Timing of food intake: sounding the alarm about metabolic impairments? A systematic review.

Timing of food intake: sounding the alarm about metabolic impairments? A systematic review

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Abstract

Growing evidence points to an association between timing of food intake and obesity in humans, raising the question if when to eat matters as much as what and how much to eat. Based on the new definition of obesity as a chronobiological disease, an unusual or late meal timing represent a circadian chronodisruption, leading to metabolic impairments.

Preliminary data from cross-sectional and experimental studies suggest that changes in meal timing can influence obesity and success of weight loss therapy, independently from total energy intake, dietary composition and estimated energy expenditure.

A systematic review of observational and experimental studies in humans was conducted to explore the link between time of food ingestion, obesity and metabolic alterations. Results confirm that eating time is relevant for obesity and metabolism: observational and experimental studies found an association between meal timing, weight gain, hyperglycemia and diabetes mellitus with benefits deriving from an early intake of food in the day in a wide range of individuals. Herein clinical, future perspectives of chronoprevention and chronotherapy of obesity and type 2 diabetes are also provided.

In conclusion, meal timing appears as a new potential target in weight control strategies, and therapeutic strategies should consider this contributor in the prevention of obesity.

1. Introduction

In the last decade, a new relevant question has arisen: when to eat [1-3]. In addition to what and how much to eat, food timing represents a novel issue in our 24-h modern society, characterized by more exposure to artificial light, later food intake and bedtimes. Food is a major synchronizer of peripheral circadian clocks, and delayed feeding due to prolonged night-time wakefulness leads to desynchrony between central circadian and peripheral clocks [4].

Growing evidence points to an association between timing of food intake and obesity in humans, suggesting that changes in meal timing can influence obesity and success of weight loss therapy [1]. Also in animals, weight regulation is affected by the timing of food ingestion [5, 6].

On this basis, obesity could now represent a "chronobiological disease" [7]. Differently from the time-restricted feeding pattern unintentionally practiced by our ancestors for thousands of years, the current trend is to shift most of the caloric intake later in the day [8]. In a few cross-sectional studies, an increased risk of overweight and obesity was found when a greater daily caloric intake was consumed in the evening [9-12], while a reduced risk was observed when consuming a larger proportion of calories at lunch or breakfast [9, 11, 13].

Even though the association between evening eating and body weight was not confirmed in a prospective US cohort, it was present in specific subgroups (smoking men, physically active men, inactive women) [14]. Another prospective study showed that late-night eaters had an increased coronary heart disease risk [15].

The clinical relevance of meal timing appears to be supported by its role in weight loss strategies. In a 20-week intervention study, as compared with early lunch eaters, late lunch eaters lost less weight independently from self-reported 24-h caloric intakes [16]. In overweight and obese women with metabolic syndrome, a 12-week weight-loss program with high caloric breakfast was more effective in reducing weight and waist circumference than an isocaloric diet with high caloric intake at dinner [17].

Aside from body composition and weight regulation, timing of food intake seems to have a negative impact also on metabolism. Eating lunch later in the day was associated with poorer insulin sensitivity assessed by HOMA-IR (Homeostasis-Model Assessment-Insulin Resistance) index [16]. Experimental studies showed a higher decrease in HOMA-IR after a high caloric breakfast *vs* dinner in women with metabolic syndrome [17] and polycystic ovary syndrome [18]. Late lunch eating was associated with decreased pre-meal resting energy expenditure, lower pre-meal carbohydrate utilization, and decreased glucose tolerance after mixed-meal test [19]. In another study exploring food-induced thermogenesis in the morning and evening, the same meal consumed in the evening determined a lower after-meal resting metabolic rate and increased, delayed concentrations of glucose and insulin [20].

These preliminary data suggest that consuming a larger proportion of total daily energy in the morning, as opposed to later in the day, might be more beneficial for weight loss.

The aim of this study was to perform a systematic review of observational and experimental studies comparing the effect of different food timing on body weight and metabolic outcomes in adults. The possibility to undertake a meta-analysis of the effects of the interventions on at least some of the outcomes was evaluated too.

2. Material and Methods

This article is structured according to the preferred items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [21].

2.1 Literature search strategy

The following electronic databases were queried using a combination of search terms: PubMed (National Library of Medicine), Trip database and The Cochrane Library, until 01 March 2017. The construction of the search strategy was performed using database specific subject headings and keywords. The search terms included combinations of “timing meal” or “timing meals” or “timing of food” or “food timing”, and Body Mass Index (BMI), obesity, weight, hyperglycemia, glycemia, insulin, insulin-resistance and type 2 diabetes mellitus (free-term and MESH as possible) (**Appendix 1**).

These search strategies were supplemented by hand searching the bibliographies of all the included studies. Searches were limited to randomized controlled trials, parallel or cross-over, and observational studies in healthy volunteers or patients (e.g. individuals with obesity/overweight, polycystic ovary syndrome, metabolic diseases or other underlying diseases). We excluded studies performed in children.

2.2 Study selection

We included studies reporting comparisons of different timing meal interventions or habits (early eaters/late eaters or different timing of daily energy intake distribution) to reduce weight, insulinemic and glycemic areas-under-the-curve values and other metabolic variables.

Two review authors (SB, CM) independently scanned the abstract, title, or both, of every record retrieved, to determine which studies should be assessed further. All potentially relevant articles were investigated as full text. Any discrepancy about inclusion was resolved by discussing with a third review author (GB).

2.3 Data collection and extraction

For the trials that fulfilled the inclusion criteria, two authors independently abstracted key participant characteristics and reported data on efficacy outcomes using standard data extraction templates.

From each included study, information was extracted on:

- Characteristics of study participants (type of population, age, BMI);
- Type of intervention;
- Outcomes:
    - Anthropometric variables (BMI, weight, waist circumference, total body fat, etc.);
    - Metabolic variables (blood glucose values, triglycerides, total cholesterol, HDL and LDL-cholesterol, etc.);
    - Hormonal variables (blood insulin, progesterone, testosterone, etc.);
    - Calorimetric variables (fasting or after-meal resting metabolic rate, fasting or after meal respiratory quotients, etc).

2.4 Risk of bias assessment

The validity of each study was independently assessed by two authors (SB, GB) using two tools: a) the 'Risk of bias' tool developed by The Cochrane Collaboration for RCT [22], and b) the 'Risk Of Bias in Non-randomized Studies of Interventions' (ROBINS-I) tool for evaluating risk of bias in estimates of the comparative effectiveness of interventions from studies not using randomization to allocate units (individuals or clusters of

individuals) to comparison groups [23]. As they were familiar with the literature, review authors were not blinded with respect to the study authors, institution or journal. We resolved possible disagreements by consensus, or with consultation with a third review author (AE).

We could not undertake a meta-analysis of the effects of the interventions due to the great variability in outcome assessment and reporting, and in the type of interventions.

3. Results

3.1 Flow and characteristics of included studies

With the initial literature search, 926 articles were found (**Figure 1**). Fifteen records were identified and carefully assessed for eligibility, after excluding non-original articles, duplicates, and articles not meeting the inclusion criteria. Only 10 studies satisfied all the inclusion criteria and were selected for the systematic review, including a total number of 6401 subjects (**Table 1**). The largest study recruited 4243 subjects [24] while the smallest one only 6 subjects [25]. Included studies were conducted in Spain [16, 19, 24, 26], Israel [17, 18], Japan [27], UK [25], and Italy [20, 28], between 2001-2014. Participants were: healthy individuals [19, 20, 25, 27], general population [24, 28], overweight/obese subjects [16, 17], post-bariatric surgery patients [26], women with polycystic ovary syndrome [18]. In one case participants were paid [27]. The demographic and clinical characteristics of the included studies are shown in Table 1.

Five of the included studies were trials: randomized cross-over [19, 20, 25, 27] and randomized controlled trials [17, 18], respectively, while four were observational prospective studies [16, 24, 26, 28]. The duration of the observational period was respectively: 6 years [26, 28], 3.5 years [24], and 20 weeks [16].

The interventions of the trials varied from the acute consumption of one or more meals a day at different hours [20, 25, 27] to early eating *vs* late eating the greater amount of kcal/day for 2 weeks [19] or 12 weeks [17, 18].

Observational studies divided participants according to the timing of the main meal (lunch before or after 15:00) [16, 26], the timing of the consumption of the larger amount of calories [24] or the tertiles of the percentage of total daily caloric intake from dinner [28].

154 The following outcomes were evaluated: variation on anthropometric variables [16-19, 24, 28], energy
155 expenditure by indirect calorimetry [19, 20, 27] or equations [16, 26], metabolic parameters [16-20, 25-28],
156 sleep pattern [16, 19, 26], body temperature [19], carbohydrate absorption [27], satiety [17], hormonal
157 assessments [18, 19], and other blood variables, such as inflammatory parameters and liver enzymes [28].
158
159 *3.2 Risk of bias assessment*
160 Most of the analyzed trials provided insufficient information about randomization procedures (**Table 2**). If
161 blinding of participants was not feasible owing to the nature of the interventions, data about blinding of the
162 personnel who performed the laboratory or statistical analyses was often unknown. In one study about 20%
163 of participants dropped out [17]. Most trials appeared to be free of selective outcome reporting and of other
164 sources of bias.
165 The risk of bias for the observational studies is reported in **Table 3**. Most of the evaluated risks of bias were
166 low/moderate. Ruiz-Lozano classified post-bariatric surgery patients by their weight-loss pattern after surgery
167 and compared the timing of meals among groups [26]. The three groups, however, significantly differed for
168 age and gender: older male patients were more frequently poor responders. Hermengildo studied the risk of
169 weight gain by the distribution of energy intake throughout the day, but weight gain was self-reported both
170 at baseline and at the end of the follow-up [24].
171
172 *3.3 Effect of timing of food intake on changes in weight and other anthropometric parameters*
173 Observational studies showed that late lunch-eaters (after 15:00) were 2-fold more frequent in poor-weight
174 loss responders to bariatric surgery, independent of dietary macronutrient composition [26]; the OR of gaining
175 weight (>3kg) was 0.79 (95% CI 0-63-0.99), 0.82 (95% CI 0.64-1.04) and 0.62 (95% CI 0.47-0.80) respectively in
176 the second, third and the highest quartile of percent energy intake at lunch, when compared to the lowest
177 quartile, in a multivariate logistic regression analysis (p for trend=0.001) [24]; being in the highest tertile of
178 daily percent caloric intake at dinner was significantly associated with an increased risk of incident obesity

(OR=2.33, 95%CI 1.17-4.65) [28]; late lunch eaters lost less weight than early lunch eaters (7.7 *vs* 9.9kg) after a 20-week weight-loss intervention [16].

Apart from two observational studies [24, 28], the nutritional composition of meals was not different between the groups of early or later-eaters. This finding strongly reinforces the role of meal timing on the studied outcomes.

The evaluated randomized trials reported: a significantly higher weight loss in the "more calories at breakfast" group when compared to the "more calories at dinner" group (-8.7±1.4 *vs* -3.6±1.5 kg, $p<0.001$) after 12-weeks of a hypocaloric diet in overweight/obese women [17]; no significant change in weight between two groups with the same distribution of calories as above reported, after 12 weeks of a maintenance diet in women with the polycystic ovary syndrome.

A few studies evaluated other indices of body fat [16-18]. No difference in waist circumference values and total body fat, as measured by bioelectrical impedance, were evident at baseline among early *vs* late lunch eaters, but these data were not available at follow-up [16]. Individual eating "more calories at breakfast" showed greater waist circumference reduction compared to the "more calories at dinner" group after a weight-loss 1400 kcal diet [17]; this difference was not confirmed after a 1800-kcal maintenance diet in women with polycystic ovary syndrome [18]. Only in 3 studies, waist circumference was described with the same methods and at the same time (baseline, follow-up); therefore, we could not undertake a meta-analysis because of the low number of individuals, not representative of the complete review [16-18].

3.4 Effects of timing of food intake on glucose and insulin blood values

At baseline, late lunch eaters when compared to early lunch eaters showed increased values of Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) index, but fasting glucose and insulin blood concentrations were similar between the two groups; no data at follow-up were available [16]. Individuals in the highest tertile of percent daily caloric intake at dinner showed an increase risk of incident type 2 diabetes (2.26; 95%CI 0.89-5.75) [28].

The trials evaluating the acute consumption of one or more meals/day reported that: a) glucose responses were greater after consuming the majority of energy load in the evening than in the morning, while insulin responses and post-prandial insulin resistance seemed to be mainly affected by the quality of carbohydrates [25]; b) the efficiency of digestion and absorption of dietary carbohydrates consumed at breakfast was higher if the previous supper was later (at 23:00) than under usual conditions (at 18:00) and, accordingly, after-breakfast glucose values were increased until 3 hours in case of previous late suppertime [27]; c) the same meal consumed in the evening determined delayed and larger increases in glucose and insulin blood concentrations and significant increases in the corresponding areas-under-the curve [20].

The study protocol 1 of Bandin showed increased post-prandial glucose responses in late lunch eaters with a 46% higher glucose area-under-the curve than in early lunch eaters [19]; women eating “more calories at breakfast” showed greater reduction in fasting glucose, insulin and insulin resistance evaluated by the HOMA-IR index and, similarly, reduced glycemic and insulinemic responses both to the oral glucose tolerance test and to a meal challenge when compared to the “more calories at dinner”, after 12 weeks of isocaloric 1400-kcal diet [17]; in lean women with polycystic ovary syndrome, a high caloric intake at breakfast resulted in significantly reduced glucose and insulin areas-under-the-curve and an improvement in insulin sensitivity than consuming a high caloric intake at dinner [18].

4. Discussion

New, intriguing contributors to the epidemic of obesity have been lately recognized, such as meal frequency and patterns [29, 30], as well as sleep duration and quality [31]. Emerging evidence sounds the alarm on the role of meal timing and questions whether when to eat matters as much as what and how much to eat.

Few cross-sectional studies tried to answer this question, finding that later timing of meals or eating more calories later in the day has a negative impact on body weight and metabolism [9-13].

Our systematic review of observational and experimental studies, including both healthy individuals [19, 20, 24, 25, 27, 28] and patients with different dysmetabolic conditions [16-18, 26] confirms the health benefits of early eating, with positive effects on body weight, weight loss success, and glucose metabolism.

4.1 Timing of food intake and obesity

Experimental studies show that animal models fed at unusual feeding time develop obesity, even without change in activity or total energy intake [5, 32]. High-fat meal at the end of the active phase leads to increased weight gain [33]. When challenged with a high-fat diet, chronodisrupted mice were more likely to be obese [34].

The pathophysiologic basis of these findings relies on the new definition of obesity as a chronobiological disease [7]. Unusual feeding time can represent a circadian disruption leading to clock gene functional alterations and uncoupling between the central and peripheral oscillators, circadian variations of peripheral clocks, gene expression, satiety hormones, and digestive processes [1]. Among mechanisms promoting obesity, diet-induced thermogenesis is lower at night [35], and the reduced thermic effect of glucose in obesity is likely related to the nocturnal insulin resistance [36]. Additionally, reduced fat oxidation has been observed during nighttime eating [37, 38].

Also in humans, cross-sectional studies suggest that eating time is relevant for obesity. Particularly, consuming a greater daily caloric in the evening is associated with higher risk of overweight and obesity [9-12], while eating more calories at lunch or breakfast appears to be protective against overweight/obesity [9, 11, 13].

The observational studies included in the present systematic review showed a positive association between meal timing and body weight [16, 24, 26, 28], that remained significant also after controlling for many counfunding factors involved in the obesity development, such as physical activity and sleep time [16, 24, 26, 28]. Even though short sleep duration is a well know, independent risk factor for obesity, self-reported data on sleep time appear similar among the different weight loss patterns [16, 26] and therefore probably did not mediate the observed outcomes. The association between meal timing and body weight was supported also by a causal direction described in the included experimental studies [17-20, 25, 27]. Furthermore, the benefits were evident in a wide range of individuals: post-bariatric surgery patients [26], women with metabolic syndrome [17], overweight/obese subjects attending nutrition clinics [16, 26] and general population [24, 28]. Specifically, in post-bariatric surgery patients, left ventricular mass was decreased one year after procedure;

this improvement correlated only with the decrease in leptin levels [39], postulating a cardiovascular protection from weight loss also mediated by hormonal changes.

This key message has a clear practice implication, and should be considered by clinicians when drawing up a nutritional scheme.

4.2 Timing of food intake and hyperglycemia

Circadian misalignment is known to result in adverse metabolic and cardiovascular consequences [40, 41]. Experimental studies explored the possible mechanisms supporting the circadian modulation of insulin secretion or action. Pathophysiological hypotheses of decreased insulin sensitivity later in the day [42] are represented by increased levels of triglycerides [43] and urinary epinephrine [44], fluctuation in cortisol serum concentrations [45] and higher morning ACTH plasma values [46], and/or a delayed peak in the counteracting activity of glucagon after evening meals [47]. Moreover, under late suppertime conditions, an increased efficacy of dietary carbohydrates absorption has been described [27]. Yet, increased evening meal emptying time seems to lead to evening delay in reaching peak plasma concentrations of the absorbed substances [48]. Metabolic consequences of experimental interventions occur rapidly and are already observed after an acute consumption of one or more meals a day at different hours [20, 25, 27].

4.3 Clinical prospective

The success of weight loss therapy seems to be predicted by food timing; evening preference has a negative impact on metabolism, too. Even though not specifically design for food timing investigation, later chronotype individuals with type 2 diabetes, more likely characterized by later food ingestion, were characterized by a poorer glycemic control [49-52]. This observation raises the question whether meal timing intervention, with or without circadian phase changes, might be helpful in type 2 diabetes management; future studies are needed to verify this hypothesis. Indeed, The Academy of Nutrition and Dietetics has recently pointed up meal timing as a new potential target in weight control strategies [53], stating that consuming most of an individual's energy earlier in the day may enhance weight loss and weight maintenance.

Among other clinical aspects of chronobiology in type 2 diabetes, it is worth considering that chronotherapy might apply not only to lifestyle but also to drug treatment. A prospective, randomized, open-label, blinded trial showed that blood pressure lowering drugs at bedtime reduced cardiovascular risk in type 2 diabetes patients with hypertension over a mean of 5.4 years, compared with the ingestion of drugs upon awakening [54]. Varying the time of day at which antihypertensive medications are taken is highly effective not only in diabetic but also non-diabetic subjects [55]. Like chronotherapy, also chronoprevention might apply to both lifestyle and drug treatment. In fact, in hypertensive patients without diabetes, administering ≥1 antihypertensive medications at bedtime, particularly angiotensin receptor blockers and ACE inhibitors, compared with medications taken after awakening, reduced risk of incident diabetes during a 5.9-year median follow-up and improved blood pressure control with significant decrease of asleep blood pressure [56].

Another clinical application of food timing intervention might be represented by type 1 diabetes, even though it was not mentioned in the studies included in our systematic review. As type 1 diabetes in affected by increased mortality [57], it would be interesting to see whether optimal food timing and daily caloric distribution may improve short-term glycemic, endothelial dysfunction, inflammation and oxidative stress outcomes as cardiovascular risk markers.

In consideration of the relevance of obesity- and type 2 diabetes- cardiovascular related diseases, it looks fundamental to search for efficient strategies for weight-loss and cardiovascular risk reduction. Future studies should verify whether well-known cardiovascular risk markers associated with obesity [39] and diabetes [58] may improve after chronotherapy intervention.

4.4 Limitations

The heterogeneity of the population studies and the evaluated outcomes has prevented us from performing a meta-analysis. The findings of the present systematic review do not allow to definitely prove the relationship between meal timing and the improvement of overweight and dysmetabolic conditions in humans. The heterogeneity of the included studies should be considered as a limitation, since either healthy individuals or patients with different dysmetabolic conditions have been enrolled. As another limitation, some studies

included in this analysis were not primarily designed to assess the effects of meal timing on weight or metabolic variables, suggesting a high risk of both publication and outcome reporting biases. The use of any drug was considered as exclusion criteria in most studies [16-20,27], but in 3 of the observational studies [24,26,28], data relative to pharmacological treatment were not reported; we therefore could not exclude that therapeutic regimens might have influenced weight loss dynamics or food intake timing in these studies. Finally, the number of trials and individuals included in the present review was small, which made it difficult to definitively assess the metabolic effect of meal timing, and required further investigations.

Nevertheless, to the best of our knowledge, this is the first systematic review on this topic and could contribute to advancing knowledge and generating new studies in the field

4.5 Conclusions

Accumulating evidence summarized in this systematic review supports the negative impact of later meal timing and calories distribution on body weight and metabolism. High quality studies are needed to clarify the effectiveness of changes in eating time as an additional strategy for obesity and diabetes prevention and treatment in adults.

Conflict of interest

The authors declare that they have no conflicts of interest with the contents of this article.

FIGURE LEGEND

Figure 1. Flow chart of the number of studies identified and included in the systematic review.

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Table 1. Characteristics of the included studies

Observational studies					
Author(year) **[ref]**	**Methods**	**Participants**	**Intervention**	**Outcomes**	**Changes in outcomes**
Ruiz Lozano (2016) [26]	Observational prospective study (2006-2011)	N=270 patients treated with bariatric surgery (Roux-en-Y gastric bypass and sleeve gastrectomy)	Early eating vs Late eating according to the timing of main meal (before and after 15.00)	*Anthropometry measures*: weight, BMI, postoperative weight loss Energy and dietary intake before/during/after bariatric surgery: 4-days food record Morningness/eveningness questionnaire	*Weight change*: 70% of late eaters in poor weight-loss responders *vs* 42% in secondarily poor weight-loss responders and 37% in good weight-loss responders (p=0.01)
Hermenegildo Y (2016) [24]	Observational prospective study (2008-2012)	N=4243 adults from a population-based cohort Inclusion criteria: ≥18y, living in Spain, alive at follow-up Exclusion criteria: institutionalized, unable to give valid data about diet, cases with missing data on the evaluated variables	Quartile of energy intake by different meals (breakfast, mid-morning meal, lunch, mid-afternoon meal, dinner, snacking)	*Anthropometry measures*: weight gain (>3 kg)	*Weight change*: compared with those in the lowest quartile of % energy intake at lunch, the multivariate OR of gaining >3kg was 0.79 (95% CI 0.63-0.99) in the second quartile, 0.82 (0.64-1.04) in the third quartile and 0.62 (0.47-0.80) in the highest quartile (Ptrend=0.001)
Bo S (2014)	Observational	N=1245 adults from a population-based cohort	Tertiles of the percentage of total daily caloric intake from dinner	*Anthropometric measures*: weight, height, BMI, waist circumference	*Incidence of obesity:* from the lowest to the highest tertiles of total % daily caloric intake at dinner,

[28]	prospective study (2001-2008)	Inclusion criteria: age 45-64y from 6 general practitioners, Caucasian, living in Asti (North-Western Italy) Exclusion criteria: obesity and/or diabetes mellitus at baseline, died during follow-up		*Metabolic parameters*: blood glucose, glycated hemoglobin, cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, HOMA-IR index Other blood parameters: C-reactive protein, alanine aminotransferase, γ-glutamyl transferase	the incidence rate of obesity increased (from 4.7 to 11.4%, p<0.01). The increased obesity risk for subjects in the highest tertile was confirmed in a multiple regression model (OR=2.33; 95% CI 1.17–4.65; p=0.02). *Incidence of diabetes:* individuals in the highest tertile of dinner % daily caloric intake showed an increase risk of incident type 2 diabetes (2.26; 0.89-5.75)
Garaulet M (2013) [16]	Observational prospective study (2007-2008)	N=420 obese/overweight individuals Exclusion criteria: special diet, weight-loss drugs, diabetes mellitus, chronic renal failure, hepatic diseases, cancers, any nutrition program within 2-y	Early eaters (lunch before 15:00) and late eaters (lunch after 15:00) All subjects received a 60-min educative program (once/week) with nutritional and exercise recommendations and a cognitive-behavioral approach	Anthropometric measures: weight, height, BMI, total body fat, waist circumference Metabolic parameters: blood glucose, cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, HOMA-IR index, leptin, ghrelin Energy intake before/during treatment: 1-day dietary recall Energy expenditure: estimated by equations Morningness/eveningness questionnaire Sleep duration: evaluated by questionnaire	*Weight change:* early lunch eaters lost more weight than late eaters during the 20-weeks of intervention (9.9±5.8 *vs* 7.7±6.1 kg, p=0.008). The weight loss, expressed as % of initial weight was respectively: 11.3±5.8 *vs* 9.0±7.1 (p=0.006)
Randomized cross over/ controlled studies					

Author(year) **[ref]**	**Methods**	**Participants**	**Intervention**	**Outcomes**	**Changes in outcomes**
Bo S (2015) [20]	Cross-over randomized trial	N=20 healthy volunteers Inclusion criteria: age 20-35y, BMI 19-26 kg/m2, habitual moderate exercise level, <10 cigarettes/day. Exclusion criteria: Any acute or chronic diseases, menopause, any drugs or supplementations, any alimentary restrictions or specific diets, being a shift or night workers, unable to give a written informed consent	The same meal at 8:00 and, 7 days after at 20:00 or vice versa Each experiment lasted about 2-h	*Calorimetric evaluation*: fasting RMR, after-meal RMR, DIT, fasting RQ, after meal RQ, RQ difference *Metabolic parameters*: blood glucose, insulin, FFA, triglycerides every 30 min after each meal for 180 min	*Metabolic variables:* delayed and larger increases in glucose and insulin concentrations were found after the evening meals.

Bandin C (2015) [19]	Cross-over randomized trial Protocol 1 Each experiment lasted 2 weeks, after 1 week wash out Protocol 2 Each experiment lasted 2 weeks, after 1 week wash out	N=32 healthy women Exclusion criteria: endocrine, renal, hepatic, psychiatric disorders, any drugs (other than oral contraceptives) Protocol 1: N=10 Protocol 2: N=22	Early eating (lunch at 13:00) vs late eating (lunch at 16:30) for 2 weeks.	Specific measurements to protocols: Protocol 1 *Calorimetric evaluation*: fasting RMR, after-meal RMR, fasting RQ, after meal RQ, carbohydrate oxidation *Metabolic parameters*: Mixed meal test for glucose tolerance Protocol 2 *Wrist temperature* *Hormonal assessments*: salivary cortisol	*Metabolic variables:* late-eating lunch individuals showed significantly increased post-prandial glucose areas-under-the-curve than early eaters (102.6±30.8 *vs* 70.0±32.9 mmol/l×h; p=0.002)
Jacubowitz D,a (2013) [17]	Randomized controlled trial	N=93 overweight and obese women. Inclusion criteria: age 20-65y, BMI 25-37 kg/m2, non-diabetic OGTT, presence of the metabolic syndrome Exclusion criteria: abnormal thyroid, liver or kidney function, cardiovascular disease,	Subjects were randomized to one of the following 1400 kcal weight-loss diet for 12 weeks: -breakfast group (700 kcal breakfast, 500 kcal lunch, 200 kcal dinner; N=46) -dinner group (200 kcal breakfast, 500 kcal lunch, 700 kcal dinner; N=47)	*Anthropometric measures*: height, weight, BMI, waist circumference *Metabolic parameters*: blood glucose and insulin after an OGTT, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, ghrelin, HOMA-IR and HOMA-b, ISI *Appetite*: evaluated by questionnaires	*Weight change:* the breakfast group showed the greater weight loss after the intervention (-8.7±1.4 *vs* -3.6±1.5 kg; p<0.001) *Metabolic variables:* % changes in fasting glucose (-11.5 *vs* -4.2%), insulin (-51 vs -29%) and HOMA-IR (-57 *vs* -32.5%) significantly

		cancer, hypoglycemic drugs			decreased in the breakfast group. Similarly, OGTT test led to a greater decrease of glucose and insulin in the breakfast group
Jacubowitz D,b (2013) [18]	Randomized controlled trial	N=60 women with polycystic ovary syndrome Exclusion criteria: BMI>24.9 kg/m2, on any diet, any drugs affecting weight, changing in weight >4.5 kg or in physical activity within the last 6 months	Subjects were randomized to one of the following 1800 kcal maintenance diet for 12 weeks: -breakfast diet (980 kcal breakfast, 640 kcal lunch, 190 kcal dinner; N=29) -dinner diet (190 kcal breakfast, 640 kcal lunch; 980 kcal dinner; N=31)	*Anthropometry measures*: BMI, waist circumference *Metabolic parameters*: blood glucose, insulin, HOMA-IR, HOMA-b *Hormonal assessments*: blood progesterone level, free and total testosterone, SHBG, 17-OH estradiol, DHEA-S, 17OHP, FAI, leuprolide stimulation test	*Weight change:* after the maintenance diets, weights did not change in the breakfast and dinner groups *Metabolic variables:* in the breakfast group, % changes of fasting glucose (-8 *vs* +2%), fasting insulin (-53 *vs* 0%), HOMA-IR (-56 *vs* +1%), HOMA-b (-35 *vs* -7%), ISI (+135 *vs* +2%), and glucose (-20 *vs* 0%) and insulin (-49 *vs* -7%) areas-under-the-curve were significantly higher

Morgan LM (2012) [25]	Cross-over randomized trial	N=6 healty volunteers	Subjects were randomized to one of the following 2000 kcal diets by cross-over: -Low glycemic index with big breakfast (1200 kcal) and small dinner (400 kcal) -Low glycemic index with big dinner (1200 kcal) and small breakfast (400 kcal) -High glycemic index with big breakfast (1200 kcal) and small dinner (400 kcal) -High glycemic index with big dinner (1200 kcal) and small breakfast (400 kcal)	*Metabolic parameters*: Blood glucose and insulin every 30 min after each meal for 120 min, post-prandial HOMA-IR, interstitial glucose by a continuous glucose monitoring system applied the day before each test	*Metabolic variables:* interstitial glucose and insulin areas-under-the curve were significantly higher after consuming a big dinner rather than a big breakfast at the same glycemic index
Tsuchida Y (2013) [27]	Cross-over random trial	12 females (paid participants) Inclusion criteria: university students Exclusion criteria: smoking, current antibiotic use	Two experimental conditions: a meal at usual suppertime (18:00) a meal at late suppertime (at 23:00), performed in different days	*Metabolic parameters*: blood glucose every 30 min after each supper and after the breakfast of the next day for 180 min, unabsorbed carbohydrates by breath hydrogen test *Calorimetric evaluation*: RQ	*Metabolic variables:* a late suppertime meal determined significantly increased glucose values at 30, 60, 120, 150 and 180-min after the breakfast consumed the day after, with respect to the usual suppertime meal

Abbreviations: 17-alpha Hydroxyprogesterone (17OHP), Body Mass Index (BMI), Dehydroepiandrosterone-Sulfate (DHEA-S), Diet-Induced Thermogenesis (DIT), Free Androgen Index (FAI), High Density Lipoprotein (HDL), Homeostasis model Assessment-Insulin resistance (HOMA-IR), Homeostasis model Assessment-beta cell function (HOMA-b), Insulin Sensitivity Index (ISI), Low Density Lipoprotein (LDL), Oral Glucose Tolerance Test (OGTT), Respiratory Quotient (RQ), Resting Metabolic Rate (RMR), Sex Hormone-Binding Globulin (SHBG).

Table 2 Risk of bias assessment in the trials included in the systematic review

Study	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Free of other bias
Bo (2015)	L	U	L	L	L	L
Bandin (2015)	L	U	U	L	L	U
Jacubowitz[a] (2013)	U	U	H	H	L	L
Jacubowitz[b] (2013)	U	U	U	L	L	L
Tsuchida (2013)	U	U	U	U	L	L
Morgan (2012)	U	U	U	L	L	U

Criteria defined for quality assessment are based on the Cochrane guidelines.
Abbreviations: H, high risk of bias; L low risk of bias; U unclear or unrevealed risk of bias

Table 3 Risk of bias assessment in the observational studies included in the systematic review

Study	Ruiz Lozano (2016)	Hermenegildo (2016)	Bo (2014)	Garaulet (2013)
Domain				
Bias due to confounding	Serious	Moderate	Moderate	Moderate
Bias in selection of participants into study	Moderate	Low	Moderate	Moderate
Bias in classification of interventions	Moderate	Moderate	Moderate	Moderate
Bias due to departure from intended interventions	Low	Low	Low	Low
Bias due to missing data	Moderate	Low	Low	Low
Bias in measurement of outcomes	Low	Serious	Low	Low
Bias in selection of the reported results	Moderate	Low	Low	Moderate
Overall*	Serious	Serious	Moderate	Moderate

*Overall assessment derived from the seven domains of ROBINS-I (Risk Of Bias In Non-randomized Studies -of Intervention scale) tool