathing problems, especially in those with OSA. In our study, we also
346 showed that patients encountering persistent pain, including knee pain, had a higher median
347 global PSQI score, while one year of the intervention effectively improved global PSQI scores in
348 these patients despite the persistence of reported pain in some patients. It is possible that
349 improvement in the sleep disturbance of the CCI patients contributed to the glycemic control
350 improvement in these patients. The effectiveness of the intervention in improving sleep in those
351 with pain, further emphasizes its' applicability in alleviating sleep disturbance.

352 Furthermore, there was a significant improvement in the daytime dysfunction component
353 of the global PSQI score in the CCI group. Excessive daytime sleepiness and dysfunction are
354 reported commonly in T2D^{45,46}, and weight loss through bariatric surgery has a positive
355 resolving effect on daytime dysfunction and sleepiness^{47,48}. In the present investigation, the
356 majority of CCI patients achieved weight loss of $\geq 10\%$, which could have contributed to the
357 significant improvement observed in daytime function. In addition, we also evaluated the effect
358 of the intervention on a subcohort of patients with a self-reported pattern of shifted non-standard
359 bedtimes and wake-up times that were not aligned to the light dark cycle, which likely affects
360 daytime functioning. Circadian rhythm disruption is frequently associated with metabolic
361 alterations, especially in an insulin resistant state^{49,50}. While patients with a normal sleep
362 chronotype benefited the most, the intervention also improved the sleep of patients with time
363 shifted bedtimes. A similar advantage of the intervention was not observed in patients with

364 shifted wake-up times, though this may be due to the limited number of patients in this subgroup
365 (n=27).

366 The improvement in the global PSQI score observed in CCI patients occurred
367 concurrently with weight reduction and glycemic control improvement^{34,35}. Martin et al⁵¹
368 reported a direct correlation between degree of weight loss and global PSQI score improvement
369 in healthy nonobese adults receiving an energy restricted diet, while Chaput et al⁵² reported an
370 improvement in global PSQI score following the initial 5-kg weight loss, but no additional
371 improvement with subsequent weight loss. A study using a ketogenic diet in children alleviated
372 abnormal sleep architecture; however, weight loss was suggested as the main determinant of
373 improved sleep³³. These studies collectively imply a direct association between weight loss and
374 improved PSQI score, but some studies also demonstrate the efficacy of anti-glycemic
375 medications for improving PSQI score concurrent with improved glycemic control⁵³. This study
376 identified associations between HOMA-IR and weight reductions with stratification of patients'
377 sleep status in the full CCI cohort even though there were no significant differences in weight
378 loss and insulin resistance reduction levels between those who had improved sleep and those
379 who did not. Patients with good sleep quality at the beginning of the intervention benefited the
380 most in reducing insulin resistance. Improvement in fasting glucose and HOMA-IR were only
381 positively associated with improved PSQI score in prediabetes patients.

382 It is not clear if nutritional ketosis achieved by substantial carbohydrate restriction
383 augmented the effect of the intervention on sleep or if weight loss and/or improved glycemic
384 control generated from the intervention contributed to sleep quality improvements. We showed
385 a significant correlation between blood beta-hydroxybutyrate (BHB) levels and PSQI
386 improvement in the prediabetes cohort. While the effect of and mechanism of BHB in sleep are
387 not clear, a positive correlation between blood BHB levels and carbon dioxide (CO₂) response
388 was previously reported in patients with obesity related hypoventilation syndrome that had
389 reduced CO₂ response⁵⁴. A continuous state of ketosis through carbohydrate restriction and fat

390 intake also induces the postprandial release of a satiety hormone, cholecystokinin (CCK)^{28,55,56}.
391 When administered in rats, CCK was shown to promote slow wave activity and NREM sleep⁵⁷.
392 CCK was also shown to induce sleep when administered in diabetic rats⁵⁸. Therefore, it is
393 possible that one mechanism of improved sleep with a ketogenic diet that increases BHB levels
394 is through CCK induction.

395 There are several limitations of our study. The study was designed mainly to assess the
396 impact of the CCI on glycemic control, medication use, weight, and cardiovascular disease risk
397 factors. Patient-reported outcomes for quality of life measures including sleep were included as
398 secondary endpoints. It is difficult to determine the causality among the intervention,
399 improvement in primary outcomes and improvement in sleep from this study. A major limitation
400 of this study is the use of subjective sleep measures as self-reported sleep assessment is
401 subject to limited self-knowledge of sleep behavior and inconsistency in reporting. Therefore,
402 future studies that use randomized controlled trial designs and objective sleep measures are
403 needed to confirm our results. In addition, patients with an established diagnosis of a sleep
404 disorder such as OSA were not separated in the analysis since complete records of their CPAP
405 usage were not collected in the questionnaire. Patient compliance with CPAP usage is essential
406 for making interpretations about the status of their OSA treatment and its effect on sleep and
407 glycemic control.

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

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1 **Figure Legends**

2
3 **Figure 1.** Distribution of global PSQI scores at baseline and 365 days in CCI T2D, CCI PreD and UC T2D. Global PSQI score was
4 significantly reduced in the CCI T2D and CCI PreD groups but not in the UC T2D group after 365 days.

5
6 **Figure 2.** Distribution of global PSQI scores in CCI T2D, CCI PreD and UC T2D at three different timepoints (0, 70 and 365 days) (A)
7 Among the full patient cohort, global PSQI were significantly lower in the CCI T2D and CCI PreD when compared to UC T2D at 365
8 days. (B) Among the “poor sleepers” at baseline, global PSQI were significantly lower in the CCI T2D and CCI PreD when compared
9 to UC T2D after 365 days. (UC T2D patients were not surveyed at 70 days.)

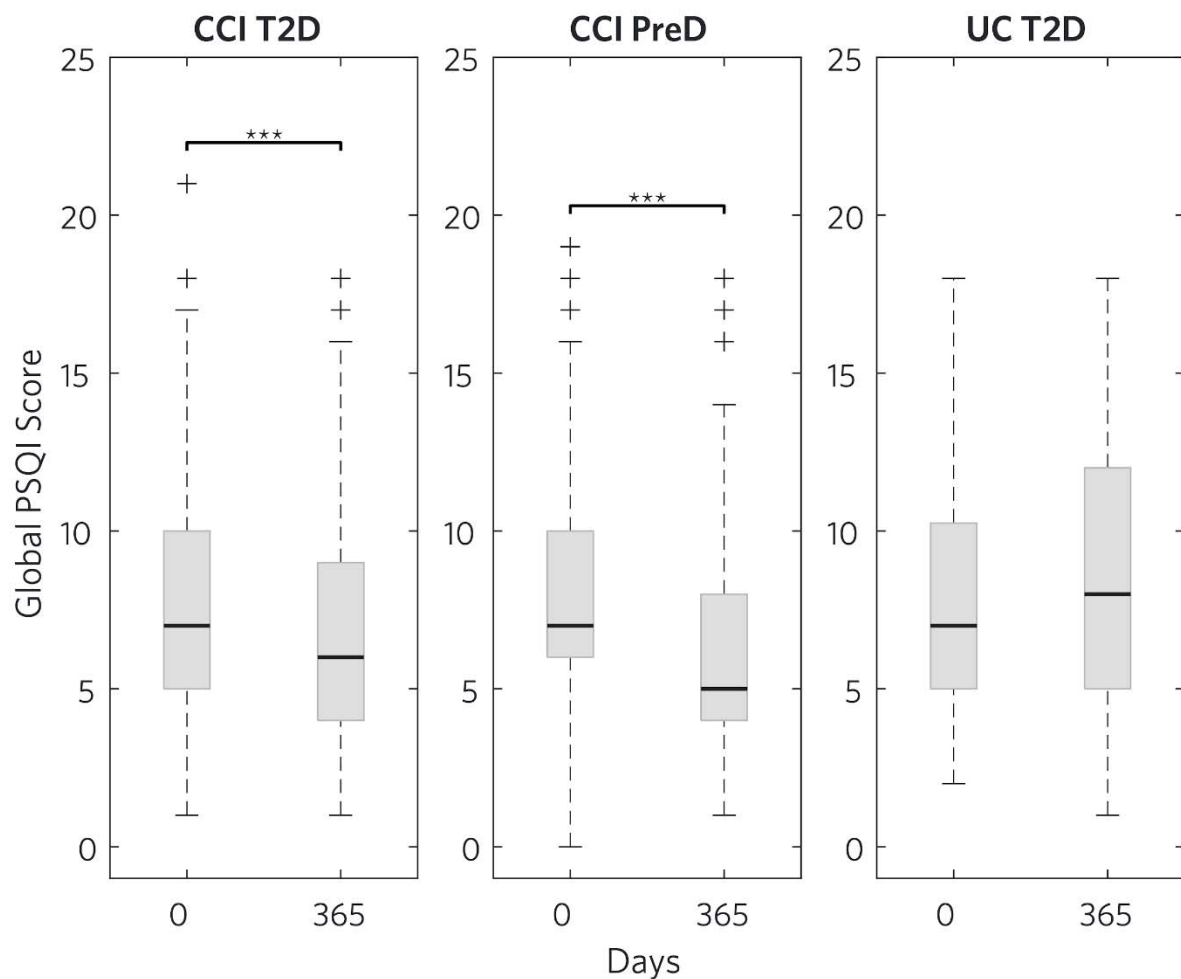
10
11 **Figure 3.** Distribution of change in global PSQI score in CCI T2D, CCI PreD and UC T2D after 365 days. The scores showed
12 significant reduction in the CCI T2D and CCI PreD groups relative to baseline and to the UC T2D group.

13
14 **Figure 4.** Distribution of PSQI components subjective sleep quality, sleep disturbances and daytime dysfunction in CCI T2D, CCI
15 PreD and UC T2D groups at three different timepoints (0, 70 and 365 days). Subjective sleep quality (A), sleep disturbances (B), and
16 daytime dysfunction (C) were significantly lower in the CCI T2D and CCI PreD groups when compared to UC T2D group at 365 days.

17
18 *Boxplot descriptors (Figures 1-4) Horizontal line within the box indicates median; upper and lower boundaries of the box represent*
19 *the 25th and 75th quartiles; whiskers of the box is the highest and lowest values and “+++” signs represent outlier values.*

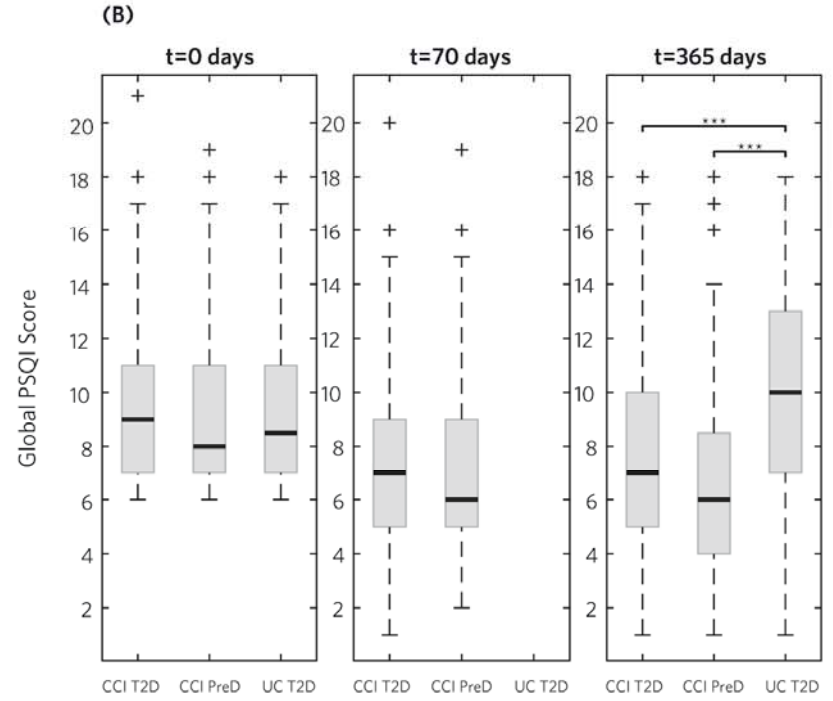
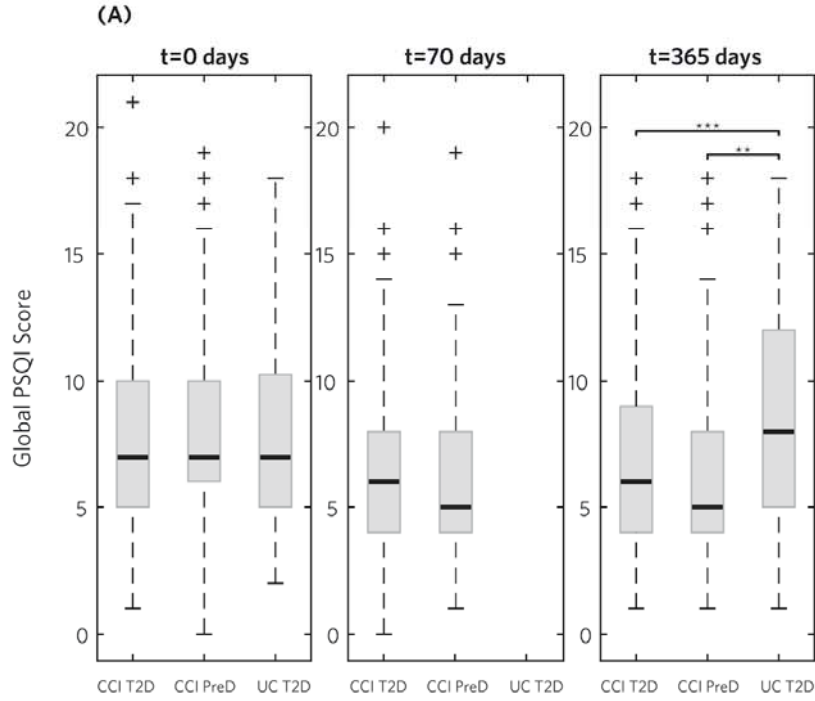
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21 **** p-value <0.01; *** p-value <0.001**

33 **Figure 1.**



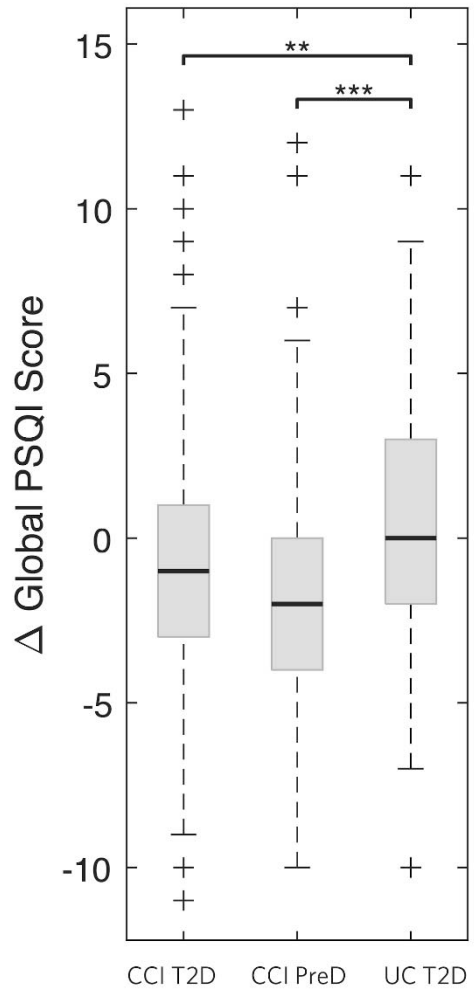
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40 **Figure 2.**
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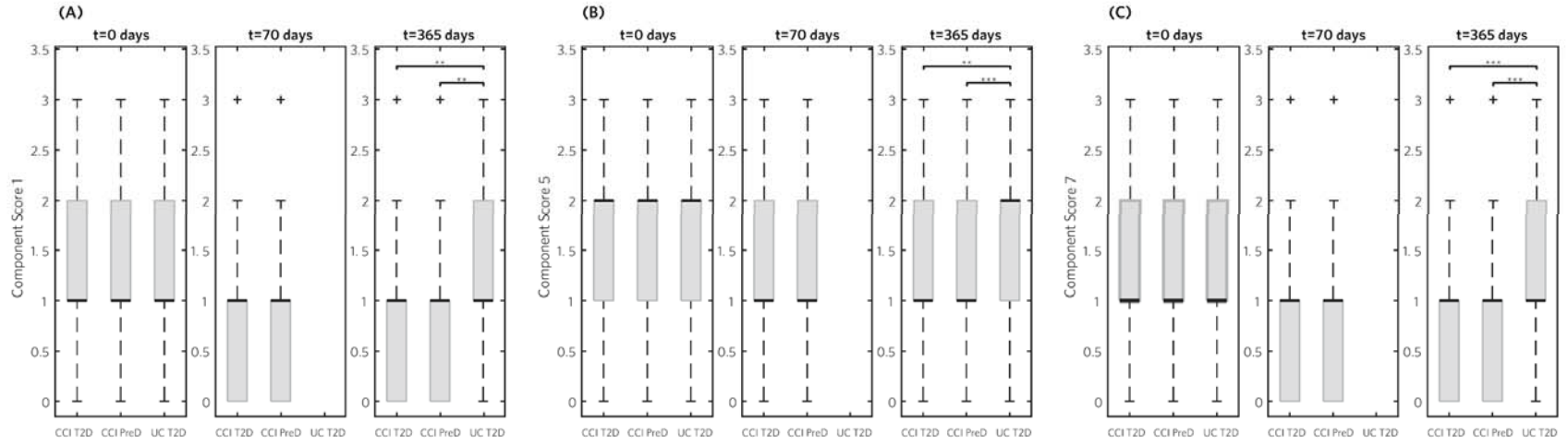
54 **Figure 3.**
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Figure 4.



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

Patient Cohorts	CCI Type 2 Diabetes	CCI Prediabetes	UC Type 2 Diabetes
Starters, Completers, PSQI Available (n)	262, 218, 143	116, 113, 61	87, 78, 53
	mean (S.D.)		
Age (years)	53.8 (± 8.4)	51.9 (± 9.4)	52.7 (± 9.3)
Male/female (ratio)	87/175 (1:2)	29/84 (1:3)	35/50 (2:3)
Body weight (kg)	116.4 (± 26.1)	109.9(± 23.6)	108.3 (± 25.1)
BMI (kg/m²)	40.4 (± 8.9)	38.8 (± 7.1)	38.2 (± 9.1)
Fasting glucose (mg/dL)	160.78 (± 61.32)	109.58 (± 15.20) *	157.08 (± 72.48)
HbA1c (%)	7.60 (± 1.50)	5.91 (± 0.24) *	7.67 (± 1.77)
HOMA-IR	11.8 (± 13.1)	7.1 (± 7.4) *	13.7 (± 17.8)
high sensitivity C-reactive protein (nmol/L)	9.31 (± 19.31)	7.46 (± 7.51)	9.34 (± 9.10)
Beta-hydroxybutyrate (mmol/L)	0.17 (± 0.15)	0.14 (± 0.13)	0.15 (± 0.12)
Global PSQI Score	7.72 (± 3.72)	7.96(± 3.43)	7.92 (± 3.85)

Subjective sleep quality	1.18 (± 0.75)	1.22 (± 0.73)	1.25 (± 0.79)
Sleep latency	1.09 (± 0.93)	1.33 (± 0.958)	1.05 (± 0.89)
Sleep duration	1.23 (± 0.92)	1.27 (± 0.96)	1.14 (± 0.94)
Habitual sleep efficiency	0.68 (± 0.99)	0.61 (± 0.89)	0.71 (± 1.04)
Sleep disturbances	1.64 (± 0.63)	1.66 (± 0.68)	1.75 (± 0.74)
Use of sleep medication	0.69 (± 1.16)	0.66 (± 1.11)	0.85 (± 1.26)
Daytime dysfunction	1.22 (± 0.77)	1.21 (± 0.76)	1.17 (± 0.86)
Poor sleepers N (%)	179 (68.3)	88 (77.9)	58 (68.2)
Good sleepers N (%)	83 (31.7)	25 (22.1)	27 (31.8)

67 **Note.** Subjective sleep quality, component 1; sleep latency, component 2; sleep duration, component 3; habitual sleep efficiency,
 68 component 4; sleep disturbances, component 5; use of sleep medication, component 6, and daytime dysfunction, component 7
 69 *p-value <0.001

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78 **Table 2.** Correlation analyses between change in the global PSQI score and change in metabolic parameters after one

79 year of CCI

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Variable	CCI T2D Cohort				CCI Prediabetes Cohort			
	N=262				N=113			
	<i>rho</i>	<i>P</i> value [†]	Adjusted <i>r</i>	<i>P</i> value ⁺	<i>rho</i>	<i>P</i> value*	Adjusted <i>r</i>	<i>P</i> value ⁺
Δ Fasting glucose (mg/dl)	0.032	0.60	0.008	0.90	0.240	0.01	0.226	0.018
Δ HbA1c (%)	-0.037	0.55	-0.049	0.44	-0.024	0.80	-0.032	0.74
Δ HOMA-IR	-0.060	0.34	-0.069	0.27	0.314	0.0008	0.323	0.0006
Δ BHB	-0.003	0.96	-0.044	0.49	-0.297	0.002	-0.242	0.011
Δ hsCRP	-0.067	0.29	-0.008	0.90	-0.022	0.82	-0.032	0.74

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82 * Spearman and [†]adjusted Pearson's correlations. Adjustments while controlling for age, sex and baseline weight

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