The Effect of Concentrating Carbohydrates to Dinner on Metabolic Syndrome: A Systematic Review of Randomised Controlled Trials

Andreas Tsiartas (Supervisor - Dr Janet Kyle)
School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Scotland

Abstract

Background

Obesity, type-2 diabetes mellitus and cardiovascular disease are at pandemic levels. An important precursor and link between them is metabolic syndrome. This review aimed to assess the effect of a unique eating pattern, concentrating carbohydrates to dinner, on the components of metabolic syndrome and other reported health outcomes.

Methods

MEDLINE, EMBASE, CENTRAL and CAB abstracts were systematically searched through May 2021. Key search terms included metabolic syndrome, insulin resistance, blood glucose, dietary carbohydrates, dinner and meal-timing. Results were presented in a narrative form, and a vote-counting procedure of effects was conducted.

Results

Six studies were included, with 311 participants aged of 44.6 (7.2) years (mean (SD)). Notable findings were positive effects on fasting blood glucose, HOMA-IR and lipid profiles. However, the definition of concentrating carbohydrates to dinner, biomarkers measured, and study designs, including interventions, varied significantly between studies. Consequently, a meta-analysis was not possible.

Conclusion

Concentrating carbohydrates to dinner leads to measurable biological effects. However, further research is needed as the evidence is mixed, and a standard definition of concentrating carbohydrates to dinner is needed. Furthermore, the concurrent consideration of several biomarkers and methods appears promising while considering the components of metabolic syndrome. These include the simultaneous measurement of postprandial glucose peaks using continuous glucose monitoring; inflammatory markers, including C-reactive protein, tumour necrosis factor-α, Interleukin-6; diet satisfaction, hunger and satiety, including through the analysis of leptin, ghrelin and adiponectin; energy metabolism and energy expenditure and possible effects on sleep.

Keywords: Metabolic syndrome, carbohydrates, macronutrients, dinner, timing

Introduction

Non-communicable diseases (NCD's) including obesity,[1,2] cardiovascular disease (CVD)[3–7], and type 2 diabetes mellitus (T2DM)[8–13] are reaching pandemic proportions. They affect numerous health outcomes[14–18] and are among the leading causes of death and disability worldwide.[3–12] They are also the costliest diseases,[10,19–22] affecting individuals, families, healthcare systems and economies with serious repercussions.[3–12] Metabolic syndrome (MetS) is a precursor and link between them.[23–25]

MetS, or insulin resistance (IR) syndrome, is the simultaneous presence of at least three of five health conditions: elevated waist-circumference (WC), elevated triglycerides, reduced HDL-cholesterol, elevated blood pressure and elevated fasting blood glucose (FBG).[26(p290)] It doubles CVD risk and increases all-cause mortality by a factor of 1.5.[27] It is estimated that around 25% of those with impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) progress to T2DM in 3-5 years. [28–30] T2DM, in turn, is a significant risk factor for developing CVD,[31–33] leading to a vicious cycle. Diet has shown promise in breaking this cycle of disease.[24,34–38]

Dietary patterns, meal-timing and, more specifically, macronutrient-intake timing[39,40] can either be beneficial or detrimental for health.[41,42] This effect, known as chrononutrition,[43] may relate to circadian rhythms (CR's), the way our bodies work in tandem with the rhythms of nature.[44] CR's are primarily controlled by the effects of the cycles of light and darkness through photosensitive retinal ganglion cells via the optic nerve on the suprachiasmatic nucleus in the hypothalamus of the brain.[44–46] The feeding and fasting cycle, however, also plays a significant role through its effect on peripheral oscillators[47–50] found throughout the body and especially throughout the gastrointestinal tract.[51] Food intake, therefore, can either beneficially reinforce natural CR's or decouple them with significant effects on NCD's.[43,47,52]

The timing of carbohydrate consumption specifically has been shown to influence several components of MetS[40] and other important determinants of health, including sleep.[41,53] Concentrating carbohydrates to dinner (CCtoD) is a dietary pattern in which carbohydrates are consumed mostly at dinner.[40,54–57] Overall macronutrient ratios remain similar to international recommendations,[58] but carbohydrates are largely excluded from breakfast and lunch. These meals, therefore, are similar to those consumed on a low-carbohydrate[59–61] or ketogenic-type diet.[62] Dinner is what could be defined as a high-carbohydrate,[59–61] low-protein, low-fat meal. Research suggests it may improve several metabolic markers of disease risk,[63] lead to greater weight loss and improve components of MetS.[40,54–56] This effect was not previously systematically reviewed.

The purpose of this review was to evaluate the evidence on the effect of CCtoD systematically. Furthermore, it aimed to elucidate potential pathways involved in the impact of CCtoD on the components of MetS and other reported health outcomes.

Methods

Information sources and search strategy

The review was conducted according to the PRISMA Guidelines,[64] and the search strategy was developed based on the PICOSS model (Table 1).

Table 1. PICOSS

Population	Adults over the age of 18.
Intervention	Any interventions controlling the intake and timing of macronutrients in which carbohydrates are eaten mostly, or are concentrated to, dinner.
Comparator	Stated interventions compared to any other intervention controlling the timing of the consumption of macronutrients or no intervention.
Outcomes	Any positive or adverse effect of any of the components of metabolic syndrome, cardiovascular disease or type 2 diabetes mellitus, any of their related biomarkers or other observed health-based outcomes from the intervention.
Study Design	Randomised controlled trials (RCT's).
Setting	Any setting; conducted anywhere worldwide.

Four electronic databases (MEDLINE, EMBASE, CENTRAL and CAB abstracts) were systematically searched through the online database Ovid by one reviewer and cross-checked by a second from inception to May 26th 2021.

The search strategy included the following key search terms: metabolic syndrome, insulin resistance, blood glucose, dietary carbohydrates, dinner, evening, evening-meal, meal-timing (full search strategy in appendix).

Eligibility criteria

Retrieved records were screened for the following criteria: (1) studies were RCT's (2) written in English; (3) involving human subjects of any gender, ethnicity, educational or socioeconomic status at any location, aged 18 or over; (4) where: (a) one of the interventions included CCtoD (b) macronutrient composition of breakfast and lunch were documented (c) the impact on at least one of the components of MetS, CVD or T2DM or any of their related biomarkers or risk factors was measured. Articles were excluded if: (1) subjects had any other complex health conditions; (2) involved pregnant or lactating women; (3) involved diagnosed eating disorders such as anorexia nervosa or bulimia nervosa.

Study selection and data extraction

Retrieved search results were first screened for duplicates using the Zotero referencing software (version 5.0.96.3). A list of titles and abstracts was generated and sorted alphabetically for initial screening based on the inclusion criteria. A shortlist of full-text articles was then screened based on the inclusion and exclusion criteria. Reference lists of included studies were also searched for relevant studies. The study selection was performed by one reviewer, and a random selection of 10% of the studies and all the final selected studies were cross-checked for validity by a second. Any discrepancies were discussed until a consensus was reached.

A modified Cochrane data-extraction form was used.[65] Items extracted included, study-type, participant characteristics, interventions and outcome measures (full form in appendix Table S2). Narrative descriptions of results were collected in the main form and quantitative-data, including any numerical-data and tables, were extracted into a Microsoft Excel spreadsheet.

Evidence quality appraisal

All studies were assessed for risk-of-bias using the Cochrane risk-of-bias assessment.[66] Authors of all studies were contacted for any necessary clarifications.

Data-analysis and narrative synthesis

Heterogeneity of the studies was assessed based on clinical diversity, methodological diversity and statistical heterogeneity,[66(p257,323)] to determine if a meta-analysis was feasible. Demographics, study-design and characteristics and biological outcome measures were considered. Wherever possible weighted mean and standard deviation (SD) was calculated. A narrative synthesis and a vote-counting assessment of effects was decided based on Cochrane guidelines.[66(p328)]

Results

Study selection

The complete search identified 436 articles; of these, 72 duplicates were removed. After title and abstract screening, 30 articles' full-text was evaluated for inclusion (Figure 1). Six articles were included in the review.

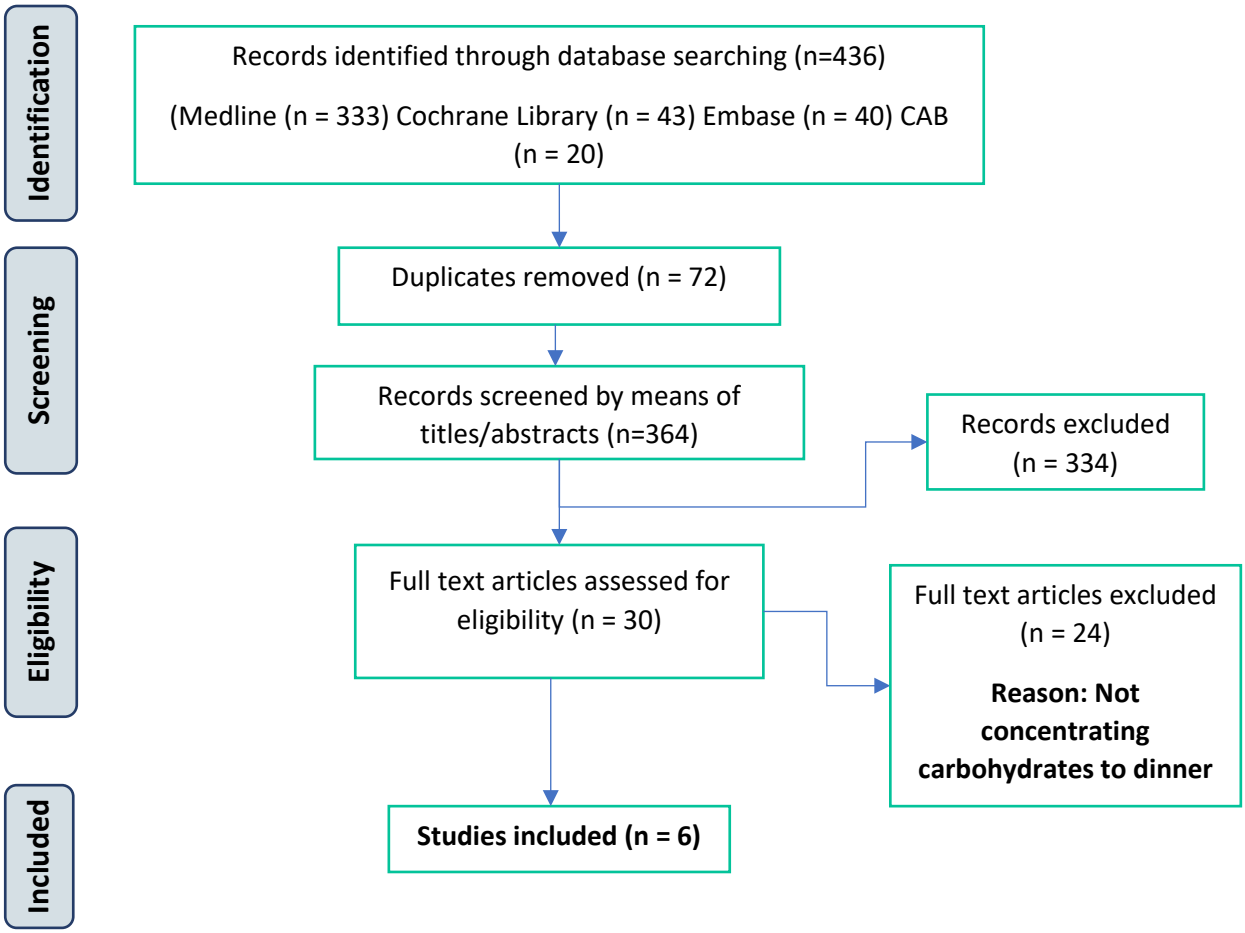


Figure 1. PRISMA flow chart for study selection.

Study characteristics

All articles were RCT's published from 2008 to 2021 (Table 2). Two used a crossover-design[67,68], and three used a parallel-design.[54,63,69] Two articles[54,55] represented one RCT; therefore, they were handled as one study. The studies were conducted in Australia, Israel, Brazil, Spain, Germany and Iran. The included sample was 311 participants (male = 199, female = 97, combined with unclear segregation = 15). The weighted-mean age and SD of participants was 44.6 ± 7.2. and the duration of interventions ranged from three to 180 days. Participants had normal glucose tolerance (NGT), IFG, IGT or T2DM.

Two studies[54,68] had one intervention and control arm, adopted different designs, parallel[54] and cross-over,[68] and intervention periods of 24[54] and 180[70] days. Two studies[69,70] Included two intervention arms and a control group, with differing durations of 56[70] and 70[69] days, respectively. However, participants in the former had no health conditions while those in the latter had T2DM. Finally, one study[67] was three days in duration and included three interventions and one control (Tables 2 and 3). Additionally, the definition of CCtoD varied significantly. As a percentage of energy for each meal, two studies[54,70] had an average of 16%, 12% and 64% carbohydrates for breakfast, lunch and dinner respectively, compared to 42%, 38% and 59% for the remaining studies[67–69] (Figure 2). Biological outcome measures between studies also differed (Table 4).

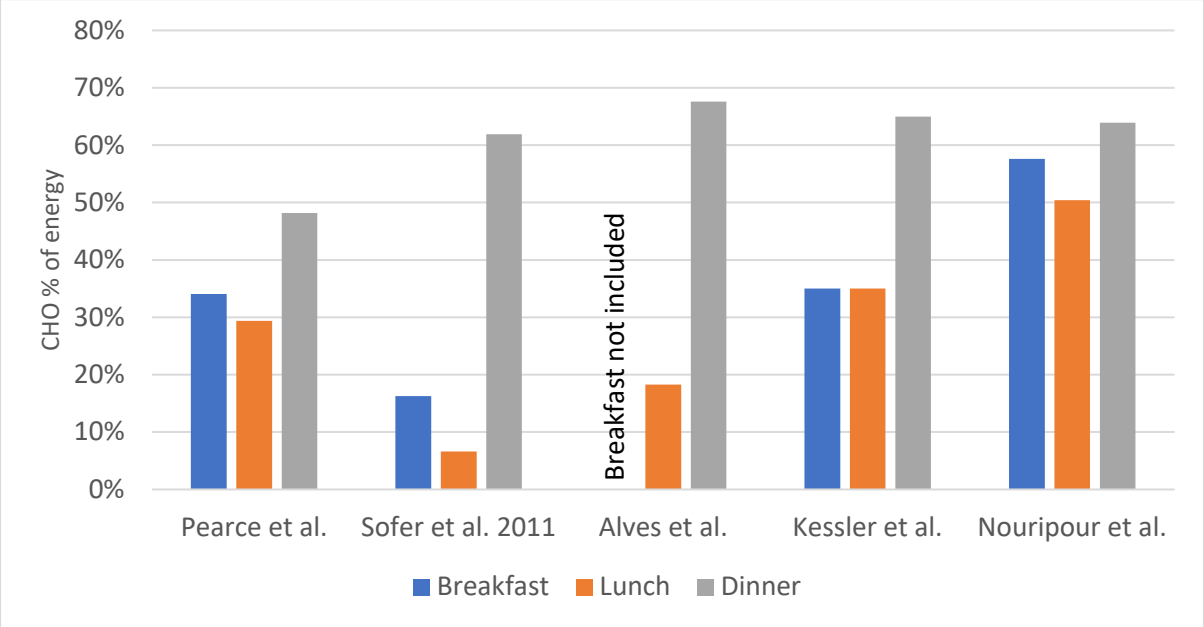
Table 2. Main characteristics of included studies

Author, Year, Reference	Country	Study Design (RCT)	Duration of Study (Days)	Maximum Duration of Single Intervention (Days)	Participant Characteristics					Risk of Bias
					Number of participants			Age range (years)§	Health Status	
					Total	Male	Female			
Pearce et al., 2008[67]	Australia	Single-blinded, Crossover Trial	12*	3	24	8	16	62.6 ± 9.3	All participants had type 2 diabetes	High
Sofer et al., 2011[54] **and 2013**[55]	Israel	Single-blinded, parallel	180	180	78	32††	31††	43 ± 7.5	No Underlying Health Conditions - BMI > 30	High
Alves et al., 2014[70]	Brazil AND Spain	Single-blinded, parallel	56	56	84	84	0	30 ± 7.4	No Underlying Health Conditions - BMI 26 - 35	High
Kessler et al.,2017[68]	Germany	Single-blinded, Crossover Trial	84†	28	29	29	0	45.9 ± 2.54	No Major underlying health conditions - BMI 22 - 34.9	High
Nouripour et al., 2021[69]	Iran	Single-blinded, parallel	70	70	96	46	50	53.8 ± 7.6	Type 2 diabetes, BMI ≥22 and <35	High

§ mean and standard deviation; *Crossover every 3 days; †56 days separated by a 28-day washout phase before crossover ††sum of male and female differs from total as data on gender was only provided for participants with follow up data

Table 3. Comparison of interventions included in review

Study	Abbreviation	Description
Pearce et al. 2008	**CARB-E**	Carbohydrate evenly distributed across the day
	CARB-B	Carbohydrates were loaded at breakfast
	CARB-L	Carbohydrates were loaded at lunch
	CARB-D	Carbohydrates were loaded at dinner
Sofer et al. 2011 & 2013	**EG**	**Experimental Group:** Low-calorie Diet - Carbohydrates mostly at dinner - No carbohydrate-rich food consumed until dinner
	CG	**Control Group:** Standard low-calorie diet - even distribution of carbohydrates throughout the day
Sofer et al. 2013		Same as Sofer 2011
Alves et al. 2014	**DCNP**	**Diurnal Carbohydrates Nocturnal Protein -** High-carbohydrate/low-protein lunch, high-protein/low-carbohydrate dinner
	NCDP	**Nocturnal Carbohydrates Diurnal Protein -** High-protein/low-carbohydrate lunch and a high-carbohydrate/low protein dinner
	CT	**Control Diet** macronutrient-balanced **lunch and dinner**
Kessler et al. 2017	**HC/HF diet**	Carbohydrates eaten mostly at breakfast and lunch
	HF/HC diet	Carbohydrates eaten mostly at afternoon snack and dinner
Nouripour et al. 2021	**ST**	Standard Evening Meal
	HC	High-Carbohydrate Evening Meal
	HP	High Protein Evening Meal



*Data for Sofer et al. 2011 were estimated from the provided sample meal menu in the study; Data for breakfast was not provided for the Alves et al. study.

Figure 2. Variability of carbohydrate content as a percentage of energy for intervention meals when CCtoD

Evidence quality appraisal

Though all studies demonstrated a low risk-of-bias regarding funding, conflicts of interest, and ethical standards, overall, they were assessed as having a high risk-of-bias, as per Cochrane guidelines (Table S1, appendix). Furthermore, due to lack of information, risk-of-bias remained unclear for several fields of two studies.[54,70]

Narrative synthesis

As heterogeneity was substantial between studies (Tables 2 and 3, Figure 2) meta-analysis was not performed. Instead, a vote-counting[66(p328)] assessment of outcome measures was conducted (Table 4), and the studies' main findings were narratively summarised (Table 5).

The vote-counting assessment of effects led to several insights. All studies measured FBG (Table 4). When comparing CCtoD with other interventions, non-significant improvements in FBG were observed by one.[69] The shortest study in duration,[67] found no significant change. One[68] found differing glucose responses when comparing healthy and glucose intolerant participants with non-significant improvements in the former but detrimental effects in the latter. Finally, two[54,70] found significant benefit from CCtoD over other interventions.

The three studies[54,69,70] that measured WC all found a reduction from CCtoD. Only two measured blood pressure; one found improvements,[69] the other found no change.[70] Non-significant improvements in triglyceride levels were found in three studies[54,69,70] and remained unchanged in one.[6] Finally, one[54] found significant improvements in HDL-Cholesterol but three studies[54,68,69] found no change.

Inflammation, hunger, satiation and diet-satisfaction, BMI, homeostasis model assessment-estimated insulin resistance (HOMA-IR), HbA1c, lipid-profiles postprandial glucose peaks (PPGP) and energy-metabolism were studied revealing several trends. Notably, four studies[54,70,68,69] found an improvement in overall lipid profiles (total cholesterol, LDL-Cholesterol, HDL-Cholesterol) when CCtoD.

Consuming most carbohydrates at dinner led to a reduction in BMI in three studies[54,69,70] with no change in one.[68] The same studies,[54,69,70] also found improvements in HOMA-IR, with Nouripour et al.,[69] also finding improvements in HbA1C.[69] However, Kessler et al.,[68] found no effect on HOMA-IR in healthy individuals but a detrimental effect in those with IGT or IFG. They[68] also found that CCtoD led to higher PPGP in both NGT and IFG/IGT individuals. In contrast, using continuous glucose monitoring (CGM), Pearce at al.[67] found that it led to lower PPGP.

Alves et al.,[70] was the only study to assess energy-metabolism and energy-expenditure by measuring the incremental area under the curve (iAUC) of energy-expenditure. They found significantly increased diet-induced-thermogenesis (DIT) and overall energy-expenditure.

Sofer et al.,[54] measured inflammation and found improvements in C-reactive protein (CRP), tumour necrosis factor-α (TNF-α), and interleukin-6 (IL-6). CCtoD also benefitted hunger and satiety,[54] measured using a modified version of hunger-satiety scales described by Paul E. Garfinkel,[71(pp343–346)] and using leptin, ghrelin and adiponectin.[55] In contrast, using a questionnaire and a simple scale of 1 to 5 (1=completely-unsatisfied, 5=completely-satisfied), Nouripour et al.,[69] found that it decreased diet-satisfaction.[69]

Table 4. Effects of CCtoD on components of MetS and other measured effects*

Study	Components of Metabolic Syndrome						Other Measured Health Effects								
	WC	SBP	DBP	FBG	TGR	HDL-C	INF	HS	DS	BMI	HOMA-IR	HbA1c	LP	PPGP	EM
Pearce et al., 2008	-	-	-	⇔	-	-	-	-	-	-	-	-	-	⇩	-
Sofer et al., 2011 and 2013	⇩	-	-	⇩	⇩	⇧	CRP ⇩ TNF-a ⇩ IL-6 ⇩	⇩	-	⇩	⇩	-	⇩	-	-
Alves et al., 2014	⇩	⇔	⇔	⇩	⇩*	⇔	-	-	-	⇩	⇩	-	⇩	-	⇧
Kessler et al., 2017 NGT	-	-	-	⇩	⇔	⇔	-	-	-	⇔	⇔	-	⇩	⇧	-
IGT/IFG	-	-	-	⇧	⇔	⇔	-	-	-	⇔	⇔	-	⇩	⇧	-
Nouripour et al., 2021	⇩	⇩	⇩	⇩	⇩	⇔	-	-	⇩	⇩	⇩	⇩	⇩	-	-

WC = Waist-Circumference; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; FBG = Fasting blood glucose; TRG = Triglycerides; HDL-C = HDL cholesterol; INF = Inflammation; HS = Hunger/satiety; DS = Diet satisfaction; BMI = Body mass index; HOMA- IR = Homeostatic Model Assessment for Insulin Resistance; HbA1c= Haemoglobin A1c; LP = Lipid Profile (total cholesterol, LDL-Cholesterol, HDL-Cholesterol); PPGP = postprandial glucose peak; EM = Energy metabolism (diet-induced thermogenesis assessed using indirect calorimetry); CRP = C-Reactive Protein; TNF-a = Tumour necrosis factor; IL-6 = Interleukin 6; NGT = Subjects with normal glucose tolerance; IGT/IFG = Subjects with impaired glucose tolerance/impaired fasting glucose

⇧ = increase in marker; ⇩= decrease in marker; ⇔ = non change in marker; - = Not measured or data not available

*The magnitude and significance of effects was not included due to inconsistency and variance of the effect measures and type of data reported between studies

Overall, the impact of CCtoD was mixed (Table 5). Two studies[67,69] involving participants with T2DM found non-significant benefits. One[54] found no significant change in NGT individuals but detrimental effects on those with IFG or IGT. Finally, two studies[54,70] found several significant benefits in individuals who were overweight or obese. The studies also provide several insights regarding the timing of carbohydrate consumption.

Table 5. Summary of main findings of concentrating carbohydrates to dinner studies

Pearce et al.[67] 2008	In individuals with T2DM: 1. Even distribution of carbohydrates is not favourable. Consuming most carbohydrates at lunch or dinner provides lower excursions of glucose compared to at breakfast. This is evident from the lower postprandial glucose peaks. 2. CCtoD might lead to delayed and sustained postprandial glucose. - This is important because hyperglycaemic spikes have been found to contribute to atherosclerosis.[72–76]
Sofer et al. 2011[54] and 2013	In individuals with a BMI greater than 30 and no other underlying health conditions, CCtoD led to: 1. Greater weight loss. 2. A significant decrease in waist circumference. 3. Improved FBG. 4. Increased insulin sensitivity (measured by HOMA-IR). 5. Improved lipid profiles. 6. Reduction in inflammatory markers (CRP, TNF-α, IL-6). 7. Decreased hunger and improved satiety. 8. CCtoD led to greater satiety and decreased hunger. It specifically increased satiety during the day through its effect on, leptin, ghrelin and adiponectin.
Alves et al.[70] 2014	In individuals with a BMI between 26 and 35 and no other underlying health conditions CCtoD led to: 1. Nocturnal Carbohydrates and Diurnal Protein led to: a. Improved atherogenic indexes. b. Improved energy metabolism. c. Improved glucose tolerance. 2. Eating carbohydrates mostly at lunch led to negative effects on glucose homeostasis. 3. Diurnal carbohydrates nocturnal protein better preserved fat-free mass.
Kessler et al.[68] 2017	1. Individuals with NGT have different metabolic responses to carbohydrates compared to those with IFG and IGT. 2. Consuming carbohydrates mostly at dinner has an unfavourable impact on the glycaemic control of individuals with IFG or IGT. 3. Consuming carbohydrates at breakfast is preferable for those with IFG or IGT.

Nouripour et al.[69] 2021	In individuals with T2DM: 1. A balanced, low-calorie diet (based on individual caloric needs), regardless of the pattern of protein and carbohydrate distribution among the meals, may improve glycaemic control, lipid profiles, blood pressure and anthropometric measurements. 2. Even distribution of macronutrients among the meals was accompanied by higher diet satisfaction. 3. Consuming protein mainly at dinner may have fewer favourable effects than CCtoD and even distribution of macronutrients.

Discussion

To the best of our knowledge, this is the first systematic review considering the impact of CCtoD on MetS and other health outcomes. Though all included studies were assessed as having a high risk-of-bias, this was largely due to the nature of nutrition research rather than lack of methodological quality. The findings of each study are varied and often conflicting revealing complex underlying mechanisms and various influences, perhaps for reasons including clinical and methodological heterogeneity. Inconsistent distribution of carbohydrate intake across the day and variable content at dinner (Figure 2) may have contributed significantly to the mixed findings.

Indeed, the studies that found the most significant benefit CCtoD most strictly.[54,55,70] This is a point acknowledged by Nouripour et al.[69] who opted for less-strict isolation of carbohydrates to dinner due to concerns over diet-adherence but noted that this difference might explain the more significant improvements observed by Alves et al.[70] in fasting insulin and HOMA-IR.

Several effects may underlie this finding. These included the impact of CCtoD on energy-expenditure, by impacting both DIT and physical activity, CR's, including wakefulness and sleep, and altered macronutrient-utilisation, possibly resulting from depleted glycogen reserves.

Alves et al.[70] found that CCtoD increased energy-expenditure by significantly increasing DIT. This may have resulted from the high-protein, low-carbohydrate lunch due to the high energy-cost of protein metabolism,[77–79] and has been observed in other research.[80]

Though these were not measured in any of the studies, CCtoD may also impact several neurotransmitters that affect both wakefulness and sleep. Avoidance of carbohydrates while eating protein-rich meals during the day may increase tyrosine absorption into the brain, affecting catecholamine production, including dopamine.[81] Wakefulness,[82] daytime-activity, motivation and consequently energy-expenditure may, therefore, also be impacted.[81,83] Conversely, carbohydrates-rich meals may increase fatigability[84] and sleepiness and reduce subjective alertness.[85–88] These effects may be undesirable during the day but are usually desirable at night. Mechanisms underlying this may relate to increased tryptophan absorption in the brain.[53,81,85] Tryptophan impacts serotonin production and acts as an intermediary in the production of the pineal-gland hormone melatonin.[89] Melatonin secretion, triggered by the absence of light, is also closely related to CR's and sleep.[90] Therefore, consuming carbohydrates at dinner may impact sleep,[91,53] which in turn, is known to affect the risk of obesity[92–95], energy-expenditure,[96] glycaemic-control,[97] IR,[98,99] MetS,[100] the risk of hypertension,[94] T2DM[94] and CVD.[101,102] Furthermore, improved sleep may lead to increased physical activity.[103] Increases in physical activity, even light, non-sedentary movement,[104] can improve insulin sensitivity.[104–107]

Importantly, research also indicates that low-carbohydrate and ketogenic-type diets improve glycaemic-control and IR.[108–110] Entry into ketosis strongly depends on the depletion of glycogen stores[111] which occurs to a large degree after an overnight fast,[112] and is likely to be accentuated by next day physical activity in the absence of carbohydrate consumption until the dinner meal. It has indeed been suggested that intermittent-energy and carbohydrate-restriction may lead to better insulin sensitivity than energy-restriction alone.[113] This effect would only occur with strict isolation of carbohydrates to dinner and may have impacted the findings of three studies.[67–69]

In essence, MetS[114] is a state of IR in which hyperinsulinemia is needed to maintain normal blood-glucose.[115,116] It is determined using five surrogate biomarkers.[26(p290)] HOMA-IR[117] is a widely used and more direct method of ascertaining levels of IR in research. It is, therefore, noteworthy that CCtoD had a positive impact on HOMA-IR in three studies[54,70,69] (Table 4). IR impairs glucose disposal from the blood,[118] and, therefore, also has an important effect on PPGP.[119]

Pearce et al.[67] found positive effects on PPGP from CCtoD, while Kessler et al.[68] found adverse effects; both studies were of crossover-design but measured glucose in different ways. Pearce et al.,[67] used CGM whereas Kessler et al.,[68] measured FBG in the morning and twice during the day (at 09.00 and 15.40). The ability of CGM to provide detailed data (with readings every 10 seconds) for the ascertainment of the effects of carbohydrate metabolism and the nuances of glycaemic patterns offers many advantages and addresses shortcomings, even of gold-standard measures such as HbA1C.[119–121] This is especially true for measuring postprandial glucose responses.

Increasing evidence suggests that high PPGP contribute significantly to atherosclerosis and CVD risk, especially in individuals with IFG, IGT and T2DM.[72–76] Links between atherosclerotic plaque formation,[122] IR and inflammation have long been understood,[123] and may relate to oxidative stress and endothelial inflammation.[124–126] Inflammation may be an important risk factor in CVD and T2DM.[127–129] Therefore, the finding by Sofer et al.,[54] that CCtoD significantly improved several biomarkers of inflammation merits further investigation. Given the possible connections between IR, PPGP, inflammation and carbohydrate-timing, their simultaneous investigation may be promising. Even though the nature of CGM makes its use impractical in longer-term studies, its strategic inclusion and use in future studies will offer unique insights.

Finally, research suggests that an increased physiological sensation of hunger is a primary reason for the failure of weight-loss efforts and diet adherence.[130,131] It is therefore noteworthy that two studies[54,55,69] considered hunger, satiety and diet satisfaction reached different conclusions. Sofer et al.,[54,55] found that CCtoD led to leptin (an anorexigenic, satiation-hormone) staying higher for longer,[55] while ghrelin (a main orexigenic-hormone) peaked in the evening rather than the afternoon.[55] These hormones are fundamental in the homeostatic regulation of both appetite and body weight.[131–135] Notably, adiponectin, widely thought to connect MetS to IR and obesity and to increase insulin sensitivity,[136–138] increased significantly leading to significant reductions in the sensation of hunger and increased satiety. Conversely, Nouripour et al., [69] found that diet satisfaction was maximised with even distribution of carbohydrates. Given the widespread difficulties in weight-loss efforts and diet-adherence, and the importance of hunger,[139–142] this effect merits further investigation.

Study Limitations

An important limitation of this review is that a meta-analysis was not possible due to the heterogeneous nature of the included studies; a common problem in systematic reviews with few relevant studies.[143] Though a vote-counting procedure was employed indicating the direction of effects, the differences between interventions and studies did not allow for meaningful comparison of p-values. Consequently, the significance of the findings could not be assessed or compared.[66(pp321-347)] Reaching clear conclusions regarding CCtoD was, therefore, impossible.

Several other considerations also merit mention. First of all, the review did not consider food selection. Though the timing of macronutrient consumption is important,[39] their source is a fundamental determinant of their effect on MetS and overall health.[144,145]

Moreover, though chrononutrition considers the timing of food or macronutrient intake,[50] this review focused on the general notion of breakfast, lunch, and dinner without considering the time these meals were consumed. The actual time of meals is significant,[50] with shift work being the most prominent example of detrimental effects.[146–149] Individual differences in chronotype may also be a factor.[39]

Finally, the timing of calorie consumption is significant. This is perhaps best illustrated by the adage attributed to philosopher Maimonides (1135–1204), "Eat breakfast like a king, lunch like a prince and dine like a pauper", the wisdom of which is supported by modern research.[39,150]

Conclusion

This review investigated the effect of CCtoD on MetS and other health outcomes. The varied and often conflicting findings reveal complex underlying mechanisms and various influences. The clinical and methodological diversity of the studies may have played a significant role in the divergent findings. Differing quantities of carbohydrates used in the studies when CCtoD, varying characteristics of study participants, and the duration of the studies are likely to have impacted the findings significantly. Therefore, no clear conclusions regarding the effects of CCtoD could be reached.

Nevertheless, a common thread through all the studies is that the timing of carbohydrate consumption led to measurable effects on several health biomarkers. Therefore, further investigation into the impact of CCtoD is merited. A standard definition of CCtoD is needed. Furthermore, the simultaneous consideration of several biomarkers and methods appears promising. Specifically, while measuring the components of MetS, concurrently considering HOMA-IR, PPGP using CGM, inflammation, energy-expenditure, sleep and hunger and satiety through the analysis of leptin, ghrelin and adiponectin.

Funding

No external funding.

Conflicts of interest

No conflicts of interest to declare.

Ethical considerations

The study protocol was published on PROSPERO on 21st June 2021.
https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=259591

References

1. Hruby A, Hu FB. The Epidemiology of Obesity: A Big Picture. *Pharmacoeconomics*. 2015;33(7):673-689. doi:10.1007/s40273-014-0243-x

2. WHO. Obesity and overweight. Published 2020. Accessed March 14, 2020. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

3. Benjamin EJ, Virani SS, Callaway CW, et al. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. *Circulation*. 2018;137(12):e67-e492. doi:10.1161/CIR.0000000000000558

4. Roth GA, Johnson C, Abajobir A, et al. Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. *Journal of the American College of Cardiology*. 2017;70(1):1-25. doi:10.1016/j.jacc.2017.04.052

5. Roth Gregory A., Mensah George A., Johnson Catherine O., et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019. *Journal of the American College of Cardiology*. 2020;76(25):2982-3021. doi:10.1016/j.jacc.2020.11.010

6. Olvera Lopez E, Ballard BD, Jan A. Cardiovascular Disease. In: *StatPearls*. StatPearls Publishing; 2021. Accessed March 16, 2021. http://www.ncbi.nlm.nih.gov/books/NBK535419/

7. McDermott MM. The International Pandemic of Chronic Cardiovascular Disease. *JAMA*. 2007;297(11):1253-1255. doi:10.1001/jama.297.11.1253

8. King H, Aubert R, Herman WH. Global Burden of Diabetes, 1995-2025: Prevalence, numerical estimates, and projections. *Diabetes care*. 1998;21:1414-1431. doi:10.2337/diacare.21.9.1414

9. van Dieren S, Beulens JWJ, van der Schouw YT, Grobbee DE, Neal B. The global burden of diabetes and its complications: an emerging pandemic. *Eur J Cardiovasc Prev Rehabil*. 2010;17 Suppl 1:S3-8. doi:10.1097/01.hjr.0000368191.86614.5a

10. Colhoun HM, McKnight J. Diabetes in Scotland: a rising tide. *The Lancet Diabetes & Endocrinology*. 2020;8(5):375-376. doi:10.1016/S2213-8587(20)30124-8

11. Number of people with diabetes reaches 4.8 million. Diabetes UK. Accessed April 10, 2021. https://www.diabetes.org.uk/about_us/news/diabetes-prevalence-2019

12. Kanavos P, Schurer W. Diabetes expenditure, burden of disease and management in 5 EU countries.

13. Colagiuri R. Diabetes: a pandemic, a development issue or both? *Expert Review of Cardiovascular Therapy*. 2010;8(3):305-309. doi:10.1586/erc.10.12

14. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: A systematic review and meta-analysis. *BMC Public Health*. 2009;9(1):88. doi:10.1186/1471-2458-9-88

15. Carbone S, Canada JM, Billingsley HE, Siddiqui MS, Elagizi A, Lavie CJ. Obesity paradox in cardiovascular disease: where do we stand? *Vasc Health Risk Manag*. 2019;15:89-100. doi:10.2147/VHRM.S168946

16. Cercato C, Fonseca FA. Cardiovascular risk and obesity. *Diabetology & Metabolic Syndrome*. 2019;11(1):74. doi:10.1186/s13098-019-0468-0

17. Ling S, Brown K, Miksza JK, et al. Association of Type 2 Diabetes With Cancer: A Meta-analysis With Bias Analysis for Unmeasured Confounding in 151 Cohorts Comprising 32 Million People. *Diabetes Care*. 2020;43(9):2313-2322. doi:10.2337/dc20-0204

18. Wolin KY, Carson K, Colditz GA. Obesity and Cancer. *Oncologist*. 2010;15(6):556-565. doi:10.1634/theoncologist.2009-0285

19. WHO reveals leading causes of death and disability worldwide: 2000-2019. Accessed May 26, 2021. https://www.who.int/news/item/09-12-2020-who-reveals-leading-causes-of-death-and-disability-worldwide-2000-2019

20. The top 10 causes of death. Accessed May 26, 2021. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

21. Dunbar SB, Khavjou OA, Bakas T, et al. Projected Costs of Informal Caregiving for Cardiovascular Disease: 2015 to 2035: A Policy Statement From the American Heart Association. *Circulation*. 2018;137(19):e558-e577. doi:10.1161/CIR.0000000000000570

22. Editor. The cost of diabetes to the NHS. Diabetes. Published January 15, 2019. Accessed April 3, 2021. https://www.diabetes.co.uk/cost-of-diabetes.html

23. Wilson PWF, D'Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. *Circulation*. 2005;112(20):3066-3072. doi:10.1161/CIRCULATIONAHA.105.539528

24. Meigs JB. Epidemiology of the Metabolic Syndrome, 2002. *THE AMERICAN JOURNAL OF MANAGED CARE*. 2002;8(11):10.

25. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet*. 2005;365(9468):1415-1428. doi:10.1016/S0140-6736(05)66378-7

26. Gropper SAS, Smith JL, Carr TP. *Advanced Nutrition and Human Metabolism*. Seventh edition. Cengage Learning; 2018.

27. Tenenbaum A, Fisman EZ. "The metabolic syndrome... is dead": These reports are an exaggeration. *Cardiovascular Diabetology*. 2011;10(1):11. doi:10.1186/1475-2840-10-11

28. Stern MP, Williams K, Haffner SM. Identification of persons at high risk for type 2 diabetes mellitus: do we need the oral glucose tolerance test? *Ann Intern Med*. 2002;136(8):575-581. doi:10.7326/0003-4819-136-8-200204160-00006

29. Gabir MM, Hanson RL, Dabelea D, et al. The 1997 American Diabetes Association and 1999 World Health Organization criteria for hyperglycemia in the diagnosis and prediction of diabetes. *Diabetes Care*. 2000;23(8):1108-1112. doi:10.2337/diacare.23.8.1108

30. Nathan DM, Davidson MB, DeFronzo RA, et al. Impaired Fasting Glucose and Impaired Glucose Tolerance: Implications for care. *Diabetes Care*. 2007;30(3):753-759. doi:10.2337/dc07-9920

31. Gu K, Cowie CC, Harris MI. Diabetes and decline in heart disease mortality in US adults. *JAMA*. 1999;281(14):1291-1297. doi:10.1001/jama.281.14.1291

32. Martín-Timón I, Sevillano-Collantes C, Segura-Galindo A, del Cañizo-Gómez FJ. Type 2 diabetes and cardiovascular disease: Have all risk factors the same strength? *World J Diabetes*. 2014;5(4):444-470. doi:10.4239/wjd.v5.i4.444

33. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. *Cardiovascular Diabetology*. 2018;17(1):83. doi:10.1186/s12933-018-0728-6

34. McGill HC, McMahan CA, Gidding SS. Preventing Heart Disease in the 21st Century: Implications of the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Study. *Circulation*. 2008;117(9):1216-1227. doi:10.1161/CIRCULATIONAHA.107.717033

35. Pérez-Martínez P, Mikhailidis DP, Athyros VG, et al. Lifestyle recommendations for the prevention and management of metabolic syndrome: an international panel recommendation. *Nutr Rev*. 2017;75(5):307-326. doi:10.1093/nutrit/nux014

36. Wycherley TP, Clifton PM, Noakes M, Brinkworth GD. Weight loss on a structured hypocaloric diet with or without exercise improves emotional distress and quality of life in overweight and obese patients with type 2 diabetes. *J Diabetes Investig*. 2014;5(1):94-98. doi:10.1111/jdi.12120

37. Davis NJ, Tomuta N, Isasi CR, Leung V, Wylie-Rosett J. Diabetes-specific quality of life after a low-carbohydrate and low-fat dietary intervention. *Diabetes Educ*. 2012;38(2):250-255. doi:10.1177/0145721711436132

38. 2. Classification and Diagnosis of Diabetes | Diabetes Care. Accessed September 24, 2021. https://care.diabetesjournals.org/content/39/Supplement_1/S13

39. Xiao Q, Garaulet M, Scheer FAJL. Meal timing and obesity; interactions with macronutrient intake and chronotype. *Int J Obes (Lond)*. 2019;43(9):1701-1711. doi:10.1038/s41366-018-0284-x

40. Sofer S, Stark AH, Madar Z. Nutrition Targeting by Food Timing: Time-Related Dietary Approaches to Combat Obesity and Metabolic Syndrome. *Adv Nutr*. 2015;6(2):214-223. doi:10.3945/an.114.007518

41. Nouripour F, Mazloom Z, Fararouei M, Zamani A. Effect of protein and carbohydrate distribution among meals on quality of life, sleep quality, inflammation, and oxidative stress in patients with type 2 diabetes: A single-blinded randomized controlled trial. *Food Science & Nutrition*. 2021;n/a(n/a). doi:10.1002/fsn3.2570

42. Kessler K, Pivovarova-Ramich O. Meal Timing, Aging, and Metabolic Health. *Int J Mol Sci*. 2019;20(8):1911. doi:10.3390/ijms20081911

43. Laermans J, Depoortere I. Chronobesity: role of the circadian system in the obesity epidemic: Role of circadian clocks in obesity. *Obesity Reviews*. 2016;17(2):108-125. doi:10.1111/obr.12351

44. Vitaterna MH, Takahashi JS, Turek FW. Overview of Circadian Rhythms. *Alcohol Res Health*. 2001;25(2):85-93.

45. Meijer JH, Watanabe K, Schaap J, Albus H, Détári L. Light Responsiveness of the Suprachiasmatic Nucleus: Long-Term Multiunit and Single-Unit Recordings in Freely Moving Rats. *J Neurosci*. 1998;18(21):9078-9087. doi:10.1523/JNEUROSCI.18-21-09078.1998

46. Paul KN, Saafir TB, Tosini G. The role of retinal photoreceptors in the regulation of circadian rhythms. *Rev Endocr Metab Disord*. 2009;10(4):271-278. doi:10.1007/s11154-009-9120-x

47. Oosterman JE, Kalsbeek A, la Fleur SE, Belsham DD. Impact of nutrients on circadian rhythmicity. *Am J Physiol Regul Integr Comp Physiol*. 2015;308(5):R337-R350. doi:10.1152/ajpregu.00322.2014

48. Damiola F, Le Minh N, Preitner N, Kornmann B, Fleury-Olela F, Schibler U. Restricted feeding uncouples circadian oscillators in peripheral tissues from the central pacemaker in the suprachiasmatic nucleus. *Genes Dev*. 2000;14(23):2950-2961. doi:10.1101/gad.183500

49. Eckel-Mahan K, Sassone-Corsi P. Metabolism and the circadian clock converge. *Physiol Rev*. 2013;93(1):107-135. doi:10.1152/physrev.00016.2012

50. Ruddick-Collins LC, Morgan PJ, Johnstone AM. Mealtime: A circadian disruptor and determinant of energy balance? *Journal of Neuroendocrinology*. 2020;32(7):e12886. doi:10.1111/jne.12886

51. Segers A, Depoortere I. Circadian clocks in the digestive system. *Nat Rev Gastroenterol Hepatol*. 2021;18(4):239-251. doi:10.1038/s41575-020-00401-5

52. Henry CJ, Kaur B, Quek RYC. Chrononutrition in the management of diabetes. *Nutr Diabetes*. 2020;10:6. doi:10.1038/s41387-020-0109-6

53. Vlahoyiannis A, Giannaki CD, Sakkas GK, Aphamis G, Andreou E. A Systematic Review, Meta-Analysis and Meta-Regression on the Effects of Carbohydrates on Sleep. *Nutrients*. 2021;13(4). doi:10.3390/nu13041283

54. Sofer S, Eliraz A, Kaplan S, et al. Greater Weight Loss and Hormonal Changes After 6 Months Diet With Carbohydrates Eaten Mostly at Dinner. *Obesity*. 2011;19(10):2006-2014. doi:10.1038/oby.2011.48

55. Sofer S, Eliraz A, Kaplan S, et al. Changes in daily leptin, ghrelin and adiponectin profiles following a diet with carbohydrates eaten at dinner in obese subjects. *Nutrition, Metabolism and Cardiovascular Diseases*. 2013;23(8):744-750. doi:10.1016/j.numecd.2012.04.008

56. Sofer S, Eliraz A, Madar Z, Froy O. Concentrating carbohydrates before sleep improves feeding regulation and metabolic and inflammatory parameters in mice. *Molecular and Cellular Endocrinology*. 2015;414:29-41. doi:10.1016/j.mce.2015.06.032

57. Sofer S, Stark A, Fink G, Madar Z. Chapter 35 - A Diet with Carbohydrates Eaten Primarily at Dinner: An Innovative, Nutritional Approach to End the Vicious Cycle of Abdominal Obesity. In: Watson RR, ed. *Nutrition in the Prevention and Treatment of Abdominal Obesity*. Academic Press; 2014:401-414. doi:10.1016/B978-0-12-407869-7.00035-0

58. Buyken AE, Mela DJ, Dussort P, et al. Dietary carbohydrates: a review of international recommendations and the methods used to derive them. *Eur J Clin Nutr*. 2018;72(12):1625-1643. doi:10.1038/s41430-017-0035-4

59. Oh R, Gilani B, Uppaluri KR. Low Carbohydrate Diet. In: *StatPearls*. StatPearls Publishing; 2021. Accessed May 8, 2021. http://www.ncbi.nlm.nih.gov/books/NBK537084/

60. El Ghoch M, Calugi S, Dalle Grave R. The Effects of Low-Carbohydrate Diets on Psychosocial Outcomes in Obesity/Overweight: A Systematic Review of Randomized, Controlled Studies. *Nutrients*. 2016;8(7). doi:10.3390/nu8070402

61. Accurso A, Bernstein RK, Dahlqvist A, et al. Dietary carbohydrate restriction in type 2 diabetes mellitus and metabolic syndrome: time for a critical appraisal. *Nutr Metab (Lond)*. 2008;5:9. doi:10.1186/1743-7075-5-9

62. Masood W, Annamaraju P, Uppaluri KR. Ketogenic Diet. In: *StatPearls*. StatPearls Publishing; 2021. Accessed May 8, 2021. http://www.ncbi.nlm.nih.gov/books/NBK499830/

63. Alves RDM, de Oliveira FCE, Hermsdorff HHM, et al. Eating carbohydrate mostly at lunch and protein mostly at dinner within a covert hypocaloric diet influences morning glucose homeostasis in overweight/obese men. *Eur J Nutr*. 2014;53(1):49-60. doi:10.1007/s00394-013-0497-7

64. Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ*. 2021;372:n160. doi:10.1136/bmj.n160

65. Cochrane Data Extraction Forms. Accessed November 29, 2020. https://dplp.cochrane.org/data-extraction-forms

66. Higgins JPT, Cochrane Collaboration, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Second edition. Wiley-Blackwell; 2020.

67. Pearce KL, Noakes M, Keogh J, Clifton PM. Effect of carbohydrate distribution on postprandial glucose peaks with the use of continuous glucose monitoring in type 2 diabetes. *Am J Clin Nutr*. 2008;87(3):638-644.

68. Kessler K, Hornemann S, Petzke KJ, et al. The effect of diurnal distribution of carbohydrates and fat on glycaemic control in humans: a randomized controlled trial. *Sci Rep*. 2017;7:44170. doi:10.1038/srep44170

69. Nouripour F, Mazloom Z, Fararouei M, Zamani A. Protein and carbohydrate distribution among the meals: effect on metabolic parameters of patients with type 2 diabetes: a single-blinded randomised controlled trial. *British Journal of Nutrition*. 2021;125(9):1007-1016. doi:10.1017/S0007114520001944

70. Alves RDM, de Oliveira FCE, Hermsdorff HHM, et al. Eating carbohydrate mostly at lunch and protein mostly at dinner within a covert hypocaloric diet influences morning glucose homeostasis in overweight/obese men. *Eur J Nutr*. 2014;53(1):49-60. doi:10.1007/s00394-013-0497-7

71. Corcoran K, Fischer J. *Measures for Clinical Practice: A Sourcebook, Volume 2, Adults*. Revised, Updated, Subsequent edition. Free Press; 2000.

72. Hanssen NMJ, Kraakman MJ, Flynn MC, Nagareddy PR, Schalkwijk CG, Murphy AJ. Postprandial Glucose Spikes, an Important Contributor to Cardiovascular Disease in Diabetes? *Frontiers in Cardiovascular Medicine*. 2020;7:168. doi:10.3389/fcvm.2020.570553

73. Cavalot F, Petrelli A, Traversa M, et al. Postprandial blood glucose is a stronger predictor of cardiovascular events than fasting blood glucose in type 2 diabetes mellitus, particularly in women: lessons from the San Luigi Gonzaga Diabetes Study. *J Clin Endocrinol Metab*. 2006;91(3):813-819. doi:10.1210/jc.2005-1005

74. Hanefeld M, Fischer S, Julius U, et al. Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study, 11-year follow-up. *Diabetologia*. 1996;39(12):1577-1583. doi:10.1007/s001250050617

75. Bonora E. Postprandial peaks as a risk factor for cardiovascular disease: epidemiological perspectives. *Int J Clin Pract Suppl*. 2002;(129):5-11.

76. Garber AJ. Postprandial dysmetabolism and the heart. *Heart Fail Clin*. 2012;8(4):563-573. doi:10.1016/j.hfc.2012.06.004

77. Halton TL, Hu FB. The effects of high protein diets on thermogenesis, satiety and weight loss: a critical review. *J Am Coll Nutr*. 2004;23(5):373-385. doi:10.1080/07315724.2004.10719381

78. Hermsdorff HHM, Volp ACP, Bressan J. [Macronutrient profile affects diet-induced thermogenesis and energy intake]. *Arch Latinoam Nutr*. 2007;57(1):33-42.

79. Westerterp-Plantenga MS. Protein intake and energy balance. *Regul Pept*. 2008;149(1-3):67-69. doi:10.1016/j.regpep.2007.08.026

80. Ebbeling CB, Feldman HA, Klein GL, et al. Effects of a low carbohydrate diet on energy expenditure during weight loss maintenance: randomized trial. *BMJ*. 2018;363:k4583. doi:10.1136/bmj.k4583

81. Wurtman RJ, Wurtman JJ, Regan MM, McDermott JM, Tsay RH, Breu JJ. Effects of normal meals rich in carbohydrates or proteins on plasma tryptophan and tyrosine ratios. *Am J Clin Nutr*. 2003;77(1):128-132. doi:10.1093/ajcn/77.1.128

82. Fernstrom JD. Carbohydrate Ingestion and Brain Serotonin Synthesis: Relevance to a Putative Control Loop for Regulating CarbohYdrate Ingestion, and Effects of Aspartame Consumption. :7.

83. Marriott BM. *Food Components to Enhance Performance: An Evaluation of Potential Performance-Enhancing Food Components for Operational Rations*. National Academy Press; 1994. Accessed February 3, 2021. http://site.ebrary.com/id/10071530

84. Pharr JR. Carbohydrate Consumption and Fatigue: A Review. :8.

85. Spring B. Recent Research on the Behavioral Effects of Tryptophan and Carbohydrate. *Nutr Health*. 1984;3(1-2):55-67. doi:10.1177/026010608400300204

86. Melaku YA, Reynolds AC, Gill TK, Appleton S, Adams R. Association between Macronutrient Intake and Excessive Daytime Sleepiness: An Iso-Caloric Substitution Analysis from the North West Adelaide Health Study. *Nutrients*. 2019;11(10):2374. doi:10.3390/nu11102374

87. Wells AS, Read NW, Craig A. Influences of dietary and intraduodenal lipid on alertness, mood, and sustained concentration. *Br J Nutr*. 1995;74(1):115-123. doi:10.1079/bjn19950111

88. Lyons PM, Truswell AS. Serotonin precursor influenced by type of carbohydrate meal in healthy adults. *Am J Clin Nutr*. 1988;47(3):433-439. doi:10.1093/ajcn/47.3.433

89. Zimmermann RC, McDougle CJ, Schumacher M, Olcese J, Heninger GR, Price LH. Urinary 6-hydroxymelatonin sulfate as a measure of melatonin secretion during acute tryptophan depletion. *Psychoneuroendocrinology*. 1993;18(8):567-578. doi:10.1016/0306-4530(93)90034-I

90. Tordjman S, Chokron S, Delorme R, et al. Melatonin: Pharmacology, Functions and Therapeutic Benefits. *Curr Neuropharmacol*. 2017;15(3):434-443. doi:10.2174/1570159X14666161228122115

91. Afaghi A, O'Connor H, Chow CM. High-glycemic-index carbohydrate meals shorten sleep onset. *The American Journal of Clinical Nutrition*. 2007;85(2):426-430. doi:10.1093/ajcn/85.2.426

92. Buxton OM, Marcelli E. Short and long sleep are positively associated with obesity, diabetes, hypertension, and cardiovascular disease among adults in the United States. *Soc Sci Med*. 2010;71(5):1027-1036. doi:10.1016/j.socscimed.2010.05.041

93. Gupta NK, Mueller WH, Chan W, Meininger JC. Is obesity associated with poor sleep quality in adolescents? *American Journal of Human Biology*. 2002;14(6):762-768. doi:https://doi.org/10.1002/ajhb.10093

94. Schlafer O, Wenzel V, Högl B. [Sleep disorders among physicians on shift work]. *Anaesthesist*. 2014;63(11):844-851. doi:10.1007/s00101-014-2374-z

95. Taheri S, Lin L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. *PLoS Med*. 2004;1(3):e62. doi:10.1371/journal.pmed.0010062

96. Markwald RR, Melanson EL, Smith MR, et al. Impact of insufficient sleep on total daily energy expenditure, food intake, and weight gain. *Proc Natl Acad Sci U S A*. 2013;110(14):5695-5700. doi:10.1073/pnas.1216951110

97. Lee SWH, Ng KY, Chin WK. The impact of sleep amount and sleep quality on glycemic control in type 2 diabetes: A systematic review and meta-analysis. *Sleep Medicine Reviews*. 2017;31:91-101. doi:10.1016/j.smrv.2016.02.001

98. Donga E, van Dijk M, van Dijk JG, et al. A single night of partial sleep deprivation induces insulin resistance in multiple metabolic pathways in healthy subjects. *J Clin Endocrinol Metab*. 2010;95(6):2963-2968. doi:10.1210/jc.2009-2430

99. Reutrakul S, Van Cauter E. Sleep influences on obesity, insulin resistance, and risk of type 2 diabetes. *Metabolism*. 2018;84:56-66. doi:10.1016/j.metabol.2018.02.010

100. Chattu VK, Manzar MdD, Kumary S, Burman D, Spence DW, Pandi-Perumal SR. The Global Problem of Insufficient Sleep and Its Serious Public Health Implications. *Healthcare (Basel)*. 2018;7(1). doi:10.3390/healthcare7010001

101. Janszky I, Ljung R. Shifts to and from daylight saving time and incidence of myocardial infarction. *N Engl J Med*. 2008;359(18):1966-1968. doi:10.1056/NEJMc0807104

102. Ayas NT, White DP, Manson JE, et al. A prospective study of sleep duration and coronary heart disease in women. *Arch Intern Med*. 2003;163(2):205-209. doi:10.1001/archinte.163.2.205

103. Kline CE. The bidirectional relationship between exercise and sleep: Implications for exercise adherence and sleep improvement. *Am J Lifestyle Med*. 2014;8(6):375-379. doi:10.1177/1559827614544437

104. Yates T, Henson J, Edwardson C, et al. Objectively measured sedentary time and associations with insulin sensitivity: Importance of reallocating sedentary time to physical activity. *Preventive Medicine*. 2015;76:79-83. doi:10.1016/j.ypmed.2015.04.005

105. Mayer-Davis EJ, D'Agostino J Ralph, Karter AJ, et al. Intensity and Amount of Physical Activity in Relation to Insulin SensitivityThe Insulin Resistance Atherosclerosis Study. *JAMA*. 1998;279(9):669-674. doi:10.1001/jama.279.9.669

106. Balkau B, Mhamdi L, Oppert JM, et al. Physical Activity and Insulin Sensitivity. *Diabetes*. 2008;57(10):2613-2618. doi:10.2337/db07-1605

107. Mann S, Beedie C, Balducci S, et al. Changes in insulin sensitivity in response to different modalities of exercise: a review of the evidence. *Diabetes/Metabolism Research and Reviews*. 2014;30(4):257-268. doi:10.1002/dmrr.2488

108. Ioanna Partsalaki, Karvela A, Spiliotis BE. Metabolic impact of a ketogenic diet compared to a hypocaloric diet in obese children and adolescents. *Journal of Pediatric Endocrinology and Metabolism*. 2012;25(7-8):697-704. doi:10.1515/jpem-2012-0131

109. Westman EC, Yancy WS, Mavropoulos JC, Marquart M, McDuffie JR. The effect of a low-carbohydrate, ketogenic diet versus a low-glycemic index diet on glycemic control in type 2 diabetes mellitus. *Nutrition & Metabolism*. 2008;5(1):36. doi:10.1186/1743-7075-5-36

110. Yuan X, Wang J, Yang S, et al. Effect of the ketogenic diet on glycemic control, insulin resistance, and lipid metabolism in patients with T2DM: a systematic review and meta-analysis. *Nutr Diabetes*. 2020;10(1):1-8. doi:10.1038/s41387-020-00142-z

111. Masood W, Annamaraju P, Uppaluri KR. Ketogenic Diet. In: *StatPearls*. StatPearls Publishing; 2021. Accessed October 22, 2021. http://www.ncbi.nlm.nih.gov/books/NBK499830/

112. El Bacha T, Luz M, Da Poian A. Dynamic adaptation of nutrient utilization in humans. *Nat Educ*. 2010;3(8).

113. Harvie M, Wright C, Pegington M, et al. The effect of intermittent energy and carbohydrate restriction v. daily energy restriction on weight loss and metabolic disease risk markers in overweight women. *British Journal of Nutrition*. 2013;110(8):1534-1547. doi:10.1017/S0007114513000792

114. Saklayen MG. The Global Epidemic of the Metabolic Syndrome. *Curr Hypertens Rep*. 2018;20(2):12. doi:10.1007/s11906-018-0812-z

115. Day C. Metabolic syndrome, or What you will: definitions and epidemiology. *Diabetes and Vascular Disease Research*. 2007;4(1):32-38. doi:10.3132/dvdr.2007.003

116. Reaven G. The metabolic syndrome or the insulin resistance syndrome? Different names, different concepts, and different goals. *Endocrinology and Metabolism Clinics of North America*. 2004;33(2):283-303. doi:10.1016/j.ecl.2004.03.002

117. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28(7):412-419. doi:10.1007/BF00280883

118. Freeman AM, Pennings N. Insulin Resistance. In: *StatPearls*. StatPearls Publishing; 2021. Accessed October 12, 2021. http://www.ncbi.nlm.nih.gov/books/NBK507839/

119. Hall H, Perelman D, Breschi A, et al. Glucotypes reveal new patterns of glucose dysregulation. *PLoS Biol*. 2018;16(7):e2005143. doi:10.1371/journal.pbio.2005143

120. Ajjan RA. How Can We Realize the Clinical Benefits of Continuous Glucose Monitoring? *Diabetes Technol Ther*. 2017;19(Suppl 2):S-27-S-36. doi:10.1089/dia.2017.0021

121. Lind M, Tuomilehto J, Uusitupa M, et al. The Association between HbA1c, Fasting Glucose, 1-Hour Glucose and 2-Hour Glucose during an Oral Glucose Tolerance Test and Cardiovascular Disease in Individuals with Elevated Risk for Diabetes. *PLoS One*. 2014;9(10):e109506. doi:10.1371/journal.pone.0109506

122. Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of Plaque Formation and Rupture. *Circ Res*. 2014;114(12):1852-1866. doi:10.1161/CIRCRESAHA.114.302721

123. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. *J Clin Invest*. 2006;116(7):1793-1801. doi:10.1172/JCI29069

124. Gerich JE. Clinical significance, pathogenesis, and management of postprandial hyperglycemia. *Arch Intern Med*. 2003;163(11):1306-1316. doi:10.1001/archinte.163.11.1306

125. Tushuizen ME, Diamant M, Heine RJ. Postprandial dysmetabolism and cardiovascular disease in type 2 diabetes. *Postgrad Med J*. 2005;81(951):1-6. doi:10.1136/pgmj.2004.020511

126. Blaak EE, Antoine JM, Benton D, et al. Impact of postprandial glycaemia on health and prevention of disease. *Obes Rev*. 2012;13(10):923-984. doi:10.1111/j.1467-789X.2012.01011.x

127. Haffner SM. The Metabolic Syndrome: Inflammation, Diabetes Mellitus, and Cardiovascular Disease. *The American Journal of Cardiology*. 2006;97(2, Supplement 1):3-11. doi:10.1016/j.amjcard.2005.11.010

128. Tsalamandris S, Antonopoulos AS, Oikonomou E, et al. The Role of Inflammation in Diabetes: Current Concepts and Future Perspectives. *Eur Cardiol*. 2019;14(1):50-59. doi:10.15420/ecr.2018.33.1

129. Dregan A, Charlton J, Chowienczyk P, Gulliford MC. Chronic Inflammatory Disorders and Risk of Type 2 Diabetes Mellitus, Coronary Heart Disease, and Stroke. *Circulation*. 2014;130(10):837-844. doi:10.1161/CIRCULATIONAHA.114.009990

130. Polidori D, Sanghvi A, Seeley RJ, Hall KD. How Strongly Does Appetite Counter Weight Loss? Quantification of the Feedback Control of Human Energy Intake. *Obesity*. 2016;24(11):2289-2295. doi:https://doi.org/10.1002/oby.21653

131. Ferraro ZM, Patterson S, Chaput JP. Unhealthy Weight Control Practices: Culprits and Clinical Recommendations. *Clin Med Insights Endocrinol Diabetes*. 2015;8:7-11. doi:10.4137/CMED.S23060

132. Weiss EC, Galuska DA, Kettel Khan L, Gillespie C, Serdula MK. Weight regain in U.S. adults who experienced substantial weight loss, 1999-2002. *Am J Prev Med*. 2007;33(1):34-40. doi:10.1016/j.amepre.2007.02.040

133. Long-Term Persistence of Hormonal Adaptations to Weight Loss | NEJM. Accessed May 9, 2021. https://www.nejm.org/doi/full/10.1056/nejmoa1105816

134. Benelam B. Satiation, satiety and their effects on eating behaviour. *Nutrition Bulletin*. 2009;34(2):126-173. doi:https://doi.org/10.1111/j.1467-3010.2009.01753.x

135. Klok MD, Jakobsdottir S, Drent ML. The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. *Obesity Reviews*. 2007;8(1):21-34. doi:https://doi.org/10.1111/j.1467-789X.2006.00270.x

136. Matsuzawa Y. Establishment of a concept of visceral fat syndrome and discovery of adiponectin. *Proc Jpn Acad Ser B Phys Biol Sci*. 2010;86(2):131-141. doi:10.2183/pjab.86.131

137. Koh SB, Yoon J, Kim JY, et al. Relationships between Serum Adiponectin with Metabolic Syndrome and Components of Metabolic Syndrome in Non-Diabetic Koreans: ARIRANG Study. *Yonsei Medical Journal*. 2011;52(2):234-241. doi:10.3349/ymj.2011.52.2.234

138. Gil-Campos M, Cañete R, Gil A. Adiponectin, the missing link in insulin resistance and obesity. *Clinical Nutrition*. 2004;23(5):963-974. doi:10.1016/j.clnu.2004.04.010

139. Pasman WJ, Saris WH, Westerterp-Plantenga MS. Predictors of weight maintenance. *Obes Res*. 1999;7(1):43-50. doi:10.1002/j.1550-8528.1999.tb00389.x

140. Gibson AA, Sainsbury A. Strategies to Improve Adherence to Dietary Weight Loss Interventions in Research and Real-World Settings. *Behav Sci (Basel)*. 2017;7(3):44. doi:10.3390/bs7030044

141. Piech RM, Pastorino MT, Zald DH. All I saw was the cake. Hunger effects on attentional capture by visual food cues. *Appetite*. 2010;54(3):579-582. doi:10.1016/j.appet.2009.11.003

142. Grodstein F, Levine R, Troy L, Spencer T, Colditz GA, Stampfer MJ. Three-year follow-up of participants in a commercial weight loss program. Can you keep it off? *Arch Intern Med*. 1996;156(12):1302-1306.

143. Statistical heterogeneity in systematic reviews of clinical trials: a critical appraisal of guidelines and practice. *J Health Serv Res Policy*. 2002;7(1):51-61. doi:10.1258/1355819021927674

144. Mozaffarian Dariush. Dietary and Policy Priorities for Cardiovascular Disease, Diabetes, and Obesity. *Circulation*. 2016;133(2):187-225. doi:10.1161/CIRCULATIONAHA.115.018585

145. Panagiotakos DB, Pitsavos C, Skoumas Y, Stefanadis C. The Association between Food Patterns and the Metabolic Syndrome Using Principal Components Analysis: The ATTICA Study. *Journal of the American Dietetic Association*. 2007;107(6):979-987. doi:10.1016/j.jada.2007.03.006

146. Sun M, Feng W, Wang F, et al. Meta-analysis on shift work and risks of specific obesity types. *Obes Rev*. 2018;19(1):28-40. doi:10.1111/obr.12621

147. Ramin C, Devore EE, Wang W, Pierre-Paul J, Wegrzyn LR, Schernhammer ES. Night shift work at specific age ranges and chronic disease risk factors. *Occup Environ Med*. 2015;72(2):100-107. doi:10.1136/oemed-2014-102292

148. Peplonska B, Bukowska A, Sobala W. Association of Rotating Night Shift Work with BMI and Abdominal Obesity among Nurses and Midwives. *PLoS One*. 2015;10(7):e0133761. doi:10.1371/journal.pone.0133761

149. Marquezea EC, Lemosa LC, Soaresa N, Lorenzi-Filhob G, Morenoa CRC. Weight gain in relation to night work among nurses. *Work*. 2012;41 Suppl 1:2043-2048. doi:10.3233/WOR-2012-0429-2043

150. Ruddick-Collins LC, Johnston JD, Morgan PJ, Johnstone AM. The Big Breakfast Study: Chrono-nutrition influence on energy expenditure and bodyweight. *Nutr Bull*. 2018;43(2):174-183. doi:10.1111/nbu.12323

Appendix

Search Strategy

MEDLINE, EMBASE, CENTRAL and CAB abstracts) were systematically searched through the online database Ovid with the following search terms:

1. Metabolic Syndrome/
2. Insulin Resistance/
3. Insulin/bl [Blood]
4. Blood Glucose/me [Metabolism]
5. exp Dietary Carbohydrates/ or exp Carbohydrates/
6. dinner.tw.
7. evening.tw.
8. evening meal.tw.
9. meal timing.tw.
10. 1 or 2 or 3 or 4
11. 6 or 7 or 8 or 9
12. 5 and 10 and 11
13. limit 12 to (English language and humans)
14. limit 13 to (meta analysis or randomised controlled trial)

Table S1. Risk of Bias of Studies

	Pearce et al., 2008			Sofer et al., 2011 & 2013			Alves et al., 2014			Kessler et al., 2020			Nouripour et al., 2021		
Domain	Risk of bias			Risk of bias			Risk of bias			Risk of bias			Risk of bias		
	Low	High	Unclear	Low	High	Unclear	Low	High	Unclear	Low	High	Unclear	Low	High	Unclear
Random sequence generation ***(selection bias)***	☒	☐	☐	☐	☐	☒	☐	☐	☒	☒	☐	☐	☒	☐	☐
Allocation concealment ***(selection bias)***	☐	☒	☐	☐	☐	☒	☐	☐	☒	☒	☐	☐	☐	☒	☐
Blinding of participants and personnel ***(performance bias)***	☐	☒	☐	☐	☐	☒	☐	☐	☒	☐	☒	☐	☐	☒	☐
Blinding of outcome assessment ***(detection bias)***	☐	☒	☐	☐	☐	☒	☐	☐	☒	☒	☐	☐	☒	☐	☐
Incomplete outcome data ***(attrition bias)***	☒	☐	☐	☐	☒	☐	☐	☒	☐	☒	☐	☐	☐	☒	☐
Selective outcome reporting? *(reporting bias)*	☐	☒	☐	☐	☐	☒	☐	☐	☒	☒	☐	☐	☒	☐	☐
Other bias (Funding, Conflicts of interest, Ethical standards)	☒	☐	☐	☒	☐	☐	☒	☐	☐	☒	☐	☐	☒	☐	☐

Table S2. Data Extraction Form

Eligibility Assessment Form[1]

Review title or ID	
Study ID *(surname of first author and year first full report of study was published e.g. Smith 2001)*	
Report ID	
Report ID of other reports of this study including errata or retractions	
Notes	

General Information

Date form completed *(dd/mm/yyyy)*	
Name/ID of person extracting data	
Reference citation	
Study author contact details	
Publication type *(e.g. full report, abstract, letter)*	
Notes:	

Study eligibility

Study Characteristics	Eligibility criteria *(Insert inclusion criteria for each characteristic as defined in the Protocol)*	Eligibility criteria met? Yes	No	Unclear	Location in text or source *(pg & ¶/fig/table/other)*
Type of study	Randomised controlled trial	☐	☐	☐	
	Quasi-randomised controlled trial	☐	☐	☐	
Participants	Is the study a *human* intervention study?	☐	☐	☐	
	Are participants aged 18 years or over?	☐	☐	☐	
Types of intervention	Is at least one of the interventions concentrating carbohydrates to dinner?	☐	☐	☐	
Types of comparison	Is the macronutrient composition of breakfast and lunch documented?	☐	☐	☐	

[1] Modified from Cochrane data extraction form - Accessed June 18, 2021. https://dplp.cochrane.org/data-extraction-forms

Types of outcome measures	Was the impact on at least one of the components of MetS, CVD or T2DM or any of their related biomarkers or risk factors measured?	☐ ☐ ☐	
IF ANY OF THE ANSWERS ABOVE IS NO DO NOT PROCEED			
EXLUSION CRITERIA	Does the study involve any complex health conditions other than MetS, CVD or Diabetes?	☐ ☐ ☐	
	Does the study involve pregnant or lactating women?	☐ ☐ ☐	
	Does the study involve any diagnosed eating disorders, anorexia nervosa or bulimia nervosa?	☐ ☐ ☐	
INCLUDE ☒	**EXCLUDE** ☐		
Reason for exclusion			
Notes:			

IF STUDY IS ELIGIBLE, PROCEED TO DATA EXTRACTION FORM

Characteristics of included studies

Methods

	Descriptions as stated in report/paper	**Location in text or source** *(pg & ¶/fig/table/other)*
Aim of study *(e.g. efficacy, equivalence, pragmatic)*		
Design *(e.g. parallel, crossover, non-RCT)*		
Start date		
End date		

Duration of participation *(from recruitment to last follow-up)*		
Ethical approval needed/ obtained for study	☐ Yes ☐ No ☐ Unclear	
Notes:		

Participants

	Description *Include comparative information for each intervention or comparison group if available*	Location in text or source *(pg & ¶/fig/table/other)*
Population description *(from which study participants are drawn)*		
Baseline characteristics of population		
Setting *(including location and social context)*		
Inclusion criteria		
Exclusion criteria		
Method of recruitment of participants *(e.g. phone, mail, clinic patients)*		
Informed consent obtained	☐ Yes ☐ No ☐ Unclear	
Withdrawals and exclusions *(if not provided below by outcome)*		
Age		
Sex		
Race/ethnicity		
Severity of illness		

Co-morbidities		
Other relevant sociodemographics		
Notes:		

Intervention groups

Copy and paste table for each intervention and comparison group

Intervention Group 1

What were the interventions?		
How many individuals were assigned to each intervention group? *(specify whether no. people or clusters)*		
Theoretical basis *(include key references)*		
Description *(include sufficient detail for replication, e.g. content, dose, components)*		
Duration of treatment period		
Timing *(e.g. frequency, duration of each episode)*		
Delivery *(e.g. mechanism, medium, intensity, fidelity)*		
Co-interventions		
Integrity of delivery		
Compliance		

Notes:

Outcomes

Copy and paste table for each outcome.

Key conclusions of study authors; implications of findings		
Notes:		

Other

Study funding sources *(including role of funders)*		
Possible conflicts of interest *(for study authors)*		
Notes:		

Risk of Bias assessment – COMPLETED IN SEPARATE EXCEL FILE

(See Handbook Chapter 8. Additional domains may be added for non-randomised studies.)

Domain	Risk of bias Low High Unclear	Support for judgement *(include direct quotes where available with explanatory comments)*	Location in text or source *(pg & ¶/fig/table/other)*
Random sequence generation *(selection bias)*	☐ ☐ ☐		
Allocation concealment *(selection bias)*	☐ ☐ ☐		
Blinding of participants and personnel *(performance bias)*	☐ ☐ ☐	Outcome group: All/	
(if separate judgement by outcome(s) required)	☐ ☐ ☐	Outcome group:	

Blinding of outcome assessment *(detection bias)*	☐ ☐ ☐	Outcome group: All/	
(if separate judgement by outcome(s) required)	☐ ☐ ☐	Outcome group:	
Incomplete outcome data *(attrition bias)*	☐ ☐ ☐	Outcome group: All/	
(if separate judgement by outcome(s) required)	☐ ☐ ☐	Outcome group:	
Selective outcome reporting? *(reporting bias)*	☐ ☐ ☐		
Other bias	☐ ☐ ☐		
Notes:			

Other information

	Description as stated in report/paper	**Location in text or source** *(pg & ¶/fig/table/other)*
References to other relevant studies	1.	
Correspondence required for further study information *(from whom, what and when)*		
	Notes:	