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EDITORIAL

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Chrono-nutrition – an emerging, modifiable risk factor for chronic disease?

INTRODUCTION

Everything around us has a rhythm, including the internal processes in our body. These are called circadian rhythms since they occur in a 24-h cycle (from Latin *circa* = around and *dia* = a day). During the COVID-19 pandemic, many people have seen their normal daily routine disrupted and they may have changed their timing of eating and sleeping. These changes in the timing of eating and sleeping may have had metabolic effects. Over the past decade, nutrition researchers have incorporated research of biological temporal rhythms, chrono-biology, into nutrition research, and this novel area of nutrition research is called chrono-nutrition (Garaulet & Gómez-Abellán, 2014; St-Onge et al., 2017; Tahara & Shibata, 2013). Chrono-nutrition includes research into the distribution of energy intake, meal frequency and regularity, the duration of eating and fasting periods, and the relative importance of these factors for metabolic health and chronic disease risk (Flanagan et al., 2020; Pot et al., 2016). This Virtual Issue brings together papers recently published in *Nutrition Bulletin* discussing different aspects of chrono-nutrition, including sleep, breakfast consumption and time-restricted feeding (Figure 1) (Clayton et al., 2020; Darzi et al., 2017; Edinburgh et al., 2017; Gibson, 2018; Gibson-Moore & Chambers, 2019; Lynch et al., 2021; Ruddick-Collins et al., 2018). Other elements of chrono-nutrition such as meal regularity, meal frequency and clock time (time of eating) are beyond the scope of this Virtual Issue. This editorial aims to set these papers in context of the wider research in this emerging field and goes on to discuss the potential public health implications of considering chrono-nutrition, including the importance of chrono-type and what findings from chrono-nutrition research might mean for shift workers.

Biological clock: Underlying mechanisms

To understand the underlying mechanisms of how chrono-nutrition can affect health, it is important to consider how the biological clock works. In brief, the circadian timing system manages daily biological rhythms and synchronises physiology and behaviour to the temporal world (Flanagan et al., 2020). The central clock, located in the hypothalamic suprachiasmatic nuclei (SCN), is entrained by two main signals (also called zeitgebers): light and food intake (Green et al., 2008). In addition, almost all tissues in our body have peripheral clocks (Flanagan et al., 2020) and are under control of circadian genes (*i.e.* clock genes) (Dashti et al., 2011, 2015b). This network of both the central clock and peripheral clocks imposes a rhythmic control over virtually all our bodily functions, for example from when we feel sleepy to when we feel hungry.

Feeding behaviour follows a strong diurnal or circadian pattern [*e.g.* nocturnal rodents such as mice and rats typically consume the majority of their calories during their active phase in the dark (Flanagan et al., 2020)]. When mice were forced to consume calories during their resting phase, they gained more weight compared with mice that consumed isocaloric meals during the active phase (Arble et al., 2009). This suggests that a calorie may not always have the same metabolic effect and that the metabolic effects may depend on the time of day it is consumed. Human intervention studies have confirmed these findings and showed that metabolic responses to meals are strongly influenced by the time of day at which they are consumed (Garaulet et al., 2013; Jakubowicz et al., 2013). Garaulet et al. were one of the first groups to observe that among women who were trying to lose weight, those consuming their main meal before 3 pm lost more weight than women who consumed their main meal after 3 pm during a 20-week weight loss intervention in 420 women with obesity (Garaulet et al., 2013). Jakubowicz et al. found similar results in 93 women with overweight or obesity and showed beneficial effects of high caloric intake at breakfast compared with in the evening in terms of weight loss, waist circumference, serum ghrelin and lipids, appetite scores and insulin resistance indices (Jakubowicz et al., 2013). Other studies have shown the importance of meal frequency and/or meal irregularity for cardiometabolic health (Farshchi et al., 2004; Farshchi et al., 2005; Madjd et al., 2016; Pot et al., 2016).

Specific examples of metabolic processes that are under tight control are the regulation of blood levels of glucose and triacylglycerol (TAG). For a healthy individual in a fasted resting state, blood glucose is under tight control at around 4.6 g or 4–5 mmol/l. Oral glucose

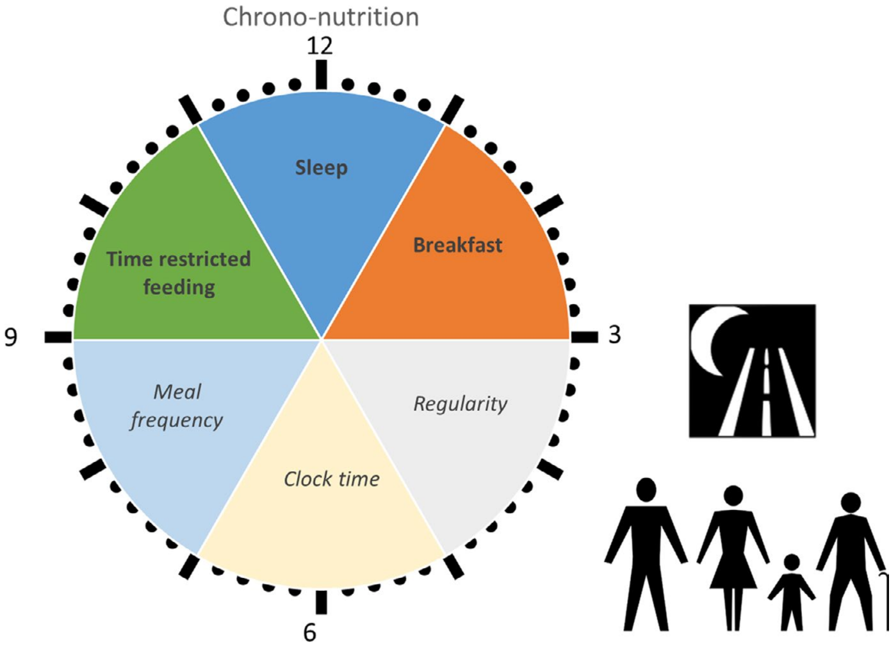

FIGURE 1 Different elements of chrono-nutrition. Those discussed in this Virtual Issue on chrono-nutrition include sleep, breakfast consumption and time-restricted feeding [Colour figure can be viewed at wileyonlinelibrary.com]

tolerance tests, as a measure of insulin sensitivity, display a diurnal rhythm that usually peaks in the morning and reduces later in the day (Jarrett et al., 1972; Van Cauter et al., 1997). The review by Edinburgh et al. in this Virtual Issue examines the role of the timing of diet and exercise in mediating postprandial glucose and TAG responses (Edinburgh et al., 2017). Many individuals typically consume three meals per day and thus spend the majority of waking hours in a postprandial state (de Castro, 2004). Exaggerated postprandial glycaemia and triglyceridaemia are associated with cardiometabolic diseases (Ning et al., 2012; Nordestgaard et al., 2009). Ingestion of carbohydrates and fat can have different effects on postprandial glucose and TAG excursions. These responses may depend on many factors, including the quantity and type of each macronutrient consumed as well as their timing in relation to physical activity and the habitual physical activity level of an individual.

Sleep

Sleeping at night and being awake during the day is also a light-related circadian rhythm. Sleep is a basic requirement for human health as it plays an essential role in physiological and psychological functioning (Van Cauter et al., 2008; Vincent et al., 2017). For example, sleep is essential for cognitive performance, metabolism, appetite regulation, immune function and hormone regulation (Vincent et al., 2017). Disruption of sleep patterns leads to metabolic and endocrine alterations, for example insulin resistance and glucose intolerance (Johnston, 2014). Research shows that decreased sleep duration is associated with an increased risk of obesity and cardiometabolic diseases, probably in a reverse J-shaped relationship with an optimal amount of sleep of around 7–8 hours per night (Zhou et al., 2019).

The winners of a British Nutrition Foundation Drummond Pump Priming award, Dr Darzi and Dr Pot, set up a PhD project to examine the effects of sleep duration and quality on energy balance, dietary intake and quality, and cardiometabolic risk factors (Darzi et al., 2017). First, they demonstrated in a systematic review and meta-analysis of human intervention studies that partial sleep deprivation resulted in increased energy intake but not increased energy expenditure, leading to a net positive energy balance of 385 kcal/day (Al Khatib et al., 2017). Subsequently, they showed in a pilot cross-sectional study (*Sleep-E* study) that sleep quality is linked to lipid metabolism (Al Khatib et al., 2016). Lastly, they showed that sleep extension is a feasible lifestyle intervention in free-living, habitual short sleepers in a randomised controlled trial (*SLuMBER* study) (Al Khatib et al., 2018). Overall, they concluded that current dietary guidelines might benefit from including advice on sleep.

The review by Gibson-Moore and Chambers in this Virtual Issue provides a summary of the evidence for a potential role of inadequate sleep in obesity and cardiometabolic disease risk (Gibson-Moore & Chambers, 2019). Although the impact of sleep on dietary outcomes tends to be relatively small, over the long-term and cumulatively, it may contribute to an increased risk of obesity and associated morbidities (Dashti et al., 2015a, 2015b). The evidence from five short-term studies of sleep extension after sleep restriction [including the aforementioned *SLuMBER* study (Al Khatib et al., 2018)] suggests some health improvements, such as regulation of appetite hormones, glucose metabolism, bodyweight and dietary intake with sleep extension in short sleepers (Pizinger et al., 2018). However, there is a need for well-designed, larger and longer studies, using objective measures of sleep duration and quality, to determine whether a good night's sleep can help tackle the obesity crisis (Gibson-Moore & Chambers, 2019).

The importance of breakfast

Most of the evidence so far on eating at specific times of day relate to the consumption of the first meal of the day (*i.e.* breakfast). In the UK, up to one third of the population sometimes or regularly skips breakfast (Reeves et al., 2013) although this might have changed during the recent pandemic. Consumption of a meal early in the day after an overnight fast may have a fundamental role in regulating normal circadian rhythms and glucose control (Clayton et al., 2020); nonetheless, the role of breakfast in the context of circadian eating patterns is complex. Most observational studies suggest a possible protective effect of consuming breakfast against increasing adiposity (Gibney et al., 2018). However, controlled interventions do not support the hypothesis that breakfast skipping positively influences energy balance (Chowdhury et al., 2016; Levitsky & Pacanowski, 2013; Sievert et al., 2019).

The paper by Ruddick-Collins in this Virtual Issue describes the rationale of the Medical Research Council-funded *Big Breakfast Study*. This study aims to investigate the mechanistic basis of the amplified morning diet-induced thermogenesis leading to enhanced weight loss, by exploring behavioural and physiological adaptations in energy expenditure alongside the underlying circadian biology (Ruddick-Collins et al., 2018). The paper briefly reports on the current research linking meal timing, circadian rhythms and metabolism and provides an overview of the studies undertaken as part of the *Big Breakfast Study* (Ruddick-Collins et al., 2018). The study will provide more insights into the mechanisms involved in mealtime-dependent metabolic processes by implementing a randomised controlled trial comparing morning-loaded versus evening-loaded weight loss diets in overweight and obese subjects, whilst monitoring all components of energy intake and expenditure over a 4-week period.

Intermittent fasting and time-restricted eating

The biological clock also needs periods of fasting in order to reset the clock (Tahara & Shibata, 2013). Implementing extended periods of fasting and restricted food consumption to specific parts of the day has become increasingly popular as it may provide an effective method for weight management and improving metabolic health. Intermittent fasting has also been associated with healthy ageing (de Cabo & Mattson, 2019). In humans, three most widely studied intermittent-fasting regimens are alternate-day fasting, 5:2 intermittent fasting (two fasting days per week) and daily time-restricted feeding (de Cabo & Mattson, 2019). Time-restricted feeding (TRF) or time-restricted eating (TRE) is a special form of intermittent fasting based on the circadian rhythm (Moon et al., 2020). Studies that have explored TRF in humans so far were often pilot or feasibility studies, with a wide range of protocols and participant characteristics limiting the ability to extrapolate to real-life settings.

In this Virtual Issue, Clayton et al. describe the exploration of independent metabolic, endocrinal and behavioural effects of extended morning and evening fasting (Clayton et al., 2020). Dr Clayton is a recent winner of a British Nutrition Foundation Drummond Pump Priming award and will conduct a randomised crossover study in lean, healthy individuals following either morning fasting or evening fasting. The main outcomes are how morning or evening fasting influence energy balance and key markers of metabolic health (*e.g.* glycaemic control), as well as information on their subjective experience. The primary hypothesis is that evening fasting will reduce energy intake and improve glycaemic control and appetite compared with morning fasting. So far, most studies on TRF have been performed in overweight or obese subjects, often with underlying health conditions. This study will contribute to the current understanding of TRE and specifically provide more insights into the use of TRE for weight management in lean individuals (Clayton et al., 2020).

The paper by Lynch et al. in this Virtual Issue describes the design of a study on the impact of early and late time-restricted feeding on established type 2 diabetes risk factors in a 10-week 3-arm parallel intervention trial (Lynch et al., 2021). The main hypothesis is that 10 weeks of daily TRF will reduce food intake, bodyweight and adiposity whilst improving markers of metabolic disease such as low-density lipoprotein (LDL)-cholesterol and insulin sensitivity. In addition, it is hypothesised that early-TRF will induce larger metabolic changes compared with late-TRF (Lynch et al., 2021). The proposed study by Lynch et al. will also investigate the practical implications of eating earlier in the day in real life, such as its impact on social interactions and food preferences.

Both the studies by Clayton et al. (2020) and Lynch et al. (2021) will shed more light on whether it is better to restrict food intake to earlier in the day or later in the day – an important question to consider when evaluating the potential role of chrono-nutrition as a modifiable risk factor for chronic non-communicable diseases.

Chrono-nutrition in the population: Shift work

The possible role of chrono-nutrition as a modifiable risk factor for many chronic non-communicable diseases is only recently starting to receive more attention, but given the ways modern lifestyles, including shift work, exposure to prolonged hours of artificial light and erratic eating patterns, disrupt the circadian system, the potential implications are large (Cornelissen & Otsuka, 2017). Research has shown that shift workers, especially those working at night, are at an increased risk of developing chronic non-communicable diseases such as type 2 diabetes and cardiometabolic diseases (Depner et al., 2014; Reutrakul & Knutson, 2015). Despite the known role of diet in the aetiology of cardiometabolic disease, gaps remain in understanding the relationship between working hours and diet (Gibson, 2018). Gibson's review in this Virtual Issue summarises the current research and future directions in the field of working hours and nutrition research (Gibson, 2018). Chrono-nutrition may be the mediator of the increased risk of chronic non-communicable diseases of shift workers. With 15% of the UK workforce working in shifts and 12% in night shifts (ONS, 2011), the public health implications could be substantial, especially as this workforce is growing in our 24-h economy.

Chrono-nutrition may not only be relevant for shift workers but for almost everybody in today's society. It is known that circadian patterns change throughout the life course (Van Someren, 2000). The circadian amplitude reduces with age and the timing of the circadian acrophase (the time period in a cycle during which the cycle peaks) becomes more variable, tending to occur earlier with advancing age (Cornelissen & Otsuka, 2017). Individuals at both ends of the age spectrum, adolescents as well as older adults, are more prone to sleeping disorders. Delayed sleep phase disorder (DSPD) occurs more often in adolescents and older adults are more prone to shift work disorder and jet-lag disorder (Duffy et al., 2015). Sleeping disorders in older adults may be due to a greater inability to sleep at an adverse biological time with age and/or a reduced ability to phase shift with age. Alterations in the regulation of circadian rhythms are also thought to contribute to the symptoms of age-related disorders, such as dementia (Van Someren, 2000). Consideration of chrono-nutrition may therefore also be relevant for adolescents and older adults as well as those who work in (night) shifts. However, further research is needed before appropriate public health recommendations can be formulated.

Public health implications: What about chrono-type?

Understanding the complex relationship between the different components of chrono-nutrition, including the importance of fasting, sleep, working hours, daily distribution of nutrient intake and how this affects cardiometabolic health will provide an opportunity to improve the health of a significant proportion of the population (Gibson, 2018). When considering chrono-nutrition as part of the management of obesity and obesity-related disorders, chrono-type also needs to be taken into account. Chrono-type refers to an individual's preferred time of day for an activity/rest cycle. Individuals can be categorised into a morning, intermediate or evening chrono-type (Roenneberg et al., 2007). Chrono-type is usually a stable trait with only minor changes over time (Druiven et al., 2020). A growing number of studies are also investigating the role of chrono-type. Recent studies found that later chrono-type or evening-type individuals displayed more unhealthy eating habits associated with obesity (Merikanto & Partonen, 2020) and found weight loss interventions more difficult (Mazri et al., 2020). Individuals with a later chrono-type tended to consume more of their energy intake later in the day (Zerón-Rugerio et al., 2020), which is associated with an increased risk of overweight/obesity (Baron et al., 2011; Martínez-Lozano et al., 2020; Xiao et al., 2019). These findings may, in part, also explain differences between people with metabolically healthy and unhealthy obesity. For example, people with metabolically healthy obesity tended to do more physical activity in the morning, had earlier bedtimes, a complete breakfast and a greater number of meals per day compared with their metabolically unhealthy counterparts (Torres-Castillo et al., 2020). Furthermore, a recent study in Finland showed that the mismatch between sleep–wake behaviour and circadian preference was particularly present for young adults, indicating a greater risk of circadian misalignment in the future Finnish adult population if this mismatch does not change (Merikanto & Partonen, 2020). Thus, consideration of chrono-type in both observational and intervention studies will add to the evidence base in real-life settings of the possible impact of chrono-nutrition on health (Flanagan et al., 2020).

In conclusion, chrono-nutrition is an emerging area of research with potentially substantial public health implications. There is an urgent need for interventions to counteract some of the adverse effects on circadian biology induced by our modern-day lifestyle and 24-h economy. Intervention studies on chrono-nutrition should ideally be practice-based in real-life settings taking into account the intra-variability (*e.g.* day-to-day variability as well as seasonal changes) and inter-variability (*e.g.* chrono-type). These chrono-nutrition intervention studies will follow the trends on personalised nutrition and will most likely not lead to a one-size-fits-all approach. Consideration of chrono-nutrition will add to the evidence base of real-life studies and benefit the management of chronic non-communicable diseases such as obesity and cardiometabolic diseases. Evidence on effective interventions for mitigating the effects of disrupted chrono-nutrition can be used to formulate public health recommendations. The knowledge so far on chrono-nutrition is already trickling through to public health recommendations such as those from the American Heart Association (St-Onge et al., 2017). For example, a more regular intake of energy during the day and with a greater proportion of calories earlier in the day could be recommended. The results of the studies described in this Virtual Issue will help to inform future advice. The public health recommendations for a healthy lifestyle should also address sleep and chrono-type alongside a healthy diet and physical activity. You are probably not only *what* you eat but also *when* and how you sleep.

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