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The effect of healthy ketogenic diet vs calorie-restricted diet on weight and metabolic outcomes among individuals with obesity: A randomized controlled trial

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Background & Current Literature

- The ketogenic or “keto” diet is a low-carbohydrate, high fat and moderate protein diet plan [1]
- Ketogenic Diet has ↑ popularity [2]
  - Reduces appetite, boosts fat oxidation, and facilitates weight loss.

[1] Harvard School of Public Health. 2024. Diet Review: Ketogenic Diet For Weight Loss2024.

[2] Kirkpatrick CF, Bolick JP, Kris-Etherton PM, Sikand G, Aspry KE, Soffer DE, Willard KE, Maki KC. Review of current evidence and clinical recommendations on the effects of low-carbohydrate and very-low-carbohydrate (including ketogenic) diets for the management of body weight and other cardiometabolic risk factors: a scientific statement from the National Lipid Association Nutrition and Lifestyle Task Force. *Journal of clinical lipidology*. 2019;13(5):689-711.

Current Literature

A Randomized Trial Comparing a Very Low Carbohydrate Diet and a Calorie-Restricted Low Fat Diet on Body Weight and Cardiovascular Risk Factors in Healthy Women [3]

Bonnie J. Brehm ✉, Randy J. Seeley, Stephen R. Daniels, David A. D'Alessio

Because low carbohydrate diets derive large proportions of calories from protein and fat, there has been considerable concern for their potentially detrimental impact on cardiovascular risk (17). Increased consumption of fat, particularly saturated fat, has been linked to increased plasma concentrations of lipids (18), insulin resistance, glucose intolerance (19, 20), and obesity (21, 22). Therefore, it is possible that many Americans could actually suffer adverse health effects by using very low carbohydrate diets in an attempt to lose weight. To evaluate the effects of a very low

Effects of carbohydrate-restricted diets on low-density lipoprotein cholesterol levels in overweight and obese adults: a systematic review and meta-analysis [4]

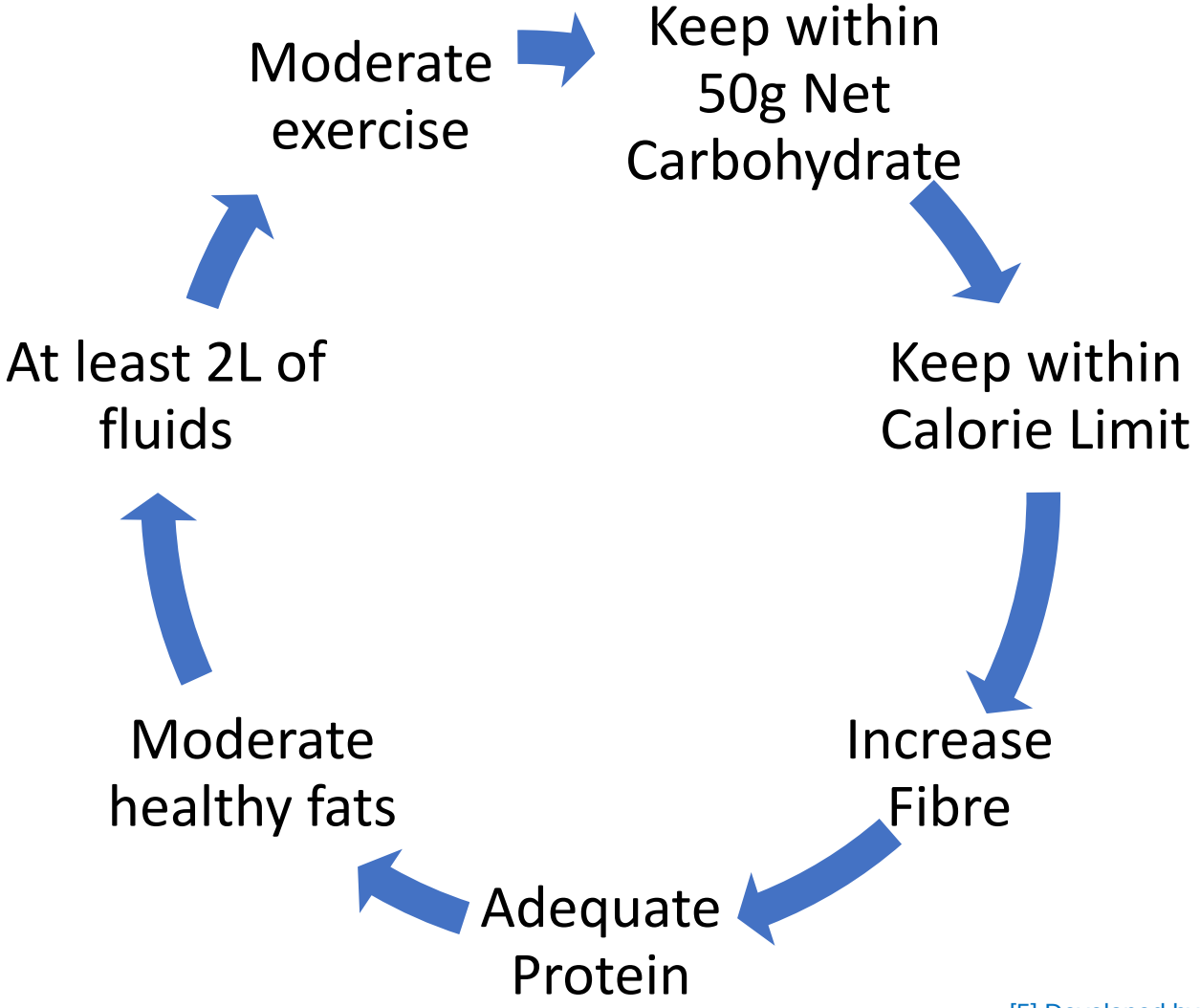
Teuta Gjuladin-Hellon, Ian G Davies ✉, Peter Penson, Raziyeh Amiri Baghbadorani

The main concern regarding CRDs, which are potentially high in total fatty acids and SFAs, is their theoretically adverse effect on low-density lipoprotein cholesterol (LDL-C) levels and, presumably, CVD risk. Saturated fat per se is not associated with

[3] Brehm BJ, Seeley RJ, Daniels SR, D'Alessio DA. A randomized trial comparing a very low carbohydrate diet and a calorie-restricted low fat diet on body weight and cardiovascular risk factors in healthy women. *The Journal of Clinical Endocrinology & Metabolism*. 2003;88(4):1617-23.

[4] Gjuladin-Hellon T, Davies IG, Penson P, Amiri Baghbadorani R. Effects of carbohydrate-restricted diets on low-density lipoprotein cholesterol levels in overweight and obese adults: a systematic review and meta-analysis. *Nutrition reviews*. 2019;77(3):161-80.

Healthy Ketogenic Diet [5]

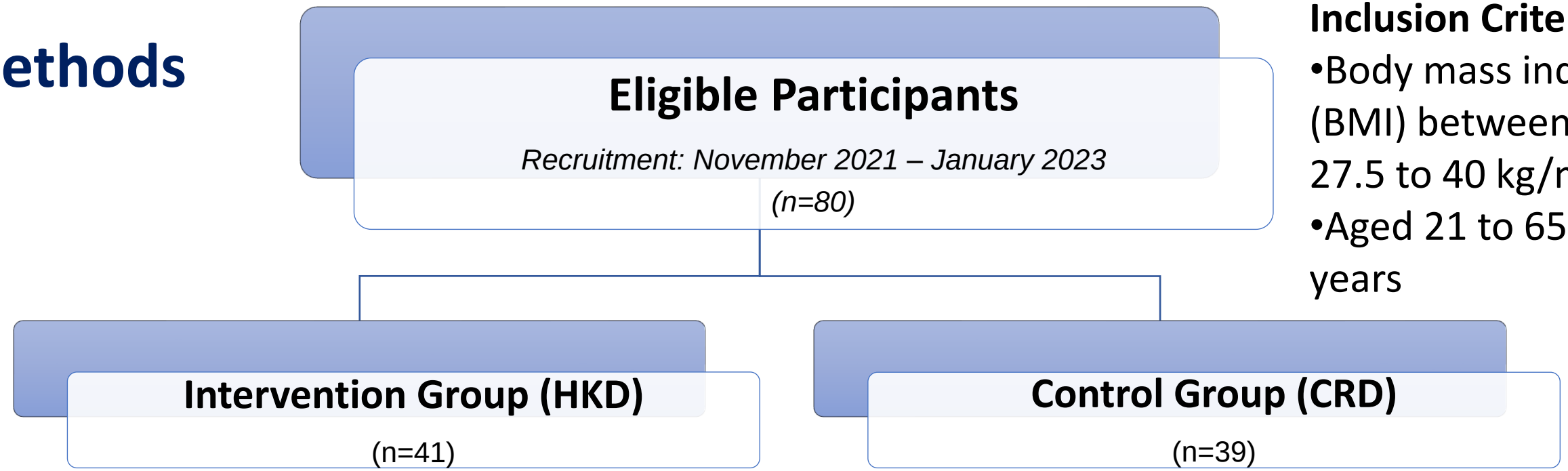


[5] Developed by Dr Lim Su Lin, Chief Dietitian, National University Hospital

Aim

To investigate the effect of a healthy ketogenic diet (HKD) versus a calorie restricted diet(CRD) on weight loss and metabolic outcomes among adults with obesity.

Methods



Inclusion Criteria:

- Body mass index (BMI) between 27.5 to 40 kg/m2
- Aged 21 to 65 years

- Keep within individualised calorie limit per day
- Keep within 50g net carbohydrates
- Increase fiber intake
- Adequate protein
- Moderate healthy fats
- At least 2L of fluids
- Moderate intensity exercises

- Keep within individualised calorie limit per day
- Increase fiber intake
- Adequate protein
- Moderate healthy fats
- At least 2L of fluids
- Moderate intensity exercises

Methods

Eligible Participants

Recruitment: November 2021 – January 2023

(n=80)

Intervention Group (HKD)

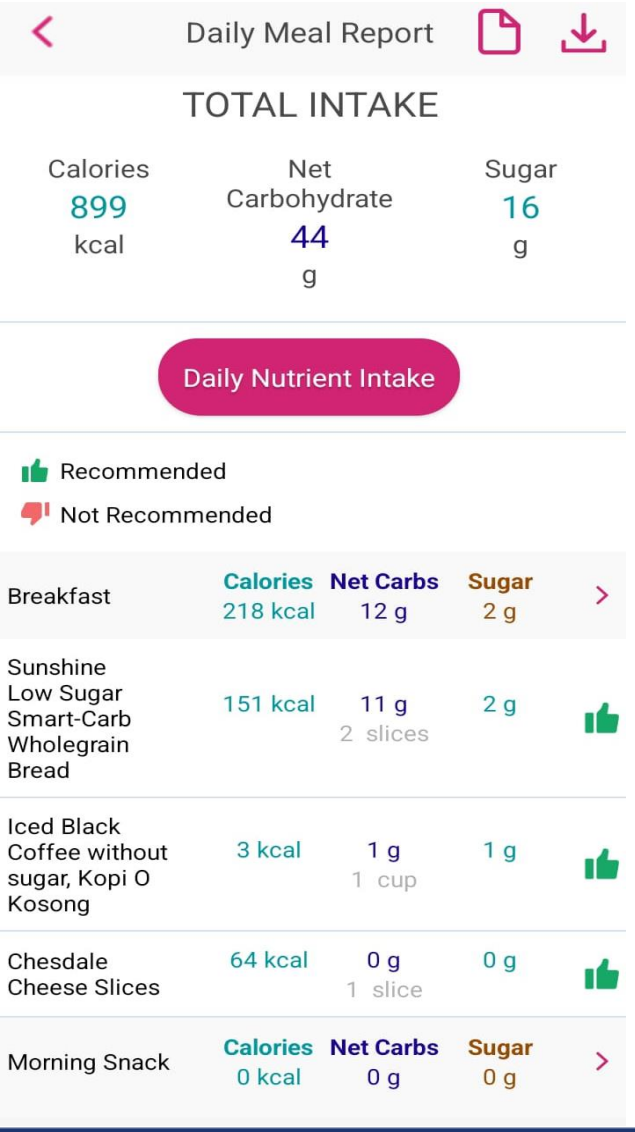
(n=41)

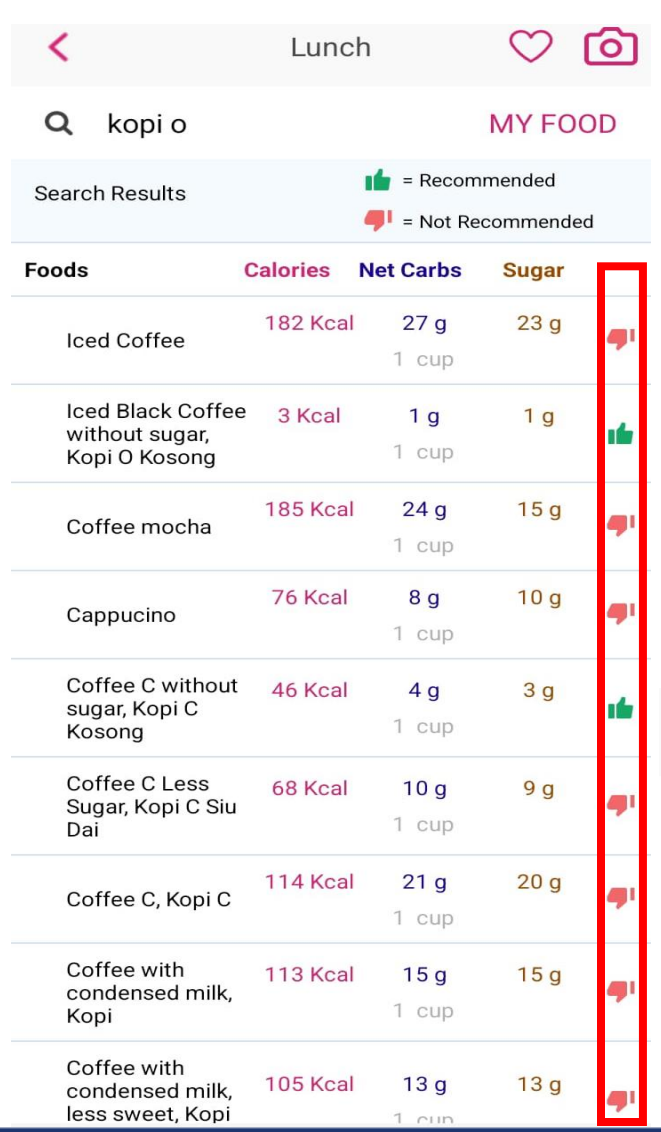
Control Group (CRD)

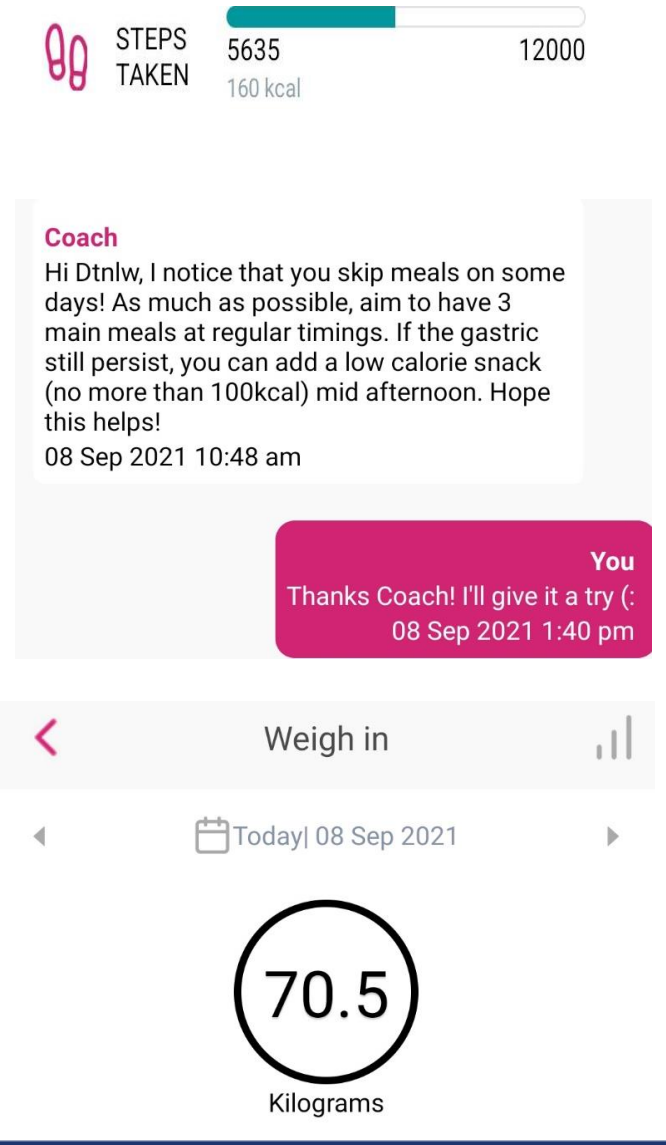
(n=39)

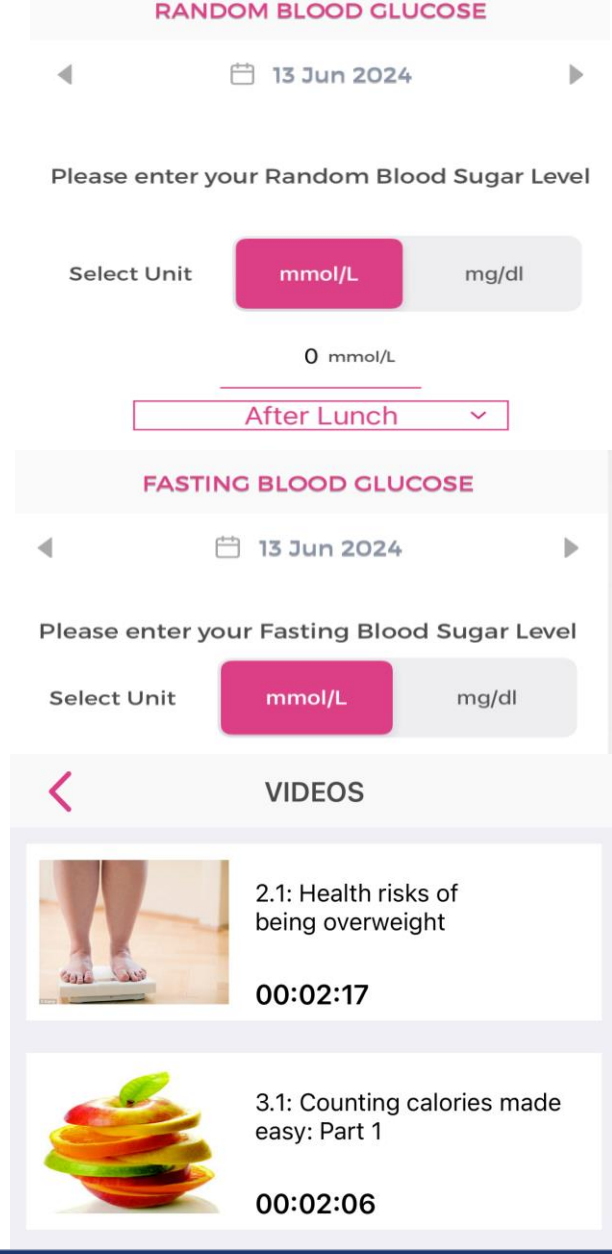
- 7 physical workshop covering similar topics.
  - Content tailored to each group's specific diet specifications.
- Nutritionist Buddy (nBuddy) app

Methods – nBuddy App Features









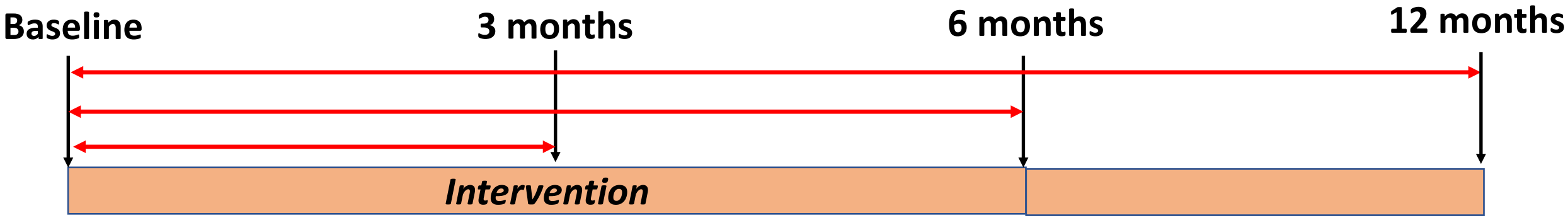
Methods

Primary Outcome:

- △ in body weight at 6 months

Secondary Outcome:

- △ in body weight at 3 and 12 months
- △ in metabolic profiles at 3, 6 and 12 months
- Dietary intake, physical activity and prescribe medications were tracked as part of secondary outcomes evaluation.



Methods - Statistical Analysis

- Baseline to 3 months
- Baseline to 6 months
- Baseline to 12 months

HKD Group

CRD Group

Change in body weight

Changes in metabolic profiles

Changes in nutritional outcomes

Linear Regression with intention-to-treat approach, *Adjusted for age, gender and baseline value of outcome* (*except for change in weight %)*

Results – Demographics of study participants at baseline

Table 1: Baseline characteristics of study participants.

Variable	HKD (n = 41)	CRD (n = 39)	P value[a]
Gender, n (%)			
Male	36 (87.8%)	33 (84.6%)	0.679
Female	5 (12.2%)	6 (15.4%)	
Ethnicity, n (%)			
Chinese	26 (63.4%)	18 (46.2%)	0.255
Malay	10 (24.4%)	9 (23.1%)	
Indian	3 (7.3%)	7 (17.9%)	
Others	2 (4.9%)	5 (12.8%)	
Age (years)			
Mean	38.4±8.8	39.4±7.6	0.600
Range	22-63	28-62	
Weight, kg	84.2±14.3	83.3±12.2	0.764
Body Mass Index, kg/m²	32.4±3.9	31.9±3.4	0.546
HbA1c, %	5.7±0.6	5.5±0.3	0.078
Fasting blood glucose, mmol/L	5.7±1.0	5.4±0.5	0.067
Systolic blood pressure, mmHg	121.7±12.7	122.5±18.5	0.823
Diastolic blood pressure, mmHg	78.0±9.8	78.6±10.5	0.796
Total cholesterol, mmol/L	5.3±0.9	5.0±1.0	0.158
LDL cholesterol, mmol/L	3.3±0.8	3.2±0.8	0.328
HDL cholesterol, mmol/L	1.4±0.2	1.3±0.3	0.647
Triglyceride, mmol/L	1.3±0.9	1.1±0.5	0.197
Alanine Transaminase, U/L	34.5±33.1	28.8±23.2	0.377
Aspartate Transaminase, U/L	27.4±16.1	24.6±9.5	0.357
Co-morbidity, n (%)			
Hypertension			
No	23 (56.1%)	19 (48.7%)	0.509
Yes	18 (43.9%)	20 (51.3%)	
Hyperlipidemia			
No	4 (9.8%)	7 (17.9%)	0.288
Yes	37 (90.2%)	32 (82.1%)	
Diabetes			
No	33 (80.5%)	34 (87.2%)	0.417
Yes	8 (19.5%)	5 (12.8%)	
Transaminitis			
No	30 (73.2%)	34 (87.2%)	0.117
Yes	11 (26.8%)	5 (12.8%)	
Nutrient intake			
Calorie, kcal	1857.7 ±400.8	1785.6 ±460.2	0.459
Protein, g	83.9 ±25.2	75.6 ±16.7	0.086
Total fat, g	81.0 ±23.0	75.2 ±22.6	0.259
Saturated fat, g	29.7 ±10.3	29.1 ±8.9	0.766
Carbohydrate, g	202.4 ±56.3	202.0 ±58.6	0.979
Net Carbohydrate, g	185.1 ±55.0	186.0 ±56.9	0.940
Sugar, g	53.1 ±29.1	48.9 ±22.3	0.468
Fiber, g	16.9 ±5.9	16.3 ±6.0	0.647
Sodium, mg	3402.3 ±1027.4	3189.9 ±1015.1	0.355

Data expressed as mean ± SD for continuous variables; absolute numbers (percentage) for categorical variables. LDL, Low-density Lipoprotein; HDL, High-density Lipoprotein.

[a]Chi-square, Fisher exact, independent samples t-test as appropriate.

Results – Weight & Metabolic Changes among HKD vs CRD group

Table 2: Primary and secondary outcomes at 3-month, 6-month and 1-year after enrolment using intention-to-treat analysis.

Outcomes	n	Mean Change from Baseline		Between-group differences[a]		
		HKD (n = 41)	CRD (n = 39)	Mean difference (95% CI)	P value	Cohen d
Δ Weight, kg						
3-month	72	-5.78 ±3.86*	-2.82 ±3.30*	-3.00 (-4.59- -1.40)	**<0.001**	0.44
6-month	59	-7.84 ±5.21*	-4.17 ±5.59*	-3.64 (-6.39- -0.89)	**0.010**	0.35
12-month	51	-6.85 ±6.37*	-4.64 ±5.77*	-1.52 (-4.77- 1.74)	0.353	0.13
Δ Weight, %						
3-month	72	-6.80 ±4.24	-3.26 ±3.62	-3.74 (-5.55- -1.93)[b]	**<0.001[b]**	0.49[b]
6-month	59	-9.29 ±5.91	-4.86 ±5.82	-4.56 (-7.59- -1.53)[b]	**0.004[b]**	0.39[b]
12-month	51	-7.93 ±7.65	-5.36 ±6.23	-2.67 (-6.58- 1.25)[b]	0.177[b]	0.19[b]
Δ BMI, kg/m²						
3-month	72	-2.21 ±1.41*	-1.03 ±1.17*	-1.23 (-1.83- -0.63)	**<0.001**	0.48
6-month	59	-3.03 ±2.03*	-1.52 ±1.88	-1.55 (-2.57- -0.53)	**0.003**	0.40
12-month	51	-2.61 ±2.48*	-1.66 ±1.97*	-0.97 (-2.24- 0.29)	0.128	0.22
Δ ALT, U/L						
3-month	71	-14.38 ±27.83*	-4.91 ±15.90	-3.55 (-7.96- 0.87)	0.113	0.19
6-month	59	-18.97 ±32.54*	-5.67 ±23.38	-3.97 (-7.97- 0.03)	0.051	0.26
12-month	51	-19.15 ±38.15*	-0.88 ±23.79	-11.08 (-21.92- -0.24)	**0.045**	0.29
Δ AST, U/L						
3-month	71	-6.68 ±14.48*	-1.41 ±8.74	-2.26 (-5.14- 0.63)	0.124	0.19
6-month	59	-7.62 ±15.52*	0.60 ±11.52	-4.05 (-7.09- -1.01)	**0.010**	0.35
12-month	51	-8.33 ±18.24*	1.79 ±11.72	-5.51 (-10.38- -0.63)	**0.028**	0.32
Δ HbA1c, %						
3-month	71	-0.27 ±0.29*	-0.11 ±0.19*	-0.09 (-0.18- 0.00)	0.060	0.24
6-month	59	-0.27 ±0.26*	-0.07 ±0.19	-0.15 (-0.25- -0.04)	**0.008**	0.37
12-month	51	-0.27 ±0.28*	-0.12 ±0.21*	-0.09 (-0.21- 0.03)	0.145	0.21
Δ Fasting Blood Glucose, mmol/L						
3-month	71	-0.36 ±0.49*	-0.22 ±0.58*	0.00 (-0.22- 0.23)	0.972	0.00
6-month	59	-0.42 ±0.48*	-0.24 ±0.52*	-0.10 (-0.35- 0.15)	0.415	0.10
12-month	51	-0.32 ±0.50*	-0.21 ±0.46*	-0.01 (-0.28- 0.26)	0.924	0.01

Outcomes	n	Mean Change from Baseline		Between-group differences[a]		
		HKD (n = 41)	CRD (n = 39)	Mean difference (95% CI)	P value	Cohen d
Δ Systolic blood pressure, mmHg						
3-month	71	-7.08 ±7.42*	-4.12 ±14.46	-3.47 (-7.87- 0.94)	0.121	0.19
6-month	59	-7.69 ±8.86*	-2.57 ±12.23	-6.38 (-10.73- -2.03)	**0.005**	0.38
12-month	51	-4.19 ±10.69	-5.67 ±9.48*	0.36 (-4.73- 5.45)	0.887	0.02
Δ Diastolic blood pressure, mmHg						
3-month	71	-3.11 ±7.03*	-4.97 ±9.85*	1.49 (-2.21- 5.18)	0.424	0.10
6-month	59	-3.72 ±6.46*	-2.37 ±7.72	-1.58 (-5.01- 1.85)	0.359	0.12
12-month	51	-2.07 ±8.84	-2.58 ±9.17	0.25 (-4.59- 5.09)	0.917	0.01
Δ Total cholesterol, mmol/L						
3-month	71	-0.42 ±0.75*	-0.16 ±0.55	-0.13 (-0.39- 0.13)	0.331	0.12
6-month	59	-0.29 ±0.75*	-0.08 ±0.67	-0.10 (-0.43- 0.23)	0.551	0.08
12-month	51	0.18 ±0.52*	0.26 ±1.00	-0.12 (-0.55- 0.32)	0.594	0.08
Δ HDL-cholesterol, mmol/L						
3-month	71	-0.04 ±0.24	-0.01 ±0.17	-0.01 (-0.11- 0.08)	0.760	0.03
6-month	59	0.05 ±0.19	0.01 ±0.20	0.04 (-0.06- 0.14)	0.406	0.11
12-month	51	0.09 ±0.19*	0.01 ±0.21	0.08 (-0.03- 0.18)	0.161	0.21
Δ Triglycerides, mmol/L						
3-month	71	-0.44 ±0.68*	-0.06 ±0.39	-0.20 (-0.34- -0.06)	**0.006**	0.33
6-month	59	-0.49 ±0.80*	-0.13 ±0.57	-0.17 (-0.42- 0.08)	0.181	0.18
12-month	51	-0.57 ±0.88*	-0.04 ±0.66	-0.40 (-0.78- -0.03)	**0.036**	0.30
Δ LDL-cholesterol, mmol/L						
3-month	71	-0.19 ±0.69	-0.11 ±0.39	-0.01 (-0.24- 0.22)	0.924	0.01
6-month	59	-0.12 ±0.60	-0.04 ±0.56	0.00 (-0.27- 0.26)	0.970	0.00
12-month	51	-0.27 ±0.58*	0.07 ±0.76	-0.33 (-0.69- 0.03)	0.073	0.26

Data expressed as mean ± SD. BMI, Body Mass Index; ALT, Alanine Transaminase; AST, Aspartate Transaminase, HbA1c, Glycated Hemoblogin; HDL, High-density Lipoprotein; LDL, Low-density Lipoprotein.

[a]adjusted for gender, age and baseline value of the outcome

[b]adjusted for gender and age

* Significant within group changes p values after Benjamini-Hochberg correction with false discovery rate at 0.20 and n=126

Significant p values after Benjamini-Hochberg correction with false discovery rate at 0.20 and n=66 in bold

Results – Participants with ≥ 5% and ≥ 10% weight loss

Table 3: Odds ratio of HKD group achieving weight loss at 3-month, 6-month and 1-year in comparison to CRD group.

	Weight loss <5%	Weight loss ≥5%	OR (95% CI)[a]	p-value
3-month				
HKD	15 (40.5%)	22 (59.5%)	3.5 (1.3- 9.4)	**0.014**
CRD	24 (68.6%)	11 (31.4%)	1.0	
6-month				
HKD	8 (27.6%)	21 (72.4%)	5.6 (1.8- 17.6)	**0.003**
CRD	20 (66.7%)	10 (33.3%)	1.0	
12-month				
HKD	11 (40.7%)	16 (59.3%)	1.5 (0.5- 4.7)	0.474
CRD	12 (50.0%)	12 (50.0%)	1.0	
	Weight loss <10%	**Weight loss ≥10%**	**OR (95% CI)[a]**	**p-value**
3-month				
HKD	28 (75.7%)	9 (24.3%)	14.5 (1.6- 131.9)	**0.017**
CRD	34 (97.1%)	1 (2.9%)	1.0	
6-month				
HKD	16 (55.2%)	13 (44.8%)	4.9 (1.3- 17.8)	**0.017**
CRD	25 (83.3%)	5 (16.7%)	1.0	
12-month				
HKD	16 (59.3%)	11 (40.7%)	3.2 (0.8- 12.3)	0.099
CRD	19 (79.2%)	5 (20.8%)	1.0	

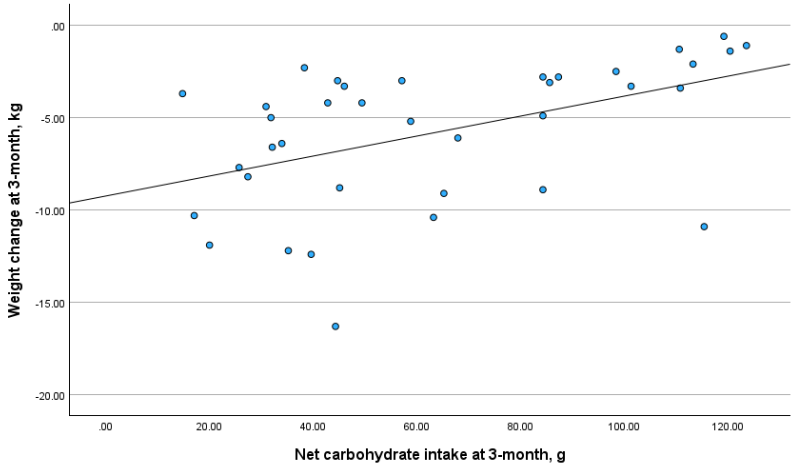
[a]adjusted for gender and age

Significant p values after Benjamini-Hochberg correction with false discovery rate at 0.20 and n=6 in bold

Results – Correlation of net carbohydrate intake and weight loss

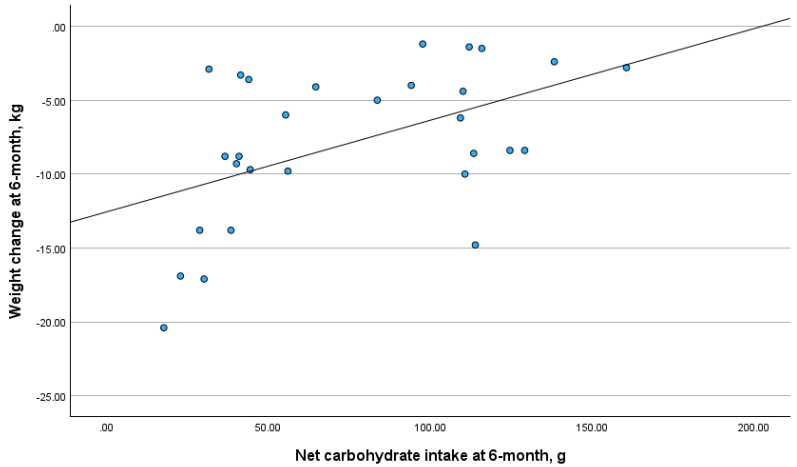
Figure 1: Correlation between net carbohydrate intake and weight loss in the HKD group at (i) 3-month, (ii) 6-month and (iii) 1-year.

(i)



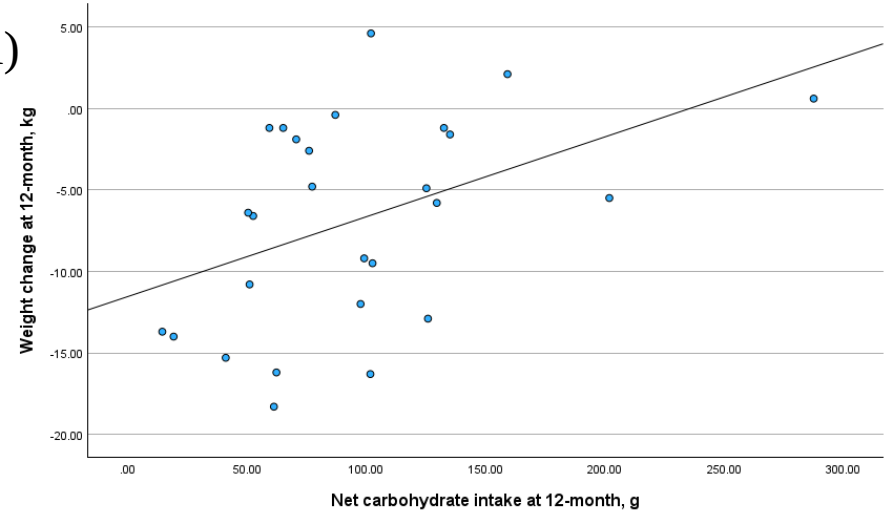
Pearson correlation: 0.476, p=**0.003**

(ii)



Pearson correlation: 0.495, p=**0.006**

(iii)

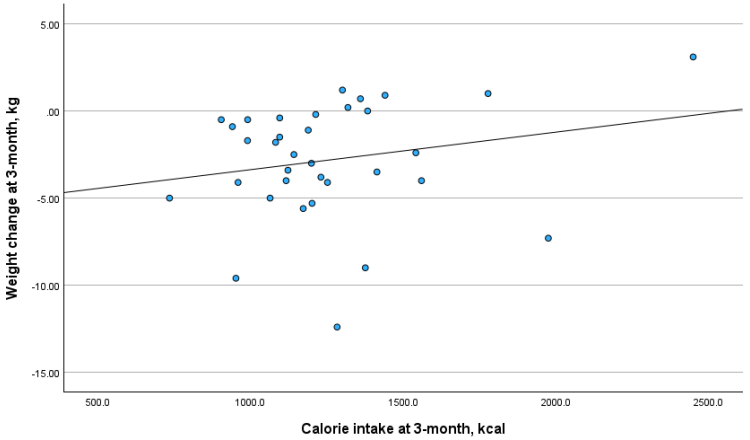


Pearson correlation: 0.441, p=**0.021**

Figure 2: Correlation between calorie intake and weight loss in the CRD and HKD group at 3-month, 6-month and 1-year.

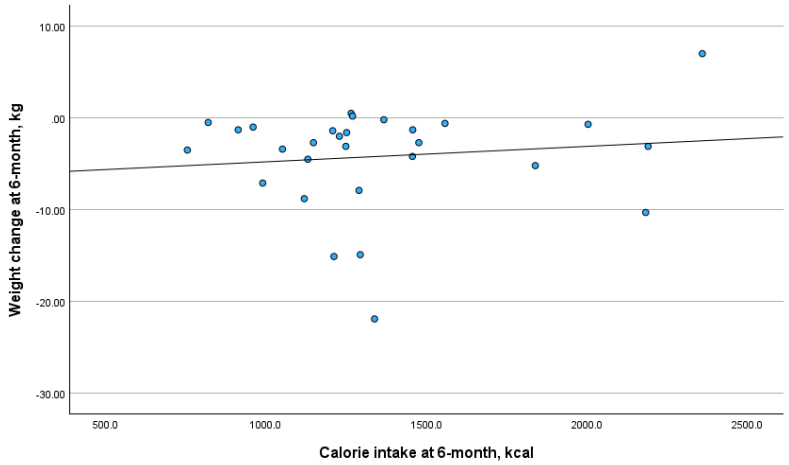
CRD Group

3 months



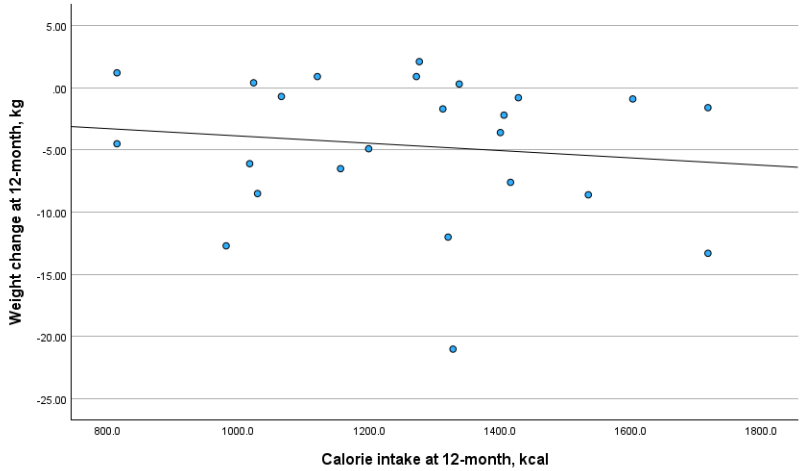
Pearson correlation: 0.209, p=0.235

6 months



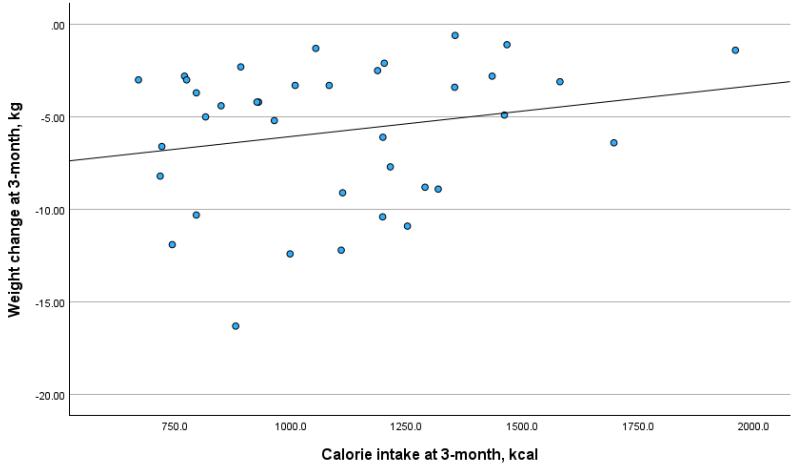
Pearson correlation: 0.120, p=0.535

1 year

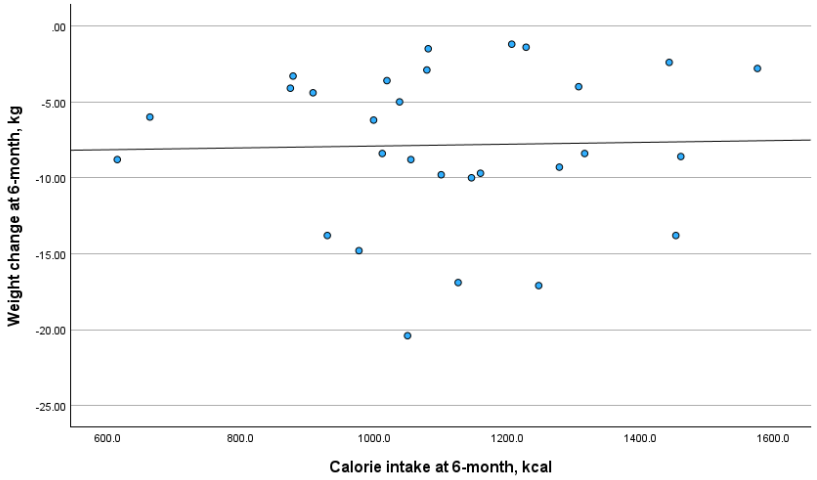


Pearson correlation: -0.127, p=0.553

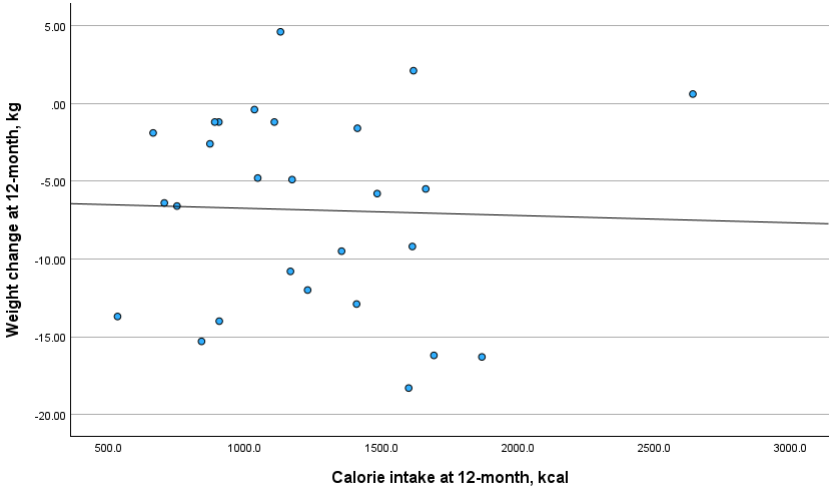
HKD Group



Pearson correlation: 0.216, p=0.199



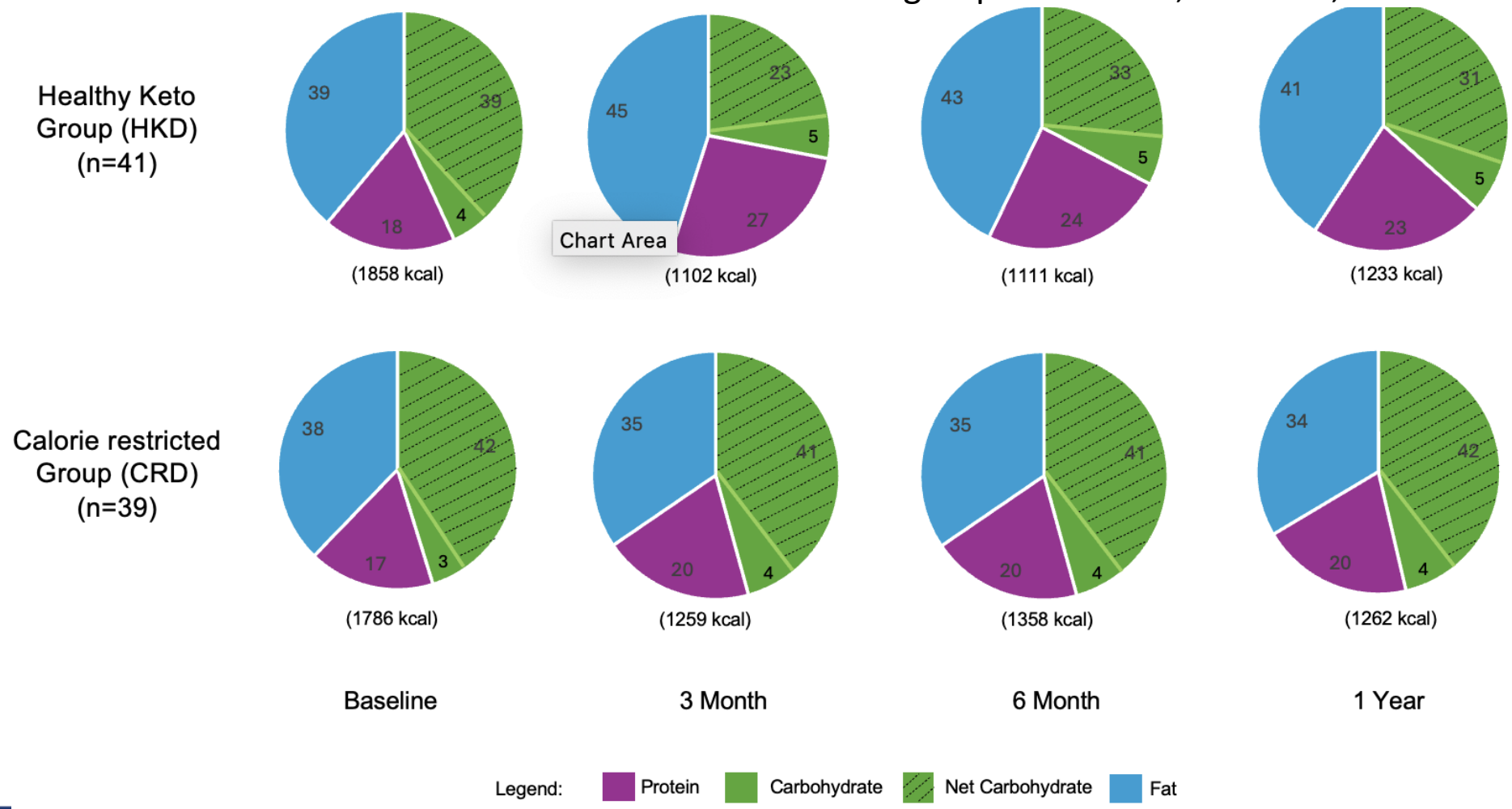
Pearson correlation: 0.026, p=0.893



Pearson correlation: -0.033, p=0.869

Results – Average macronutrients consumption among HKD and CRD group

Figure 3: Macronutrient intake distributions in the CRD and HKD group at baseline, 3-month, 6-month and 1-year.



Results – Self Reported Symptoms by HKD and CRD group

Table 4: Self-reported symptoms experienced by participants at 3 months, 6 months and 1 year post-intervention.

Symptoms Experienced Days/Week (Number of responders)	**HKD**			**CRD**		
	3-month	6-month	1-year	3-month	6-month	1-year
Hunger Pangs	2.5 (22)	2.1 (21)	2.7 (8)	2.6 (21)	2.2 (18)	2.4 (8)
Nausea	1.5 (4)	2 (1)	0.5 (1)	1 (1)	0 (0)	1.5 (1)
Headache	1.4 (8)	2 (3)	1.8 (5)	1.7 (3)	1.4 (5)	2.5 (3)
Constipation	2.2 (15)	2 (9)	2.2 (6)	2 (11)	2.4 (6)	1.75 (6)
Bad Breath	2.2 (6)	2 (2)	1.75 (2)	1 (2)	3 (1)	0 (0)
Decreased concentration	2 (1)	1.5 (2)	3.25 (2)	2.5 (4)	1.5 (2)	0 (0)

Conclusion

HKD is helpful with achieving a clinically meaning weight reduction and improving cardiometabolic outcomes compared to CRD

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