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A randomised controlled trial

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Randomized Control Trials

Weight-loss induced by carbohydrate restriction does not negatively affect health-related quality of life and cognition in people with type 2 diabetes: A randomised controlled trial

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S U M M A R Y

Background & aims: We evaluated the effect of weight loss induced by dietary carbohydrate restriction on health-related quality of life (HRQoL) and cognition in type 2 diabetes (T2D).

Methods: In this randomised parallel trial, 72 adults with T2D and overweight/obesity (mean ± SD, HbA1c: 57 ± 8 mmol/mol and BMI: 33 ± 5 kg/m²) were randomly assigned to a carbohydrate-reduced high-protein diet (CRHP: C30%E%-P30E%-F40E%) or conventional diabetes diet (CD: C50E%-P17E%-F33E%) for 6 weeks, targeting a 6% weight loss. HRQoL was assessed from the short form 36 (SF-36) questionnaire, including physical and mental component summary (PCS and MCS) scores; global cognition, verbal memory, attention and psychomotor speed, and executive function were assessed from a neuropsychological test battery.

Results: Both diet groups achieved a 5.8 kg weight loss and improved PCS (median [25th;75th percentiles], CD: 2.7 [1.1; 4.2] vs. CRHP: 2.1 [0.7; 3.7]), with no difference between diets. The CRHP diet resulted in a clinically relevant improvement of MCS, albeit non-significantly different compared with the change after the CD diet (2.0 [-0.7; 4.8], p = 0.15). Global cognition, attention, and verbal memory were unaffected by the CRHP diet, which selectively worsened the Symbol Digit Modality Test assessing psychomotor speed when compared with the CD diet (−4.1 [−7.2; −1.1], p < 0.01).

Conclusion: Physical health improved by weight loss independently of macronutrient distribution, while mental health and cognition may be affected by the amount of carbohydrate, protein and fat in the diet.

Abbreviations: CD, Conventional diabetes; CGM, Continuous glucose monitoring; CRHP, Carbohydrate-reduced high-protein; CV, Coefficient of variation; E%, Percentage of energy intake; HOMA2-IR, Homeostatic Model Assessment 2 for insulin resistance; HRQoL, Health-related quality of life; IPAQ, International Physical Activity Questionnaire; MCS, Mental component summary; PCS, Physical component summary; RAVLT, Rey Auditory Verbal Learning Test; SDMT, Symbol Digit Modalities Test; SF-36, Short form 36; T2D, Type 2 diabetes; TBR, Time below range; TMT, Trail Making Test.

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Collectively, our data suggest that weight loss through moderate carbohydrate restriction has no clinically important impact on HRQoL and global cognition in patients with T2D. Registered under ClinicalTrials.gov Identifier no. NCT03814694.

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1. Introduction

Lifestyle modification is the cornerstone of treatment for type 2 diabetes (T2D), involving exercise and calorie-restricted diets often relatively high in carbohydrate, to achieve weight loss and improve glycaemia [1,2]. In recent studies, however, dietary carbohydrate restriction has been shown to attenuate hyperglycaemia and risk factors of cardiovascular disease more than carbohydrate-rich diets, both under eucaloric, weight-maintaining conditions [3] and under hypocaloric conditions causing weight loss [4]. Thus, dietary carbohydrate restriction is now recognised as a viable treatment strategy in individuals with T2D [5].

T2D and obesity are associated with reduced quality of life [6] that seems to worsen when glycaemia is poorly controlled [7]. Consequently, a consensus report from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) stated that optimising health-related quality of life (HRQoL) should be at the centre of T2D management alongside preventing and delaying complications [8]. In fact, diabetic complications may further worsen HRQoL, while poor HRQoL may be an independent risk factor for increased mortality [9]. Nevertheless, investigations into various T2D treatments have been focusing more on glycaemic control and comorbidities than on HRQoL [10].

The effects of reducing dietary carbohydrate intake on HRQoL are generally unknown [11]. Evidence suggests that loss of excess body weight improves HRQoL in T2D [12,13], but whether restricting carbohydrate intake improves HRQoL beyond the effect of weight reduction [14] or causes harm, as suggested in recent meta-analyses [10,15], requires further investigation.

Cognitive dysfunction, both modest and more severe (e.g. overt dementia), has been increasingly recognised as a complication of T2D [16,17] and is often associated with HRQoL [18]. Glucose availability is highly important for proper brain function by virtue of glucose being the primary energy source for the brain [19]; even mild hypoglycaemia severely affects cognitive performance [20]. Consequently, carbohydrate restriction may raise concerns in relation to cognitive functioning and, indeed, impairments of memory, processing speed, and mental flexibility have been reported in subjects with overweight or obesity following very low carbohydrate hypocaloric diets [21–23], although this is not a consistent finding [24]. The only study to date that has examined this in patients with T2D found no adverse effects of carbohydrate restriction [25]. That study, however, included a rather extreme reduction in dietary carbohydrate (14% of total energy) and was limited by the concomitant inclusion of exercise, which benefits cognition [26,27], and may have therefore confounded the results. Therefore, in the present study, we aimed to investigate the effect of matched weight loss induced by carbohydrate restriction or by a more conventional diet on HRQoL and cognitive function in patients with T2D. Furthermore, we wanted to explore the association between weight loss and key metabolic parameters with HRQoL and cognition.

2. Material and methods

The outcomes presented here are secondary to a dietary intervention trial for which the main results including changes in body composition, fat distribution and metabolic function have been reported in detail previously [28]. The methodology is briefly summarised in the following sections.

2.1. Participants

Patients diagnosed with T2D, BMI >25 kg/m², Hba1C of 48–97 mmol/mol (6.5–11.0%), and treated with or without mono- or combination therapy of metformin or dipeptidyl peptidase-4 inhibitors were eligible for participation. Exclusion criteria were treatment with systemic corticosteroids, sulfonylureas, sodium-glucose co-transporter 2 inhibitors or injectable glucose-lowering medications, critical illness, and renal failure (estimated glomerular filtration rate <30 ml/min/1.73 m² or urine albumin-creatinine ratio >300 mg/g). Participants were enrolled between January 2018 and July 2019 at Copenhagen University Hospital Bispebjerg, Denmark, and they all provided written informed consent prior to enrolment. The study protocol was approved by the Health Ethics Committee of Copenhagen and the Danish Data Protection Agency and was carried out in accordance with the Declaration of Helsinki. The study is registered at clinicaltrials.gov (NCT03814694).

2.2. Study design and intervention

In this open-label, parallel randomised controlled trial, participants were allocated in a 1:1 ratio to a 6-week fully furnished hypocaloric diet with different macronutrient distribution: a conventional diabetes (CD) or a carbohydrate-reduced high-protein (CRHP) diet, consisting of 50 or 30% of total energy (E%) from carbohydrate, 17 or 30E% from protein, and 33 or 40E% from fat, respectively (Supplementary Table S1). As such, the CD diet was in accordance with recommendations from the EASD [29]. All meals, providing all daily calories, were prepared ready for consumption in the metabolic kitchen at the Department of Nutrition, Exercise and Sports, University of Copenhagen, and distributed free-of-charge twice weekly. The full list of ingredients and daily menus are provided elsewhere [28]. Participants were instructed to consume all meals and abstain from any calorie-containing foods or beverages not provided by the research team. In addition, alcohol intake was prohibited during the study period.

Weight management consisted of a controlled 6% loss of baseline body weight during the first 5 weeks followed by 1 week of weight maintenance at the new lower body weight to avoid a catabolic state during post-intervention measurements, as this could affect outcomes independently of diet composition and weight loss. Energy requirements for weight maintenance were determined by using the Mifflin–St Jeor equation [30] and an expected physical activity level of 1.6. The weight loss regimen was individualised and managed according to a fixed algorithm, described in detail previously [28]. Physical activity was assessed with the long version of the International Physical Activity Questionnaire (IPAQ) at baseline and during week 5 of the intervention, and participants were instructed throughout the study not to change their habitual physical activities. In addition, no changes in glucose-lowering, lipid-lowering or anti-hypertensive medications were allowed during the study period and for at least 2 months prior to study commencement.
2.3. Outcomes

At baseline and week 5, participants were asked to fill out the short form 36 (SF-36) questionnaire in an undisturbed room to evaluate self-perceived physical and mental components of HRQoL. The SF-36 questionnaire comprises 36 items that can be divided into the following eight health domains: physical functioning (10 items), physical role limitation (4 items), bodily pain (2 items), general health perception (5 items), vitality (4 items), social functioning (2 items), emotional role limitation (3 items), and mental health (5 items), plus an additional item evaluating health change over the last year [31]. All items were re-scaled to a score from 0 to 100 and averaged according to each domain with a higher score reflecting better HRQoL [31]. In case of missing values, domains were calculated if less than 50% of the items within that domain were missing as recommended by Ware et al. [31]. Physical (PCS) and mental (MCS) component summary scores were calculated using weighted summations of standardised scores from the eight domains. Standardisation was accomplished by z-score transformation using US population norms. PCS and MSC were further transformed to a norm-based ($\mu = 50, \sigma = 10$) scoring [32].

Cognitive function was assessed in the afternoon at baseline and week 6 immediately after participants had completed a 4-h oral glucose tolerance test. The neuropsychological test battery consisted of the Rey Auditory Verbal Learning Test (RAVLT; including total recall, immediate recall, delayed recall and recognition) [33], Trail Making Test (TMT) part A and B [34], and Symbol Digit Modalities Test (SDMT) [35], which all previously have been shown to be affected in T2D [16,36]. Alternative versions of RAVLT and SDMT were used in a randomised order to minimise learning effects from baseline to week 6. All test scores were transformed into z-scores using baseline values (our study population’s mean and SD) and averaged to construct the following three cognitive domains: verbal memory (all four RAVLT measures), attention and psychomotor speed (TMT-A and SDMT), and executive function (TMT-B). In the computation of cognitive domains, test scores were inversed if a higher score represented a worse performance (TMT-A and -B). The three domains were further averaged to get a global cognitive score.

Furthermore, following key metabolic parameters were included to investigate their associations with HRQoL and cognition: HbA1c, Homeostatic Model Assessment 2 for insulin resistance (HOMA2-IR), and continuous glucose monitoring (CGM; FreeStyle Libre Pro, Abbott Diabetes Care, CA, USA) including measures of 24-h mean glucose, glucose variability assessed as the coefficient of variation (CV), and time below range (TBR) of 3.9 mmol/l; methods are described previously [28].

2.4. Statistics

Sample size calculation was performed according to the primary and leading secondary outcome (changes in HbA1c and hepatic fat content, respectively) and has been described previously [28]; 80 participants were computed to provide adequate power with an anticipated attrition rate of 20%. Outcomes of HRQoL and cognition, reported here, were exploratory to this study and, accordingly, not adjusted for multiplicity in the data analyses. Two-tailed statistical tests were used and considered significant when $p < 0.05$.

All available data were analysed by a constrained linear mixed model with inherent baseline adjustment to evaluate between-group differences as well as the time effect within each group. Repeated measurements were accounted for by assuming an unstructured covariance matrix pattern, and missing values were imputed by maximum likelihood estimation, and thereby assumed to be missing at random. Residual diagnostics were used to assess model assumptions, and variables were log-transformed, in case of skewness, prior to analysis. Between-group differences are estimated marginal means [95% CI], representing the absolute or, when log-transformed, relative difference. Descriptive data are presented as mean ± SD or median (25th;75th percentiles) depending on whether data were normally distributed or not, respectively.

The relationship between weight loss and improvements in HbA1c, HOMA2-IR, mean 24-h glucose, and glucose variability and change in HRQoL and cognitive function were evaluated by simple linear regression analysis. TBR was dichotomised by median split and treated as a categorical variable and its relationship with changes in HRQoL and cognition was evaluated by two-samples t-test.

Randomisation was performed in blocks of random size by an unrelated study nurse; the investigators and participants were blinded to randomisation until allocation and first dietary provision, respectively. Randomisation list and all statistical analyses and graphics were conducted with R (Version 3.6.0, R, Boston, MA, USA).

3. Results

3.1. Participant characteristics and body weight

Participant flow and baseline characteristics have been described elsewhere [28]. In short, 72 participants were allocated to the dietary interventions, of which a subgroup of 59 were scheduled for neuropsychological assessment (Fig. 1). Five participants (of which three were included in the subgroup) withdrew consent from the study, and one participant did not wish to perform the neuropsychological assessment; therefore, complete datasets on HRQoL and cognitive function were available for 67 and 55 participants, respectively (Tables 1–3).

Groups were well-balanced on all baseline characteristics, except for the proportion being male and being treated with dipeptidyl peptidase-4 inhibitors; both were higher in the CRHP than the CD group (Table 1). Body weight for the main population was reduced equally after 6 weeks of CD and CRHP feeding, by 5.8 ± 2.3 kg and 5.8 ± 1.8 kg, respectively (from a baseline value of 97.5 ± 25.4 kg and 98.0 ± 14.2 kg, respectively). During the weight loss phase, the extent of energy restriction was also similar between diets, by 3102 ± 1230 kJ (28 ± 8%) at week 1 and by 4712 ± 1855 kJ (42 ± 12%) at week 5. Weight loss and caloric deficit were also similar among the subgroup of participants who performed the neuropsychological assessment (data not shown). Adverse events have previously been reported [28]. Overall, hypoglycaemia, defined as more time spent below 3.9 mmol/l measured by CGM, was more prevalent in the CRHP group than the CD group.

3.2. HRQoL

No difference was found between diets in PCS after the 6-week intervention (0.5 [-1.6; 2.5], $p = 0.65$), however both intervention groups exhibited significant improvements in the PCS, with an increase of 2.7 (1.1; 4.2) after the CD diet and 2.1 (0.7; 3.7) after the CRHP diet. Additionally, MCS was not significantly different between diets (2.0 [-0.7; 4.8], $p = 0.15$), although MCS improved after the CRHP diet (1.8 [-0.7; 5.7], $p < 0.01$) and did not change after the CD diet (0.4 [-0.9; 2.3], $p = 0.39$). None of the domains differed significantly between diets, but the domains of psychological functioning, physical role limitation, general health perception, vitality, emotional role limitation, mental health and health change improved after the CRHP diet, whereas only physical functioning and general health perception improved after the CD diet (Table 2). Reduction in body weight correlated significantly with the increase

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Fig. 1. Study flow diagram. CD, conventional diabetes; CRHP, carbohydrate-reduced high-protein; HRQoL, health-related quality of life.

**Table 1**
Baseline characteristics.

| Baseline characteristics                  | Main population ($n = 67$) | Sub-population ($n = 55$) |
|------------------------------------------|-----------------------------|---------------------------|
|                                          | CD diet ($n = 33$)          | CRHP diet ($n = 34$)      | CD diet ($n = 28$) | CRHP diet ($n = 27$) |
| Male/female ($n$)                        | 15/18                       | 20/14                     | 13/15            | 14/13              |
| Age (years)                              | 67.0 (±8.8)                 | 66.4 (±6.9)               | 66.0 (±8.6)      | 67.1 (±6.4)        |
| Duration of T2D (years)                  | 7.7 (2.8; 10.1)             | 8.5 (3.5; 11.9)           | 7.6 (2.7; 9.8)   | 9.8 (5.6; 12.3)    |
| HbA1c (mmol/mol)                         | 57.4 (±7.7)                 | 57.6 (±8.4)               | 56.7 (±8.4)      | 56.4 (±6.4)        |
| HbA1c (%)                                | 7.3 (±0.7)                  | 7.4 (±0.8)                | 7.3 (±0.8)       | 7.3 (±0.6)         |
| Body weight (kg)                         | 97.5 (±25.4)                | 98.0 (±14.2)              | 97.5 (±27.3)     | 98.4 (±12.3)       |
| BMI (kg/m²)                              | 33.2 (±5.1)                 | 33.6 (±4.6)               | 33.1 (±5.5)      | 34.0 (±4.8)        |
| Estimated daily TEE (kcal)               | 2600 (±632)                 | 2652 (±364)               | 2605 (±657)      | 2630 (±328)        |
| Medication use ($n$ (%))                 |                             |                           |                 |                   |
| Glucose-lowering therapy                | 21 (64)                     | 26 (76)                   | 16 (57)          | 21 (78)            |
| Lifestyle intervention only             | 12 (36)                     | 8 (24)                    | 12 (43)          | 6 (22)             |
| Biguanides                               | 21 (64)                     | 25 (74)                   | 16 (57)          | 21 (78)            |
| DPP-4 inhibitors                        | 3 (9)                       | 11 (32)                   | 1 (4)            | 9 (33)             |
| Lipid-lowering therapy                  | 23 (70)                     | 26 (76)                   | 20 (71)          | 21 (78)            |
| Antihypertensive therapy                | 26 (79)                     | 29 (85)                   | 22 (79)          | 23 (85)            |
| Antidepressant therapy                  | 2 (6)                       | 5 (15)                    | 2 (7)            | 4 (15)             |

Data are presented as means (±SD) or medians (25th;75th percentiles) unless otherwise specified. CD, conventional diabetes; CRHP, carbohydrate-reduced high-protein; T2D, type 2 diabetes; BMI, body mass index; TEE, total energy expenditure; DPP-4, dipeptidyl peptidase-4.
in physical functioning (β = 1.67 [0.32; 3.02], p = 0.017). Furthermore, reductions in insulin resistance (HOMA2-IR) correlated positively with improvements in general health perception and negatively with emotional role limitation. The latter was also inversely associated with changes in HbA1c and mean 24-h glucose. No other correlations were found (Supplementary Table S2).

3.3. Cognition

Neither global cognition nor the domains of verbal memory and attention and psychomotor speed significantly differed between or within the two diet groups. A tendency towards worse executive function was found for the CRHP diet compared to the CD diet (−0.3 [−0.5; 0.0], p = 0.058), partly due to increased speed on the TMT-B test by −7.5 (−26.3; 5.3) seconds (p = 0.023) while on the CD diet. Performance on SDMT, assessing psychomotor speed, was reduced after the CRHP diet compared with the CD diet (−4.1 [−7.2; −1.1], p < 0.01), albeit no significant change in performance was found within either group. No within or between group differences were found for the remaining tests (Table 3). Furthermore, weight loss and improvements in metabolic control did not correlate with changes in cognitive performance (Supplementary Table S2).

4. Discussion

In this study of patients with T2D and overweight or obesity, a moderate 6% weight loss induced by the CRHP diet did not adversely affect self-perceived HRQoL. In fact, the CRHP diet caused clinically relevant, although non-significant, improvements in mental components of HRQoL when compared with the same amount of weight loss induced by the CD diet. Overall, cognition was unaffected by the CRHP diet compared with the CD diet, except for worsening of the SDMT test for psychomotor speed. For the most part, changes in HRQoL and cognition did not associate with changes in body weight or metabolic function parameters and could not be explained from these metadata.

4.1. Physical HRQoL

Carbohydrate-restricted diets are increasingly recommended for T2D management due to their ability to improve metabolic control [5], but their effect on HRQoL has been suggested to be neutral [11,37] or even harmful in the long-term [10,15]. However, evidence is limited by the sparse number of available studies which, furthermore, show heterogeneity with respect to the characteristics of the lifestyle intervention (e.g. caloric restriction, physical activity, or behavioral modifications).
weight reduction and exercise) and the methods used to measure HRQoL. Weight loss induced by exercise training as part of an intensive lifestyle intervention has been shown to markedly improve self-perceived physical health in patients with T2D and obesity [13]. Even without exercise training, weight reduction induced by severe calorie restriction seems to cause similar benefits [38]. Accordingly, in the present study, physical health improved by a less severe weight reduction as both groups had similar and significant increments in PCS with median change scores >2, which may be of clinical importance [32]. Importantly, PCS increments were similar between diet groups, suggesting physical health is improved by weight loss, but is unaffected by the macronutrient distribution of the hypocaloric diet. At odds with our findings, Gulbrandsen et al. found that weight loss induced by a low-carbohydrate diet improved PCS more than an energy-matched low-fat diet after 12 months [14]. However, this dietary effect was absent at 6 and 24 months, and as such should be interpreted with caution.

4.2. Mental HRQoL

Mental health may be affected differently than physical health by weight reduction. In the study by McDonald et al., a clinically meaningful weight loss induced by intensive lifestyle intervention did not improve MCS [13]. Deterioration of mental health may even occur when body weight is reduced with a low-calorie formula diet [38], perhaps because of severe calorie deficiency or other factors inherent to liquid meals, thereby complicating this approach in weight management. In our study, we used more real-life dietary regimens, neither of which harmed mental health. In fact, a small but clinically relevant difference in MCS [32] favoured the CRHP diet when compared with the CD diet. However, our results did not reach statistical significance and remain to be confirmed by larger studies. Others have shown no effect on MCS following 24 weeks and 2 years of weight loss management by carbohydrate-restricted diets possibly due to poor dietary adherence [14,39].

Dietary carbohydrate restriction can increase risk for hypoglycaemic events [40], which are inversely associated with quality of life in patients with T2D [41]. This was not the case in the present study as participants receiving the CRHP diet perceived each domain and the component summary scores equally good or even better than participants receiving the CD diet, in spite of spending significantly more time of the day below 3.9 mmol/l [28].

4.3. Cognitive functioning

Hypoglycaemia has been shown to impair cognitive performance and increase risk of dementia in T2D [20,42], and since avoiding hypoglycaemia is believed to prevent cognitive decline, recent guidelines now recommend less intensive treatment in cognitively vulnerable patients [43]. Despite concerns about hypoglycaemia, we found no deterioration in global cognition after 6 weeks of consuming a CRHP diet, and no association between the time spent below 3.9 mmol/l and cognitive performance. As such, our data suggest that intentional moderate weight loss through a hypocaloric carbohydrate-restricted diet is safe in terms of cognitive functioning in patients with T2D. However, it should be noted that the CRHP diet tended to impede improvements in executive function and significantly decreased SDMT performance assessing psychomotor speed when compared with the CD diet. Interestingly, SDMT test performance in particular has been shown to be susceptible to hypoglycaemia in T2D patients [20]. It is therefore not unreasonable to assume that this minor cognitive difference found in the present study would diminish over time, as another study in patients with T2D found no effect after 1 and 2 years of severe carbohydrate restriction [25,37]. Likewise, short-term impairments from carbohydrate-restricted diets are no longer apparent at follow-up or in longer-term studies in overweight and obese individuals [24,44].

Very-low carbohydrate (<10%) diets have been shown to impair processing speed, memory functions and mental flexibility (executive function), but improve some attentional tasks, when compared with a carbohydrate-rich diet during 3–8 weeks of energy restriction in overweight and obese individuals [21–23]. On the contrary, we found no decline in memory and executive function after 6 weeks of moderate carbohydrate restriction, possibly emphasising the importance of the different extent of carbohydrate restriction (and thus glucose availability) for some cognitive functions. Accordingly, the more moderate carbohydrate restriction applied in the present study may have prevented cognitive impairment in this population.

4.4. Limitations and strengths

Limitations of this study include an unblinded design (investigators as well as the participants were aware of the allocated diet), a relatively short intervention period, and lack of objective evaluation of physical activity. Importantly, this study was powered to assess changes in HbA1c and not HRQoL or cognition after 6 weeks of dietary intervention, and consequently, it may have missed a true difference, e.g. the clinically relevant difference in MCS. Moreover, all outcomes were exploratory in nature and we did not adjust for multiplicity, which increases risk of false-positive findings. Some participants preferred allocation to the CRHP diet, and we cannot rule out some degree of performance bias in this unblinded design, as self-perceived HRQoL is a purely subjective measure. The small cognitive test battery applied limits a complete exploration of the specific domains, e.g. executive function was derived from a single test score, but learning effects between measurements were minimised by the use of alternative test versions. Finally, as dietary carbohydrate was substituted by protein and fat in the CRHP diet, other dietary components (e.g. saturated and monounsaturated fat and fibre) were allowed to vary naturally and could therefore be primarily responsible for the observed changes. When comparing different carbohydrate-restricted dietary patterns, differences in the distribution of protein and fat as well as macronutrient quality may affect HRQoL and cognition instead of carbohydrate content per se.

The strengths of our study include the standardised intervention with provision of all meals and regular visits to maximise compliance and ensure a highly controlled rate of weight loss, thereby minimising confounding from competing factors such as dietary non-adherence or differences in weight loss between groups. Importantly, participants in both diet groups in our study did not change their habitual physical activity level and were adherent to the provided diets (from measurements of 24-h urinary excretion of urea as a marker of protein intake) [28].

5. Conclusion

In conclusion, moderate carbohydrate restriction did not negatively affect self-perceived HRQoL or global cognition when compared with a conventional carbohydrate-rich diet during 6 weeks of hypocaloric feeding inducing a 6% weight loss and, thus, may be a safe dietary strategy in managing T2D and obesity.

Author contributions

M.N.T. was responsible for conducting the study and contributed equally with N.J.J. in writing of the manuscript, producing as well as...
analysing the data, and planning of the study. H.Z.W. contributed with production of data. M.J.S. and A.S. assisted with planning of the study. S.B.H. and T.K. conceptualised the study, obtained funding, and supervised the study. A.A., J.F., B.H., J.J.H., and S.M., contributed with conception and design of the study. T.M.L. and F.M. contributed to the study design, supervised the food production and distribution. K.W.M. and J.R. contributed to the study design and interpretation of data. All authors participated in critically revising the manuscript and approved the version to be published. N.J.J. and M.N.T. are guarantors of this manuscript and take responsibility for the integrity of the data and the accuracy of its analysis.

Data availability statement

The data supporting the findings in this study are available upon reasonable request and approval from the Danish Data Protection Agency.

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Conflict of interest

A.A. is currently employed by The Novo Nordisk Foundation to establish a National Centre for Healthy Weight and is a member of advisory board/consultant for: Gelesis, USA; Groupe Ethique et Santé, France; Weight Watchers, USA. A.A. is co-owner of the University of Copenhagen spin-off Flax-Slim ApS and co-inventor on a pending provisional patent application for the use of biomarkers to predict responses to weight-loss diets and other related patents and patent applications that are all owned by the University of Copenhagen in accordance with Danish law. A.A. is co-author of a number of diet and cookery books, including books on personalised diet but is not an advocate or activist for specific diet. T.M.L. is advisor for the “Sense” diet program. The remaining authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2022.05.005.

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