Conference on 'Roles of sleep and circadian rhythms in the origin and nutritional management of obesity and metabolic disease'
Symposium 3: Importance of meal timing

Meal irregularity and cardiometabolic consequences: results from observational and intervention studies

Gerda K. Pot[1,2]*, Suzana Almoosawi[3] and Alison M. Stephen[4]

[1]*Faculty of Earth and Life Sciences, Vrije University Amsterdam, Section of Health and Life, de Boelelaan 1085, 1081 HV Amsterdam, The Netherlands*
[2]*King's College London, Diabetes and Nutritional Sciences Division, School of Medicine, Franklin-Wilkins Building, London, 150 Stamford Street, London SE1 9NH, UK*
[3]*Institute of Health & Society and Human Nutrition Research Centre, Newcastle University, Newcastle Upon Tyne NE2 4HH, UK*
[4]*Department of Nutritional Sciences, Faculty of Health and Medical Sciences, University of Surrey, Guildford GU2 7XH, UK*

Studying irregular meal patterns fits in with the latest research focusing not only on what people eat but also when they eat, also called chrono-nutrition. Chrono-nutrition involves studying the impact of nutrition on metabolism via circadian patterns, including three aspects of time: (ir)regularity, frequency and clock time. The present paper aimed to narratively review research on irregular meal patterns and cardiometabolic consequences. Only few cross-sectional studies and prospective cohort studies were identified, and most of these suggested that eating meals irregularly is associated with a higher risk of the metabolic syndrome and cardiometabolic risk factors, including BMI and blood pressure. This was supported by two randomised controlled intervention studies showing that consuming meals regularly for 2 weeks *v.* an irregular meal pattern, led to beneficial impact on cardiometabolic risk factors as lower peak insulin, lower fasting total and LDL-cholesterol, both in lean and obese women. In conclusion, the limited evidence on meal regularity and cardiometabolic consequences supports the hypothesis that consuming meals irregularly is adversely associated with cardiometabolic risk. However, it also highlights the need for more large-scale studies, including detailed dietary assessment to further advance the understanding of the impact of chrono-nutrition on public health.

Chrono-nutrition: Irregularity: Meal frequency: Cardiometabolic disease risk: Meal patterns

Chrono-biological effects of nutrition: what *v.* when we eat

Our current lifestyle has become demanding and more irregular. This is reflected in food consumption patterns, which have changed markedly over the past decades: more meals are skipped, consumed outside the family context, on-the-go, later in the day and more irregularly[1,2]. The importance of eating regularly was highlighted early by Hippocrates (460–377 BC) and later by Florence Nightingale in her *Notes on Nursing*, in which she emphasised rest and regularity, including for food intake[3]. More recently, irregularity of food intake has emerged as a new potential risk factor for

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Abbreviations: CLOCK, circadian locomotor output cycles kaput; RR, risk ratios.
*Corresponding author: G. K. Pot, email G.k.pot@vu.nl

non-communicable chronic diseases such as CVD and metabolic syndrome[4–6]. It has been hypothesised that consuming irregular or inconsistent meals affects our internal body clock, also called chrono-biological or circadian rhythms, and could thereby have an impact on metabolic disease risk. Circadian rhythms are biological rhythms that follow a 24 h cycle, from Latin meaning 'approximate day'[7]. It is known that many physiologically and nutritionally relevant processes in the human body have circadian rhythms, including glycolysis and gluconeogenesis, cholesterol and lipid metabolism, oxidative phosphorylation and detoxification pathways[8,9]. This raises the question as to whether when we eat is equally important as to what we eat. This also highlights the need for understanding how the timing of dietary intake could affect chronic disease risk.

The term chrono-nutrition was introduced by Delabois in France in 1986 and was mainly applied in the context of specific diets, with guidelines about what foods to eat when[10]. The term can be applied more broadly when studying the impact of the timing of eating, combining elements from both nutritional research and chrono-biology[6]. Using the term chrono-nutrition, it is important to consider which aspects of time are included. In the definition used here, chrono-nutrition includes three aspects of time: (i) (ir)regularity (events at specific times), (ii) frequency (number of events over a period of time) and (iii) clock time (actual time of day). The present paper is mainly focused on the first aspect of time: (ir)regularity. Irregular meal patterns are defined here as food eaten in varying amounts through the day and at different times from one day to the next. Before going into the evidence on meal irregularity in relation to cardiometabolic disease risk, the effects of chrono-disruption in one specific group of the population, shift workers, will be presented.

Shift workers, disease risk and dietary patterns

An extreme form of living against internal body clocks is observed in those working shifts, particularly night shifts. It is known that shift workers have an increased risk of chronic diseases such as cancer[11], CVD and the metabolic syndrome[12]. The evidence for the relationship between shift work and increased disease risk is strongest for cancer. In 2007, the World Health Organisation/ International Agency for Research on Cancer published a brief report based on an expert meeting and concluded that shift work involving circadian disruption could be considered probably carcinogenic to human subjects[13]. This was based on sufficient evidence from experimental animal studies and limited evidence from human studies. Most epidemiologic evidence has been focused on breast cancer with meta-analyses showing a 40–50 % increased risk of breast cancer associated with long-term (minimally 20–30 years) night shift work[14]. For other types of cancer, such as prostate and colorectal cancer, the evidence was less conclusive but suggestive[12,15–17]. The evidence for a link between shift work and diseases other than cancer is less conclusive, but suggests that those working shifts have an increased risk of weight gain,

metabolic syndrome and vascular events. For weight gain, a systematic review by van Drongelen *et al.* in 2011 of eight studies showed strong evidence for a crude relationship between weight gain and shift work[18]. However, when confounders were taken into account, the evidence for a relationship between shift work and body weight change became insignificant. Of the eight studies, five adjusted for potentially relevant confounding variables, including age, gender, body weight at baseline and physical activity, and only two of the five were of high quality. These showed a positive association between shift work and body weight gain[18].

For the metabolic syndrome, a systematic review by Canuto *et al.* in 2013 of ten studies, identified eight studies that found a positive association between shift work and metabolic syndrome after adjustment for sociodemographic and behavioural factors[19]. However, only three studies also adjusted for sleep duration and these showed conflicting results. Sleep duration is considered an important potential confounding variable for the relationship between shift work and disease risk. The reduction of sleep duration, probably brought on by working in shifts, can exert important adverse metabolic effects. A systematic review by Patel and Hu in 2008, including both cross-sectional and longitudinal studies revealed that short sleep duration is independently associated with weight gain, particularly in children aged 10 years or less[20], thereby highlighting the need to consider sleep duration as a potential confounder.

For vascular events, the evidence of a positive association with shift work seems more convincing. A systematic review and meta-analysis by Vyas *et al.* in 2012 of eleven prospective cohort studies, thirteen retrospective cohort studies and ten case–control studies showed convincing evidence that people working shifts have an approximately 20 % increased risk of myocardial infarction (risk ratios (RR) 1·23 (95 % CI 1·15, 1·31)), coronary events (RR 1·24 (95 % CI 1·10, 1·39)) and ischaemic stroke (RR 1·05 (95 % CI 1·01, 1·09))[21]. Their analysis of unadjusted and adjusted RR both indicated similar results.

Thus, compared with individuals who work solely during the day, shift workers, whose working routine leads to chrono-disruption, are at a higher risk of developing a range of metabolic diseases[22]. It is quite possible that this is related to changes in dietary patterns. A discussion paper by Lowden *et al.* in 2010 on eating and shift work, effects on habits, metabolism and performance showed that at least some of the increased disease risk of shift workers may be linked to diet and the irregular timing of eating[22]. Their review comprised twenty-three studies, and dietary intake information included data on meal frequency, meal times and total energy intake and the dietary intake data were assessed using different methods, including FFQ and 24 h recalls. The results of this review showed that total daily energy intake was similar for shift workers compared with non-shift workers. However, shift workers had more irregular eating patterns, altered meal frequency, usually impaired quality of dietary intake and the distribution of dietary intake over the day. For example, one study investigated

dietary intake of 101 mine workers in the USA and found that those working night shifts reported an increased number of meals consumed at different times, more changes in their dietary patterns than when not working at night, with a shift from three meals to often one meal/d[23]. Subjects also noted the changes in their perception of eating habits when working night shifts and reported increasing dissatisfaction with their eating habits[23].

The findings of Lowden et al. are supported by results from other cohort studies of shift workers[24–26]. A study in ninety-six male Swedish industrial workers found that energy intake and quality of food were not affected by shift work, but that the circadian distribution of food changed and coffee consumption increased[24]. A study of twenty-two Brazilian garbage collectors working in shifts also found no difference in their daily energy intake when working night shifts in spite of differences in food choices (which became mainly starchy foods, alcoholic drinks and sweets) and circadian ingestion rhythms[25]. However, their total average daily energy intake was very high (12–71 MJ/d (3000–6000 kcal/d)). Another study of twenty-eight Brazilian shift workers found circadian rhythmicity of energy consumed by night workers but only during the summer[26]. A study on anthropometry and food intake patterns in bus drivers in Brazil reported higher proportions of inappropriate feeding practices, excess weight and abdominal obesity amongst drivers who worked night shifts[27].

So far, few studies have specifically investigated how consuming at a particular time of day relates to overall dietary intake in human subjects[28,29]. De Castro was one of the first nutritional researchers to demonstrate that dietary intake in the morning is particularly satiating and can reduce the total amount consumed in a day, while eating later in the evening is less satiating and can lead to a greater overall daily intake[28]. De Castro also investigated specific types of foods and found that eating low-density foods in the morning, such as fruit, breakfast cereals, coffee and tea, and avoiding high-density foods at night, such as meat, chips and snacks, and alcohol, could be an overall strategy to reduce overall dietary intake[29]. These studies demonstrated that eating at a particular time of day was associated with total daily dietary intake.

Overall it seems that when shift work leads to chrono-disruption, changes in dietary patterns are an important aspect to consider. Conversely, not only shift workers are exposed to chrono-disruption. A less extreme form of living against our internal body clock, but which affects far more people, is caused by the so-called social jetlag[30]. Social jetlag is the discrepancy between our internal body clocks and our social clock and this has also been associated with increased risk for non-communicable chronic diseases such as obesity[30] and the metabolic syndrome[7]. It has been estimated that social jetlag affects more than 80 % of the general population in central Europe[30], especially people living in urban areas. The focus of this narrative review was to study the evidence about consuming meals irregularly in relation to cardiometabolic consequences in the general population.

Almoosawi et al. further discusses the impact of clock time on nutritional intake and its association with disease risk[31].

Evidence for meal irregularity and cardiometabolic consequences

Observational studies

A summary of the evidence from observational studies on meal irregularity and cardiometabolic consequences is presented in Table 1. The first study identified was a cross-sectional study of 3607 Swedish men and women (1686 men and 1921 women) aged 60 years by Sierra-Johnson et al. in 2008[32]. Information on meal regularity was assessed using a questionnaire, including a question 'do you eat regular breakfast, lunch or evening meal each day?'. Based on their answers, participants were categorised as either regular eaters (answering 'usually' or 'always') or irregular eaters (answering 'sometimes' or 'never'). Information on cardiometabolic risk factors was assessed by a medical examination that included laboratory tests assessing serum concentrations of glucose, insulin, cholesterol and TAG. The metabolic syndrome was calculated based on the updated Adult Treatment Panel III criteria[33]. Results showed that irregular eaters had significantly greater mean weight, waist circumference, BMI and TAG than regular eaters. Irregular eaters had an increased prevalence of metabolic syndrome components compared with regular eaters ($P < 0.001$). Moreover, eating regularly was inversely associated with the metabolic syndrome (OR 0·63 (95 % CI 0·45, 0·88)) and this was independent of traditional risk factors, such as sex, smoking, education, physical activity and consumption of fruit, vegetables and fish. Eating regularly was particularly inversely associated with waist circumference (OR 0·64 (95 % CI 0·47; 0·88)) and directly related to HDL-cholesterol (OR 0·63 (95 % CI 0·45, 0·91)) and circulating γ-glutamyl transferase concentrations (OR 0·54 (95 % CI 0·35, 0·84)), believed to be a marker of oxidative stress[34].

A study by Shin et al. in 2009 of 5337 Korean men aged 30 years and over in a cross-sectional survey investigated the association between the intake frequencies of certain foods and eating habits and the risk of the metabolic syndrome[35]. Eating habits included information on meal frequency, breakfast frequency, mealtime regularity, meal speed and overeating frequency. For the question on mealtime regularity, participants either answered always regular, often irregular or always irregular. In addition to this self-reported questionnaire, information on the metabolic syndrome was assessed via a clinical examination, including assessment of height and weight, and taking of fasting venous blood samples to assess glucose, TAG, and total and HDL-cholesterol. Participants with the metabolic syndrome were more likely to eat quickly (OR 2·23 (95 % CI 1·60, 3·12) for fast v. slow) and overeat frequently (OR 2·37 (95 % CI 1·85, 3·05) comparing more than four times per week v. less than once weekly). However, no statistical significant association was found for meal time regularity

Table 1. Summarising the main findings of reviewing the literature on the association between meal irregularity and cardiometabolic consequences

		Population		Intervention			Control		Outcome	
Reference	Author and year	Location	Sample size	Study design	Duration	Intervention	Control	Measurement	Outcome	Main finding

Meal irregularity

Reference	Author and year	Location	Sample size	Study design	Duration	Intervention	Control	Measurement	Outcome	Main finding
[32]	Sierra-Johnson *et al.* (2008)	Sweden	*N* 3607 (*n* 1686 m, *n* 1921 f)	Cross-sectional study, population based	NA	NA	Always *v.* never	Questionnaire	MS IS γ-G	MS OR 0·27 (0·13, 0·54) IS OR 0·68 (0·48, 0·97) γ-G OR 0·52 (0·33, 0·83)
[35]	Shin *et al.* (2009)	South Korea	*N* 7081 m	Cross-sectional study	NA	NA	Not at all *v.* always	Questionnaire (meal freq, breakfast freq, meal time regularity, meal speed, overeating freq)	MS	OR M freq OR 1·04 (0·78, 1·39) B freq OR 1·10 (0·88, 1·37) MT reg OR 0·97 (0·71, 1·31) M speed OR 2·23 (1·60, 3·12) Overeat freq OR 2·37 (1·85, 3·05)
[36]	Pot *et al.* (2014)	UK	*N* 1768	Cross-sectional analysis (in prospective cohort study)	NA	NA	Low *v.* high irregularity score	Meal irregularity score based on 5 d food diary	MS (and MS components)	OR Daily: 1·09 (0·81, 1·47) Breakfast: 1·34 (0·99, 1·81) Lunch: 0·92 (0·68, 1·25) Ev meal: 1·26 (0·93, 1·70) Between meals: 1·36 (1·01, 1·85)
[37]	Pot *et al.* (2016)	UK	*N* 1381	Prospective cohort	10 and 17 years follow-up	NA	Low *v.* high irregularity score	Meal irregularity score based on 5 d food diary	MS (and MS components)	*10 years follow-up* Breakfast 1·53 (1·15, 2·04) *17 years follow-up* Lunch 1·42 (1·05, 1·91) Between meals 1·35 (1·01, 1·82)
[39]	Wennberg *et al.* (2015)	Sweden	*N* 889	Prospective cohort	27 years follow-up	NA	All meals regularly *v.* all meals irregularly	Questionnaire	MS (and MS components)	OR 1·74 (1·12, 2·71)
[42]	Farshchi *et al.* (2004)	UK	Lean f (*n* 9)	RCT, cross-over	14 d	6 meals/d *v.* 3–9 meals/d	6 meals/d *v.* 3–9 meals/d	3 d Food diary	CVD risk markers	Lower peak insulin and AUC Lower fasting total and LDL-cholesterol No effect on fasting glucose or insulin
[43]	Farshchi *et al.* (2005)	UK	Obese f (*n* 10)	RCT, cross-over	14 d	6 meals/d *v.* 3–9 meals/d	6 meals/d *v.* 3–9 meals/d	3 d Food diary	CVD risk markers	Lower EI Greater postprandial thermogenesis Lower fasting total and LDL-cholesterol Lower peak insulin and AUC

AUC, area under the curve; B, breakfast; EI, energy intake; EO, eating occasion; Ev, evening; f, female; f-gluc, fasting glucose; γ-G, γ-glutamyltransferase; IS, insulin resistance; m, male; M, meal; MS, metabolic syndrome; MT, meal time; NA, not applicable; OR, odds ratio; RCT, randomised controlled trial; RR, relative risk; WC, waist circumference.

(OR 0·97 (95 % CI 0·71, 1·31), when comparing always regular to always irregular).

Although the studies by Sierra-Johnson et al.[32] and Shin et al.[35] provided interesting insights into the possible associations of meal irregularity and risk of the metabolic syndrome, both studies were limited by the fact that meal irregularity was assessed via a single question in a questionnaire. Detailed dietary assessment could provide more insight into the impact of meal irregularity on cardiometabolic consequences.

Two observational studies on meal irregularity and cardiometabolic consequences based on detailed dietary assessment have been conducted by the authors[36,37]. Both were performed in the National Survey for Health and Development, also known as the 1946 British birth cohort[38]. The first analysis investigated the association between meal irregularity and the metabolic syndrome in 1768 men and women aged 53 years[36]. The metabolic syndrome was assessed during a nurse visit and was based on the Adult Treatment Panel III criteria with a minor adaption of using Hb1Ac as fasting blood glucose was not available[33]. Dietary assessment was based on 5-d estimated food diaries, which included pre-defined meal slots for breakfast, lunch, evening meal, and between meals. We developed a score for meal irregularity which was based on the variability in energy intake per meal relative to the 5-d mean of energy intake during that meal, with a lower score indicating a more regular meal pattern and a higher score indicating greater irregularity[36]. Mean irregularity scores were calculated for each of the four time slots (breakfast, lunch, evening meal and between meals) as well as for the daily total. These irregularity scores were related to the metabolic syndrome using logistic regression models, adjusting for relevant confounding variables (sex, physical activity, socio-economic status, marital status and smoking). An increased risk of the metabolic syndrome was associated with more irregular energy intake at breakfast (OR 1·34 (95 % CI 0·99, 1·81) comparing the highest tertile of irregularity score with the lowest tertile; P trend = 0·04) and between meals (OR 1·36 (95 % CI 1·01, 1·85); P trend = 0·04). When investigating the components of the metabolic syndrome, the strongest associations were found for central obesity (based on waist circumference) and obesity (based on BMI). For the other components of the metabolic syndrome, including HDL-cholesterol, TAG and systolic and diastolic blood pressure, no statistical significant associations were found with meal irregularity. It could be argued that those who consume meals more irregularly may also underreport their total energy intake more than regular consumers. However, these associations remained when those who underreported their total energy intake were excluded.

We next investigated how meal irregularity was associated with subsequent risk of developing the metabolic syndrome in the same National Survey for Health and Development cohort[37]. Five-day estimated food diaries were available at ages 36, 43 and 53 years, and the metabolic syndrome was assessed during a nurse visit at age 53 years as previously described. Similar to the cross-sectional analysis, a score for meal irregularity was calculated for breakfast, lunch, evening meal, between meals and a daily total[36]. Results showed that irregularity scores changed significantly over the years from when the cohort members were aged 36 years (1982) to when the cohort members were 53 years (1999; P linear mixed models <0·05), and the largest changes in meal irregularity were observed for between meals, which declined over time. At age 36 years, cohort members with a more irregular intake of energy during lunch (OR 1·42 (95 % CI 1·05, 1·91)) and between meals (OR 1·35 (95 % CI 1·01, 1·82)) had an increased risk of developing the metabolic syndrome 17 years later. At age 43 years, cohort members with a more irregular intake during breakfast had an increased risk of developing the metabolic syndrome 10 years later (OR 1·53 (95 % CI 1·15, 2·04)).

Thus, by using this score for meal irregularity based on detailed dietary information, we found that individuals with a more irregular intake, especially at breakfast, lunch and between meals, had an increased risk of the metabolic syndrome. These findings were confirmed by a recent prospective cohort study from Norway by Wennberg et al.[39] who found that irregular eating of meals at age 16 years was associated with a higher prevalence of the metabolic syndrome 27 years later at age 43 years in 889 participants. However, they found that this was largely explained by an unhealthy lifestyle at age 16 years and when correcting for lifestyle factors (such as BMI at age 16 years, smoking, alcohol consumption, physical activity and consumption of sweets and pastries at age 16 years), the only statistically significant association was observed for poor breakfast consumption.

A study in 6851 Spanish university graduates investigated the specific impact of snacking on metabolic syndrome risk[40]. Participants were classified into two categories based on the response to the question 'do you have the habit of snacking between main meals?' (yes or no). After a median follow-up time of 8·3 years they found that 34·6 % of cohort members reported consuming snacks between meals. Snacking between main meals was statistically significantly associated with a higher risk of developing the metabolic syndrome (RR 1·44 (95 % CI 1·18, 1·77)). Furthermore, adherence to a 'unhealthy snacking pattern' was independently associated with an increased incidence of the metabolic syndrome (RR 1·66 (95 % CI 1·23, 2·29)).

One study was identified that included measures of meal irregularity, but did not assess cardiometabolic risk factors per se. Sjöberg et al. studied meal patterns, food choice and lifestyle factors in 1518 boys and girls and found that a meal pattern with omission of breakfast and lunch was related to a clustering of less healthy lifestyle factors (e.g. smoking and consumption of snacks) and food choice leading to poorer nutrient intake[41].

Therefore, although the evidence from observational studies, especially those including detailed dietary information, is scarce, it does point in the direction that consuming meals irregularly is associated with an increased risk of the metabolic syndrome.

Randomised controlled trials

Although no specific randomised controlled trials were identified that studied the effects of meal irregularity and cardiometabolic consequences, two randomised controlled trials were identified that examined the effects of regular meal frequency. Farshchi *et al.* conducted two randomised cross-over dietary intervention studies investigating the impact of irregular meal frequency pattern on circulating lipids, insulin, glucose and uric acid in nine healthy lean women[42] and ten healthy obese women[43]. The intervention consisted of two phases of 14 d each, during which the cohort members consumed their normal diet on six occasions/d (regular) or by varying meal frequency (3–9 meals/d) with a 2-week washout period between the two phases. The first study in lean women (BMI 23·7 (sd 7·4) kg/m^2) showed that fasting glucose and insulin concentrations were not affected by meal frequency, but peak insulin and area under the curve responses to a test meal were higher after the irregular meal routine compared with the regular meal routine[42]. Irregular meal frequency was also associated with higher fasting total and LDL-cholesterol ($P < 0.01$) suggesting that the irregular meal routine appeared to produce a degree of impaired insulin resistance and higher fasting lipid profiles. In the obese women (BMI 37·1 (sd 4·8) kg/m^2), results were very similar to what was found in lean women, with no effect on fasting glucose and insulin, but peak insulin responses to a test meal lower after the regular meal pattern than after the irregular meal pattern[43]. In addition, the regular eating frequency was associated with lower energy intake, greater postprandial thermogenesis and lower fasting total and LDL-cholesterol[43].

These randomised controlled trials showed that an irregular eating frequency seem to negatively impact fasting lipid and postprandial insulin profiles and thermogenesis, confirming the importance of meal patterns in influencing carbohydrate and lipid metabolism in addition to the amount and composition of food consumed.

Proposed underlying mechanisms

Although the evidence from observational and intervention studies on meal irregularity and an increased cardiometabolic risk is limited, a number of underlying mechanisms serve to explain the results, mainly related to chrono-biology[5,44,45]. Many nutritionally related processes in the body follow a circadian pattern, such as glucose homeostasis, insulin sensitivity, postprandial response and plasma lipids[9]. Circadian rhythms in the human body are a complex interaction of many circadian patterns, which are thought to be controlled in two main ways: via the central clock, the suprachiasmatic nucleus in the hypothalamus, and by peripheral circadian clocks which are present in nearly all organs and cells[6,8]. The suprachiasmatic nucleus is thought to be the master clock and is entrained by external cues ('zeitgebers'), mainly light from eyes, as well as age and genes. The suprachiasmatic nucleus coordinates the many peripheral clocks, so that they maintain proper phase-relationships

with each other[8]. In turn, peripheral clocks can be entrained by zeitgebers, with dietary intake being a dominant zeitgeber for many of these[46,47].

Animal models provide an excellent opportunity to elucidate how circadian dysfunction could lead to different pathologies and research has been primarily focused on shifting the night–day cycle to imitate human jet lag or shift work to study the effects of circadian rhythms. Animal studies have indicated that the increased weight gain observed within the shift work population is caused, at least partly, by eating during the 'wrong' time of day[6,48]. A major finding to link chrono-disruption and metabolic homeostasis at the molecular level was the discovery of a specific 24-h circadian rhythmicity in adipose tissue genes in 2005[49,50]. Basic mechanistic links between circadian rhythms and metabolic regulation were uncovered with the discovery of genes that showed circadian rhythmicity. One example of such a gene is the circadian locomotor output cycles kaput (CLOCK) gene in mutant mice, which was shown to greatly attenuate diurnal feeding rhythm. Mice lacking this gene were hyperphagic, obese and rapidly developed the metabolic syndrome[51]. Other genes, like Bmal1 and Per1/2 and Cry1/2 were found to form an important transcriptional–translational feedback loop in the circadian system[6,52]. The CLOCK and Bmal1 transcriptional–translational feedback loop stimulates the transcriptional activity of three period (Per) and two crytochrome (Cry) genes. After appropriate temporal delay caused by post-transcriptional modifications, the translated Per and Cry proteins then form protein complexes that translocate into the nucleus and inhibit their own transcription via interaction with CLOCK and Bmal1[9]. Two recent reviews by Johnston in 2014 summarise the evidence on the link between circadian rhythms, metabolism and nutrition with a particular focus on mouse and human studies[9] and the physiological responses to food intake throughout the day[53]. It seems that the relationship between food intake and circadian rhythms are often reciprocal: circadian systems can drive temporal changes in metabolic pathways and changes in metabolic pathways can alter core molecular components of circadian rhythms[53]. Metabolic rhythms include daily changes in glucose homeostasis, insulin sensitivity, postprandial response and plasma lipids. Interestingly, it appears that the amplitude of some of these rhythms is reduced in the obese, although this varies from study to study and by hormone[9,53].

Recent work by Garaulet *et al.* investigated the link between the timing of food intake during weight loss studies and found that eating late may negatively impact the success of weight loss in a cohort of 420 participants (49·5 % female, aged 42 (sd 11) years, BMI 31·4 (sd 5·4) kg/m^2). They also included a SNP of CLOCK in their investigations and found that the CLOCK rs4580704 was associated with the timing of the main meal, with a higher frequency of minor allele C carriers among late eaters. However, this CLOCK SNP, sleep duration or chrono-type (morningness/eveningness) was not associated with weight loss[54].

To summarise the possible impact of meal irregularity on cardiometabolic consequences, and the processes
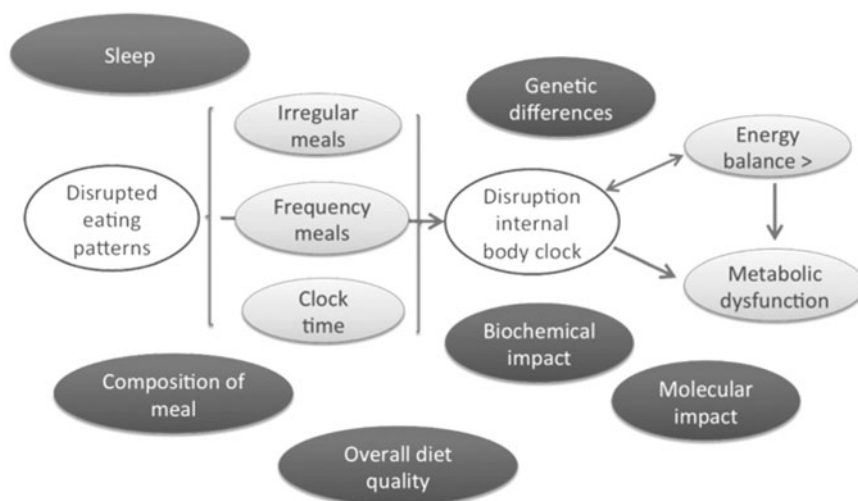
Fig. 1. Conceptual framework of how meal irregularity could impact on metabolic dysfunction.

involved, a conceptual framework is presented in Fig. 1. Disrupted eating patterns, consisting of irregular meals, different frequency of meals, as well as specific clock time of meals, could lead to disruption of the internal body clock. This in turn could lead directly to a positive energy balance, which could then lead to metabolic dysfunction. Circadian disruption could also directly lead to a positive energy balance. It is known that this disruption of the internal body clock is affected by genetic differences, for example in CLOCK genes[9]. Disruption of the internal body clock could have biochemical and molecular impacts, such as an effect on the circadian responses of glucose and lipids[9]. Furthermore, when investigating the impact of disrupted eating patterns on cardiometabolic risk, it is important to consider the bigger picture of the meal, in other words the composition of a meal, such as its fat content, and overall dietary quality as this could directly affect cardiometabolic disease risk[55–57]. Lastly, one element that is very closely related to chrono-disruption and indirectly also with food intake is sleep. Short sleep duration has been associated with a positive energy balance[20]. A systematic review from our group showed a 1158 kJ (277 kcal) higher energy intake after partial sleep deprivation compared with control in seventeen studies, including 496 participants (Al Khatib *et al.*, unpublished results). Sleep is therefore an important element of this complex picture to consider when investigating the link between meal irregularity and cardiometabolic risk. In conclusion, irregularity of meals could lead to a wide range of responses that could in turn lead to increased cardiometabolic risk. Investigating the effects of meal irregularity on cardiometabolic risk is just one piece of the puzzle of the effects of the timing of eating.

Meal irregularity and meal frequency

Whilst the present paper was not specifically focused on meal frequency and cardiometabolic risk factors, meal irregularity is closely inter-linked with meal frequency, as could also be observed in the randomised controlled trials by Farshchi *et al.*[42,43]. It has been hypothesised that consuming small but frequent meals helps with weight maintenance and enhances fat loss[58–60], a concept that has been applied in many fad diets.

A number of observational studies support this hypothesis, although it seems that this association differs somewhat for children compared with adults[61–64]. A recent review in children showed that three of five studies comprising overall 13 998 children and adolescents showed a significant reduction of obesity risk with increasing number of meals, which persisted after adjustment for confounders; two other studies found non-significant trends in the same direction[61]. Smith *et al.* studied the association between daily eating frequency and cardiometabolic risk factors in 2775 young Australian adults aged 26–36 years and found that a higher number of eating occasions was associated with reduced cardiometabolic risk factors in young men but not in young women[62].

In adults, the evidence for a relationship between meal frequency and obesity is more mixed. Some studies have found an inverse association between meal frequency and overweight, for example a Swedish survey including 3610 men and women aged 25–74 years[63]. However, a review by Palmer *et al.* in 2009 specifically focusing on weight loss intervention studies concluded that the limited evidence available suggested that there is no association between eating frequency and weight or health in either weight loss or weight maintenance intervention studies[64]. Nonetheless, a possible inverse association between eating frequency and lipids in weight-maintenance studies was observed. Of the twenty-five studies included in their review, only ten were specifically focused on weight-loss. In addition, sample sizes were generally small, interventions were relatively short-term and the definition of eating occasion varied from study to study.

More recently, the association between eating frequency, meal frequency and snack frequency and obesity

was investigated using data from the National Health and Nutrition Examination Survey (2003–2012), a large observational study in 18 696 US adults based on two 24 h dietary recalls[65]. Results showed a statistically significantly higher risk of overweight and obesity for those consuming ⩾5 meals compared with those consuming ⩽3 meals/d with an OR 1·54 (95 % CI 1·23, 1·93) for men and an OR of 1·45 (95 % CI 1·17, 1·81) for women; for central obesity an OR of 1·42 (95 % CI 1·15, 1·75) for men and an OR of 1·29 (95 % 1·05;1·59) for women when adjusting for confounders including dietary misreporting. However, the direction of the association between eating frequency and overweight and obesity radically changed when adjustment for dietary misreporting was not taken into account, highlighting the need to consider dietary mis-reporting in these types of analyses.

As there seems to be a positive association of meal frequency and obesity risk in adults, one could argue that we should consume fewer meals/d. A randomised controlled cross-over pilot study investigated the effects of consuming one meal/d *v.* three meals/d in twenty men and women (aged 40–50 years, BMI normal range)[66]. The intervention lasted for 8 weeks with 11 weeks washout between the two treatments and both treatments were iso-energy. Fifteen subjects (ten women and five men) completed the study (dropout rate 28·6 %). Results showed that blood pressure, both systolic and diastolic, was significantly lower (6 %) when consuming three meals/d *v.* one meal/d. However, body weight was significantly higher when consuming three meals/d as well as fat mass. Moreover, they found pro-atherogenic effects (increased total and LDL-cholesterol) and anti-atherogenic effects (increased HDL-cholesterol and decreased TAG) after consuming three meals/d. Consuming one meal/d decreased cortisol concentrations and led to more hunger, desire to eat, and prospective consumption was estimated higher and feelings of fullness were significantly lower. Although the results of this pilot study showed that normal-weight subjects were able to comply with a one meal/d regimen, the findings suggest that, without a reduction in energy intake, a reduced meal frequency does not offer major health benefits in human subjects[66].

Proposed mechanisms that explain the association between meal frequency and obesity include better appetite control, improved glucose homeostasis and increase in the thermic effect of food[58]. With ageing comes a decline in the ability to regulate food intake, e.g. less able to compensate for higher energy intake, due to altered hormonal signals such as cholecystokinin, glucagon-like peptide 1 and peptide YY cholecystokinin, glucagon-like peptide 1, and peptide YY and impaired senses taste and smell[60], which may explain some these differences observed in children and adults.

Food for thought

This new emerging line of research warrants further food for thought and there are several aspects to consider related to the research included in the present paper.

The inconsistency in terminology used in this novel area made it difficult to identify all the evidence. The term chrono-nutrition was introduced in 1986 by Delabois[10] but was not much used beyond its application in weight loss diets. Other commonly used terms include circadian patterns of nutrition intake, (ir)regular feeding pattern, meal patterns and meal routines. Therefore, we propose use of the term chrononutrition when studying the impact of food intake on metabolism via the circadian clock system.

The present paper was focussed on the irregularity of meals and for this it is important to consider the diversity in definitions of meals or meal patterns as discussed by Berg and Forslund[67]. The inconsistency in definitions of eating occasions or meals may complicate interpretation and comparison of research results. For example, the term 'meal' is common in literature and often corresponds to the main meal: breakfast, lunch or evening meal. The classification of temporal distribution of meals is usually based on cultural norms[67,68]. Recent analysis by Leech *et al.* showed in an Australian survey that a neutral definition (individual eating occasions separated by a specific time interval, such as 15 min) was best in predicting variance in total energy intake[69]. A review by Leech *et al.* in 2015 found that most studies included in their review use a participant-identified approach[70]. This is in line with our studies using food diaries with pre-structured mealtime slots where it was up to participants who completed these food diaries to interpret what these labels meant.

The word irregularity can also be interpreted in several different ways. In this research, irregular meal patterns were defined as food being eaten in varying amounts through the day and at different times from one day to the next. However, meal irregularity could also be interpreted as being related to meal frequency, as was observed in the studies by Farshchi *et al.*[42,43] making the distinction between meal irregularity and meal frequency somewhat distorted.

The results of this review did not allow us to investigate whether the impact of the timing of eating on cardiometabolic risk could differ in specific groups of the population, e.g. men *v.* women, or children *v.* older adults although the evidence from experimental studies seems to suggest there could be differences between these groups. For example, the differential relationship of eating frequency and cardiometabolic risk factors between men and women was discussed by Smith *et al.*[62]. They speculated as to why they observed an association of daily eating frequency and cardiometabolic risk factors in men but not in women and suggested that women who ate more often were eating unhealthy snacks and underreported these items in the FFQ or their extra meals and snacks, which resulted in higher energy intakes. In addition, they speculated that it might be due to the different fat distribution in men and women with men storing their fat more centrally and women more peripherally. Generally, central obesity is considered to be more harmful for cardiometabolic health than peripheral fat.

The possible differences between younger and older adults in meal irregularity and cardiometabolic

consequences could be related to a decline in the ability to regulate food intake, e.g. less able to compensate for higher energy intake, due to altered hormonal signals such as cholecystokinin, glucagon-like peptide 1 and peptide YY and impaired senses taste and smell[60].

The findings of this review also emphasised the importance of the assessment method for meal irregularity and raises the question whether meal irregularity can be assessed in a single question or whether more detailed dietary information, such as food diaries, provides more insight into this important topic. As with other studies that include dietary assessment, dietary underreporting is also essential to consider. Studies have shown that underreporters on one occasion were likely to be an underreporter on other occasions[71], therefore including dietary misreporting the analyses of meal regularity and any health outcome seems essential.

When comparing the levels of underreporting in children and adults, it has been shown that the percentage of children who underreport energy intake is usually somewhat smaller compared with adults[72], which may in part also contribute to the differences in findings observed for children and adults with regards to meal irregularity and cardiometabolic consequences.

Further directions

In general, the impact of dietary intake on metabolic health is a complex multi-dimensional picture and to unravel this complex picture, one has to focus on one particular aspect first before this can be placed in the bigger context. To fully understand the impact of the timing of eating on metabolic disease risk other elements, such as frequency and clock time also need to be taken into account. A review by McCrory and Campbell in 2011 suggested that when examining eating patterns, such as eating frequency, snacking or breakfast consumption, it is not very meaningful to do so in isolation as in the real world these eating behaviours are very much intertwined[73]. Moreover, when studying the impact of irregular meal patterns, it is also important to consider what people eat, for example regular overconsumption of unhealthy foods is not considered to be beneficial for our health. It has been observed that there is an association between meal patterns and diet quality. This is supported by the recent review by Leech et al. who found that an association with meal patterns and diet quality, and more specifically an inverse association between breakfast skipping and diet quality[70].

An even further step after studying the impact of what and when we eat is to study where we eat and with whom we eat. A recent meta-analysis showed that family meal frequency contributes to more healthy eating among children and adolescents[74], with positive associations between family meals and adolescent dietary intake including fruit and vegetables consumption, dairy consumption and less consumption of sugar-sweetened beverages[75]. Sleep timing is the most prominent expression of the internal body clock[76] and hence it would be

crucial to include sleep in the overall picture of the complex associations of chrono-nutrition and disease risk.

This review was concentrated on the impact of meal irregularity on cardiometabolic risk factors, but studies in shift workers indicate that they are also at an increased risk of developing other diseases such as cancer[6]. Cancer is among the leading causes of death worldwide and evidence from the World Cancer Research Fund/American Institute of Cancer Research has estimated that about one third of all cancers could be prevented by a healthier diet, having a healthier weight and being more physically active[77]. Therefore, it would be very relevant to study the impact of meal irregularity on cancer risk. The evidence from the 2007 World Cancer Research Fund/American Institute of Cancer Research report on food, nutrition, physical activity and the prevention of cancer suggests that people are at an increased risk of stomach cancer when consuming meals irregularly as opposed to regular eating, however there was too much heterogeneity amongst the studies to make a firm judgement[77]. Therefore, more studies are needed, particularly with detailed dietary information, which would allow the study of chrono-nutritional effects in large prospective cohorts and in disease outcomes like CVD as well as cancer.

Public health implications

When combatting the effects of chronic disease, food timing has emerged as a new approach to the treatment of obesity and the metabolic syndrome[78]. A recent review of dietary therapies and innovative time-associated dietary approaches concluded that regular meal eating habits might facilitate maintaining weight while unplanned snacking as well as consuming the major part of the energy intake at the end of the day seem to be unfavourable[67]. The work by Garaulet and Gómez-Abellán also showed the importance of the timing of eating in weight loss studies[79,80].

Another important aspect to consider when studying meal habits and its potential use for public health interventions is to consider when dietary habits are formed. Generally, dietary habits are formed early in life and it is therefore important to consider the context of eating, and to study young adults to identify meal routines and practices and healthy dietary factors[81].

Conclusions

Overall, this narrative review showed that it is important to further advance research about not only what people eat but also when they eat. Although the evidence from robust observational and intervention studies including those based on detailed dietary assessment is limited, research to date appears to indicate that consuming meals irregularly could increase cardiometabolic risk. It also highlights the need for more large-scale observational and intervention studies, which have detailed dietary assessment, to further advance the understanding of the

impact of chrono-nutrition on public health. The circadian clock appears to operate as a critical interface between nutrition and homeostasis, and this calls for more attention to the beneficial effects of chrono-nutrition[82], including the adaptation of the term 'chrono-nutrition'. Until then, the advice from Hippocrates and Florence Nightingale emphasising the importance of regularity probably also holds for dietary intake.

Acknowledgements

Financial Support

Conflicts of Interest

None.

Authorship

G. P. designed and conducted the review; G. P., S. A. and A. M. S. contributed to the paper.

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