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REVIEW

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Chrono-nutrition: From molecular and neuronal mechanisms to human epidemiology and timed feeding patterns

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Abstract

The circadian timing system governs daily biological rhythms, synchronising physiology and behaviour to the temporal world. External time cues, including the light-dark cycle and timing of food intake, provide daily signals for entrainment of the central, master circadian clock in the hypothalamic suprachiasmatic nuclei (SCN), and of metabolic rhythms in peripheral tissues, respectively. Chrono-nutrition is an emerging field building on the relationship between temporal eating patterns, circadian rhythms, and metabolic health. Evidence from both animal and human research demonstrates adverse metabolic consequences of circadian disruption. Conversely, a growing body of evidence indicates that aligning food intake to periods of the day when circadian rhythms in metabolic processes are optimised for nutrition may be effective for improving metabolic health. Circadian rhythms in glucose and lipid homeostasis, insulin responsiveness and sensitivity, energy expenditure, and post-prandial metabolism, may favour eating patterns characterised by earlier temporal distribution of energy. This review details the molecular basis for metabolic clocks, the regulation of feeding behaviour, and the evidence for meal timing as an entraining signal for the circadian system in animal models. The epidemiology of temporal eating patterns in humans is examined, together with evidence from human intervention studies investigating the metabolic effects of morning compared to evening energy intake, and emerging chrono-nutrition interventions such as time-restricted feeding. Chrono-nutrition may have therapeutic application for individuals with and at-risk of metabolic disease and convey health benefits within the general population.

KEYWORDS

circadian, clock gene, energy balance, meal timing, metabolism, time-restricted feeding

Abbreviations: AHS-2, adventist health study 2; ARC, arcuate nucleus; AUC, area under the curve; BBP, bath breakfast project; BMAL1, brain and muscle ARNT-like protein-1; BMI, body mass index; CA, cluster analysis; CCK, cholecystokinin; CLOCK, circadian locomotor output cycles kaput; CRY, cryptochrome; DIT, diet-induced thermogenesis; DLMO, dim light melatonin onset; DMH, dorsomedial hypothalamus; DQI, diet quality index; EO, eating occasion; eTRF, early time-restricted feeding; FAA, food anticipatory activity; FEO, food entrainable oscillator; FFQ, food frequency questionnaire; GI, glycaemic index; GIP, glucose-dependent insulinoptropic polypeptide; GLP1, glucagon-like peptide-1; HFD, high-fat diet; HOMA-IR, homeostatic model assessment of insulin resistance; IGF-1, insulin-like growth factor-1; IGT, impaired glucose tolerance; INTERMAP, International study of macro-and micro-nutrients; LCA, latent class analysis; LH, lateral hypothalamus; MPO, median preoptic nucleus; NAc, nucleus accumbens; NEFA, non-esterified fatty acids; NHANES, National Health and Nutrition Examination Survey (USA); NTS, nuclei of the solitary tract; OGTT, oral glucose tolerance test; OR, odds ratio; PAT, physical activity thermogenesis; PER, period; PFC, prefrontal cortex; PVN, paraventricular nucleus; RFS, restricted feeding schedules; RR, relative risk; SCN, Suprachiasmatic nuclei; SPZ, Subparaventricular zone; T2DM, Type-2 diabetes mellitus; TEF, thermic effect of feeding; TRE, time-restricted eating; TRF, time-restricted feeding; TTFL, transcriptional-translational feedback loop; VMH, ventrolateral hypothalamus; VTA, ventral tegmental area.

1 | INTRODUCTION

'Chrono-nutrition' is the study of the interaction between biological rhythms and nutrition, along with the relationship between these factors and human health. Chrono-nutrition encompasses distribution of energy, meal frequency and regularity, duration of the eating period, and the relative importance of these factors for metabolic health and chronic disease risk. An ever-growing body of evidence in both animal and human studies indicates that the timing of food intake across the day can profoundly impact metabolic health and general wellbeing (Almoosawi et al., 2016; Johnston et al., 2016; Potter et al., 2016; West & Bechtold, 2015). The importance of when we eat is tied to our internal 24-hr biological timing system, the circadian clock (from the Latin circa 'about' diem 'a day'), and the influential role that it plays in regulating metabolic processes across the body. Almost all organisms on the planet have evolved intrinsic biological rhythms anchored around the light-dark cycle caused by Earth's daily 24-hr rotation. These endogenous rhythms are driven by a circadian system, which allows coordination of appropriate behavioural and physiological responses relative to recurring fluctuations in the surrounding environment, and to changing demands of an organism's own biology. Circadian clocks are capable of maintaining autonomous periodicity of approximately 24 hr yet remain highly responsive to external inputs that synchronise them to the outside world (Dunlap et al., 2004).

Environmental cues capable of entraining circadian rhythms, i.e., aligning internal clock timing with external time cues, are known as 'zeitgebers' (German for 'time-givers'). The daily light/dark cycle provides the most conspicuous and potent signal for most organisms on our planet. In mammals, including humans, the circadian system is headed by a 'master clock' located in the suprachiasmatic nuclei (SCN) of the hypothalamus, which is sensitive to external light via direct connect to the retina (Brown et al., 2020). In addition to the SCN, virtually all cells and tissues of the body exhibit molecular clock activity which contribute to local tissue function across the day and night. This network of circadian clocks imposes rhythmic control over virtually every aspect our biology, from gross behavioural cycles, such as when we sleep and eat, through to cellular rhythms in gene expression and energy metabolism. Importantly, the molecular components which make up the circadian clock are also highly responsive to food intake and related nutrient and hormone signals. Under normal circumstances, this serves to reinforce our natural rhythms, where food intake is both driven by, and feeds back onto, circadian clock timing (West & Bechtold, 2015). However, what and when we eat has changed substantially within our modern society. It is now clear that circadian dysfunction contributes to metabolic disorders, and conversely that aberrant eating habits undermine our endogenous circadian system (Maury et al., 2010; Parsons et al., 2014).

The intimate links between circadian clocks and metabolism, together with the central control of feeding behaviour, have implicated circadian dysfunction and/or loss of normal rhythmicity in the development of cardiometabolic diseases. The challenge now is to better understand the reciprocal nature of this interaction and investigate further the potential benefit of timed dietary manipulations and chrono-nutrition for cardiometabolic diseases. Factors such as greater distribution of daily energy intake to the evening, irregular or erratic meal patterns, increased frequency of eating occasions, and extended duration of daily eating periods, may all contribute to cardiometabolic disease (Gill & Panda, 2015; Kahleova et al., 2017; Pot et al., 2015). Conversely, recent research indicates that timed feeding paradigms offer a novel avenue of behavioural intervention to achieve reductions in cardiometabolic risk (Hawley et al., 2020; Ruddick-Collins et al., 2020). This review will briefly discuss the contribution of the circadian system to normal control of food intake and energy balance, then explore the reciprocal regulatory nature of clock function and energy metabolism. It will then examine evidence from epidemiological and intervention studies in human on how temporal patterns of energy intake and meal timing can contribute to metabolic health and disease, and discuss the potential for chrono-nutrition as an approach for achieving therapeutic benefit.

2 | Circadian clocks and rhythms in feeding behaviour

2.1 | Anatomical and molecular clock networks

In mammals, the circadian system operates with a hierarchical structure, headed by the SCN clock. The SCN exhibits autonomous timekeeping, which is robust even when all external time cues are removed (Patton & Hastings, 2018). Nevertheless, clock neurons of the SCN are highly sensitive to the external light-dark cycle through retina input via the retinal-hypothalamic tract. Indeed, it has become clear in recent years that the SCN is sensitive to not only overall light intensity, but also the spectral quality of light inputs (Mouland et al., 2019; Brown et al., 2020). Timing information generated within the SCN provides a coherent rhythmic patterning to major behavioural and physiological processes, whereby destruction of the SCN results in behavioural arrhythmia with loss of consolidated sleep and feeding cycles (Moore & Eichler, 1972; Stephan & Zucker, 1972). In addition to the SCN, numerous brain regions and peripheral tissues house robust circadian clock function, and components of the molecular clock are rhythmically expressed in virtually every cell of the body. These local tissue and cellular clocks have been shown to be critical to normal tissue, organ, and cell function (Gibbs et al., 2011; Lamia et al., 2008; Perelis et al., 2015). Clocks across the body are normally held in synchrony by the SCN, with temporal coordination involving afferent projections from the SCN to key regulatory nuclei across the brain, and through SCN influence over autonomic and neuroendocrine activity (Dibner et al., 2010). Importantly, SCN and peripheral clock timings are, in turn, reinforced by our strong behavioural and physiological cycles (e.g., as we discuss below, hormones such as insulin and glucocorticoids produced in a rhythmic pattern under the influence of our behaviour and the action of peripheral clock activity, can themselves influence clock function). Thus, it is

the coordinated activity of a network of body clocks that underpins our highly rhythmic physiology (West & Bechtold, 2015).

At the heart of circadian clock timing is a highly conserved transcriptional-translational feedback loop (TTFL), within which reciprocal regulatory interaction between core clock factors drives a ~24 hr oscillation (Takahashi, 2016). This feedback loop centres on the transcriptional activators CLOCK and BMAL1, which drive the expression of negative regulators PERIOD (PER) and CRYPTOCHROME (CRY). PER and CRY serve to inhibit CLOCK/BMAL1 transcriptional activity, and in doing so repress their own expression. Once levels of PER and CRY fall, the cycle starts again. This basic loop engages a number of secondary transcriptional/translational loops and involves numerous post-translational events, which together provide the robust near 24-hr molecular rhythm of the clock. An influential secondary loop driven by BMAL1 activity involves the nuclear hormone receptors, REVERB and ROR, with REVERB repressing and ROR enhancing *Bmal1* expression (Preitner et al., 2002; Schibler et al., 2001).

Importantly, the transcriptional regulators of the clock not only act within the TTFL, but also drive rhythmic gene expression (through direct transcriptional activation/repression, chromatin modulation, and epigenetic modification) at thousands sites across the genome. Indeed, most tissues examined exhibit substantial rhythmic mRNA and protein expression in mice (Hughes et al., 2009; Reddy et al., 2006; Robles et al., 2014; Wang et al., 2018) and humans (Christou et al., 2019; Laing et al., 2015; Perrin et al., 2018). Furthermore, mouse studies suggest that ~40% of all genes are expressed in a circadian manner in at least one tissue. Comparative analyses indicate that a number of specific genes, in particular *NR1D1* and *NR1D2*, display circadian rhythmicity in ~96% of human and mouse tissue samples (Laing et al., 2015). It has become eminently clear that the circadian system is intimately coupled to energy metabolism in most organisms, including mammals. Metabolic pathways and genes are common direct targets of the transcriptional regulators of the circadian clock in most tissues (Bass, 2012; Bechtold & Loudon, 2013), and metabolic disturbances and altered feeding behaviours are commonly observed in mice in which one or more of the core clock components (*Bmal1*, *Clock*, *Per1/2*, *Cry1/2*, or *Reverba*) have been deleted or mutated (Challet, 2019). For example, mice with a mutation in Clock (ClockΔ19) exhibit hyperphagic behaviours, metabolic dysregulation, and obesity (Turek et al., 2005). Intense research over the past two decades has highlighted the interdependence of circadian clock function with rhythms in energy metabolism (Jovanovic, Gerrard, et al., 2009); this extends to system-wide regulation of food intake and overall energy balance.

2.2 | Metabolic clocks and feeding control

Conceptually, from the perspective of homeostasis, feeding behaviour would be solely governed by the body's energy requirements; a well-guarded balance in which energy intake is matched to expenditure (basal metabolic rate, diet-induced thermogenesis, and physical activity thermogenesis) and vice versa. However, homeostatic controls must be able to anticipate and mitigate periods of uncertain or limited food availability, as well as behavioural patterns which limit or prevent feeding (e.g., during extended sleep) or increase energy demand over prolonged periods. Thus, regulation of food intake, especially in humans, is far more complex, involving short- and long-term homeostatic controls, food-related motivational and reward inputs, and higher cognitive decision making (Figure 1). Feeding behaviour follows a strongly diurnal/circadian pattern, wherein mice and rats normally consume >70% of their food during the dark/active phase of the day. Moreover, rat studies have shown that preference for diet composition (e.g., carbohydrates vs. fats) and the magnitude of fast-induced re-feeding vary by time of day (Rivera-Estrada et al., 2018; Tempel et al., 1989). Along with more generalised behavioural arrhythmia, SCN-lesioning disrupts the normal feeding–fasting cycle, yet without a significant change in overall food intake (Challet, 2019; Mistlberger & Antle, 2011). This highlights a specific role for SCN output in setting the daily patterning of feeding.

Homeostatic regulation of feeding is centred on the relative activity of orexigenic and anorexigenic neurons (driving or repressing food intake, respectively), most notably within the hypothalamus and brainstem (Lenard & Berthoud, 2008; Morton et al., 2014). These populations of regulatory neurons are sensitive to circulating nutrient (e.g., glucose, fatty acids, amino acids) and hormone (e.g., leptin, ghrelin, insulin, cholecystokinin (CCK)) levels that reflect nutritional status and peripheral energy stores (Coll et al., 2007; Williams & Elmquist, 2012) (Figure 1). Within the hypothalamus, several nuclei have clear and profound impacts over the control of feeding behaviours and maintenance of energy balance. This includes the arcuate nucleus (ARC), lateral hypothalamus (LH), ventrolateral hypothalamus (VMH), paraventricular nucleus (PVN), and the dorsomedial hypothalamus (DMH) (Figure 1). The SCN projects heavily to the subparaventricular zone (SPZ; a relay site which projects widely through the hypothalamus), median preoptic nucleus (MPO), and DMH (a key site for integration of circadian timing into numerous physiological processes including sleep, feeding and energy expenditure) (Abrahamson & Moore, 2001; Watts et al., 1987). SCN projections to the PVN have also been demonstrated in rats and humans (Cui & Dyball, 1996; Dai et al., 1997), through which SCN clock neurons provide temporal modulation over the activities of pre-autonomic and neuroendocrine pathways (Acosta-Galvan et al., 2011; Buijs et al., 2017; Kalsbeek et al., 2006; Paul et al., 2020). Additional targets include arousal-promoting orexin neurons in the lateral hypothalamus (LH) (Abrahamson et al., 2001), sleep-promoting neurons of the ventrolateral preoptic nucleus (Sun et al., 2001), and energy-sensing neurons of the ARC (Buijs et al., 1994). Moreover, transplantation of encapsulated SCN tissue (thereby preventing formation of new axonal contacts) can restore behavioural rhythmicity, indicating that SCN timing is also conveyed through secreted factors (Silver et al., 1996).

In addition to recurving temporal information from the SCN, many of the areas discussed above exhibit circadian clock function, as reflected by rhythmic neuronal activity and clock gene expression

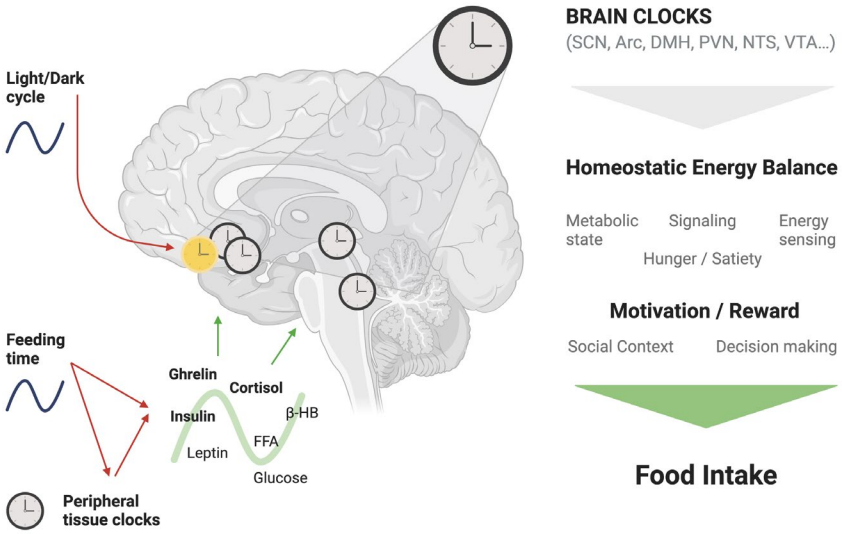

FIGURE 1 Clocks within the hypothalamus and sites outside the hypothalamus, together with reinforcement from peripheral circulating metabolic hormones and nutrients, influence control of feeding behaviour. The suprachiasmatic nuclei (SCN) clock (yellow) regulates diurnal patterns in feeding behaviour, while extra-SCN hypothalamic sites are sensitive to peripheral circulating nutrients (e.g., free fatty acids (FFA), betahydroxybutyrate (BHB), glucose) and nutrient-related hormones (e.g., ghrelin, leptin, insulin) levels. Nuclei outside the hypothalamus, including the brainstem nuclei of the solitary tract (NTS) sense peripheral metabolic state and are also responsive to circulating feeding and satiety-related hormones. Clocks are also present in sites including the nucleus accumbans (NAc), ventral tegmental area (VTA), and prefrontal cortex (PFC), involved in dopaminergic motivation-reward circuits that influence eating behaviours. Clocks throughout the brain are thus likely to mediate important energy balance and motivation-reward pathways, thus regulating food intake

(Paul et al., 2019). This suggests that local clock function in energy responsive neuronal populations may exert influence over feeding behaviour. Unfortunately, this has been difficult to demonstrate because of the relative dominance of the SCN over behavioural rhythms, which would likely mask more subtle changes in food-related behaviour. Nevertheless, some compelling evidence has linked local clock function with aspects of energy balance. Within the ARC, for example, robust circadian rhythms in neuronal activity, clock gene/protein expression, and feeding-related neuropeptide expression has been demonstrated (Guilding et al., 2009; Kalra et al., 2004; Tan et al., 2014). Moreover, loss of clock function in Agouti-related peptide (AGRP) neurons through cell specific *Bmal1* deletion disrupts the normal response of these cells to leptin (Cedernaes et al., 2019). This study also examined the transcriptional and post-transcriptional programme within these cells and revealed a pronounced time-of-day and energy-state dependent rhythm in bioenergetics and peptidergic pathways.

Sites outside of the hypothalamus important to feeding control also exhibit circadian properties. This includes brainstem sites such as the area postrema and nuclei of the solitary tract (NTS) are critical to sensing of peripheral metabolic state (Grill et al., 2012) (Figure 1). These sites are responsive to circulating feeding and satiety-related hormones, such as leptin, GLP1, and CCK, and receive visceral input via the vagus nerve that inform the brain of gastric distension and nutrient intake. Clock gene expression in the brainstem has been reported (Herichová et al., 2006; Kaneko & Sawamoto, 2009), and recent work has shown both the NTS and AP to house robust circadian clock function (Chrobok et al., 2020). Chrobok and colleagues (2020) demonstrated that electrophysiological responses of the AP/NTS complex to feeding related cues (CCK, glucose, and ghrelin), as well as blood-brain-barrier function at the AP, vary in a time-of-day dependent manner. Although the physiological impact of these oscillators remains to be demonstrated, an influence over energy balance seems likely.

The clock is also likely to impinge on hedonistic, reward-based aspects of feeding behaviour. Both human and animal studies demonstrate time-of-day and circadian rhythmicity in reward and motivational responses (DePoy et al., 2017; Murray et al., 2002) (Figure 1). Rhythmic activity and clock gene expression has been demonstrated in brain sites involved in dopamine signalling, including nucleus accumbans (NAc), ventral tegmental area (VTA), and prefrontal cortex (PFC) (Ángeles-Castellanos et al., 2008; Chung et al., 2014; DePoy et al., 2017; Verwey et al., 2016). Recent work by Koch et al. (2020) demonstrated a role for the VTA in modulating rhythms in hedonic appetite regulation and sensitivity to hyperpalatable food overconsumption. Although not investigated in the context of food intake, an influential role for REVERBa in regulating dopamine production (via direct regulation of tyrosine hydroxylase, the rate limiting enzyme in dopamine production) in the VTA has been reported (Chung et al., 2014). In support, mice lacking *Reverba* expression show increased consumption of palatable foods (Feillet et al., 2015).

Rhythms in feeding are reinforced by food-related feedback from the periphery (Figure 1). Circulating metabolic hormones and nutrients, and sensory input from the gastrointestinal tract which following feeding patterns, both engage acute homeostatic responses in a rhythmic fashion (because of normal feeding/fasting cycle), as well as influence central circadian clocks directly, through responsiveness

of the molecular clockwork to metabolic state (discussed in more detail below). This sensitivity of the clockwork to food-related input is exemplified by the strong behavioural and physiological entrainment observed in laboratory animals to restricted feeding schedules (Mistlberger, 2011).

2.3 | Meal timing as an entraining signal for the circadian system

The neurochemical processes and molecular clockwork outlined above have important implications for feeding behaviour. Research demonstrating that food consumption can influence internal timing and subsequent food-related behaviours stretches back to the 1920s, where consistent patterns of food-seeking behaviours emerged in response to restricted feeding schedules (RFS) in rats (Richter, 1927). These early observations of food anticipatory activity (FAA), and many subsequent studies, brought about the theory of food-entrainment (Mistlberger, 2011). Indeed, placing rodents on a restricted feeding schedule, based on temporal-restriction of food availability with or without addition caloric restriction, rapidly leads to an alignment of behavioural (e.g., increased locomotor activity) and physiological (e.g., body temperature rhythms, hormone production) profiles to the timing of food intake. It was subsequently established that such food-related rhythms can manifest independently of the SCN, with destruction of the SCN in rats unable to attenuate behavioural entrainment and emergence of FAA in response to time-restricted feeding conditions (Stephan et al., 1979a, 1979b). Nonetheless, circadian clock timing properties clearly underpin many aspects of food entrainment, in particular continued expression of appropriately timed bouts of activity to a previous meal schedule upon return to ad libitum feeding, and the re-emergence of FAA upon subsequent fasting periods (Challet et al., 1997; Rosenwasser et al., 1984). This led to the concept of a 'food-entrainable oscillator' (FEO) capable of driving food-related behavioural entrainment and FAA, but which is distinct from the master circadian clock in the SCN (Stephan, 2002).

Despite many decades of research, the physiological basis for, and potential location of, a discrete FEO responsible for behavioural entrainment remains elusive. This search has almost certainly been complicated by the fact that many neural sites involved in regulating food intake and energy balance have a strong influence over behavioural and motivational state, including food-directed activity. Moreover many of these sites exhibit some level of circadian function either via local clock function or connection with the SCN. Thus, there may not be any single site responsible for behavioural entrainment to food (Figure 2). There is relatively strong evidence for the involvement of the mediobasal hypothalamus and dopaminergic reward pathways (Mistlberger, 2020; Smit et al., 2013). Regardless of the exact nature of FAA-generating FEO(s), it is clear that timed or temporally-restricted feeding provides a powerful drive for behavioural and physiological processes in mammals, including humans (discussed further below). What does appear from both animal and human research is that the central circadian clock can remain entrained to the light-dark cycle, while circadian rhythms in peripheral tissues can shift dynamically in response to altered feeding cycles (Dibner et al., 2004; Wehrens et al., 2017) (Figure 2).

It has also remained controversial whether the canonical molecular clockwork is required for emergence and timing of FAA under conditions of restricted feeding (Pendergast et al., 2018; Pitts et al., 2003; Storch et al., 2009). Mice deficient for *Bmal1*, *Cry1/Cry2*, and *Per1/Per2* have all been shown to display increased activity prior to mealtime under RFS (Pendergast et al., 2009). This would suggest that the circadian clock is not required, however, it is important to distinguish between food-drive behaviour per se, and clock-driven FAA. Circadian properties underlying FAA, such as persistence of FAA upon return to ad libitum feeding, and re-emergence of FAA under subsequent fasting periods, are particularly difficult

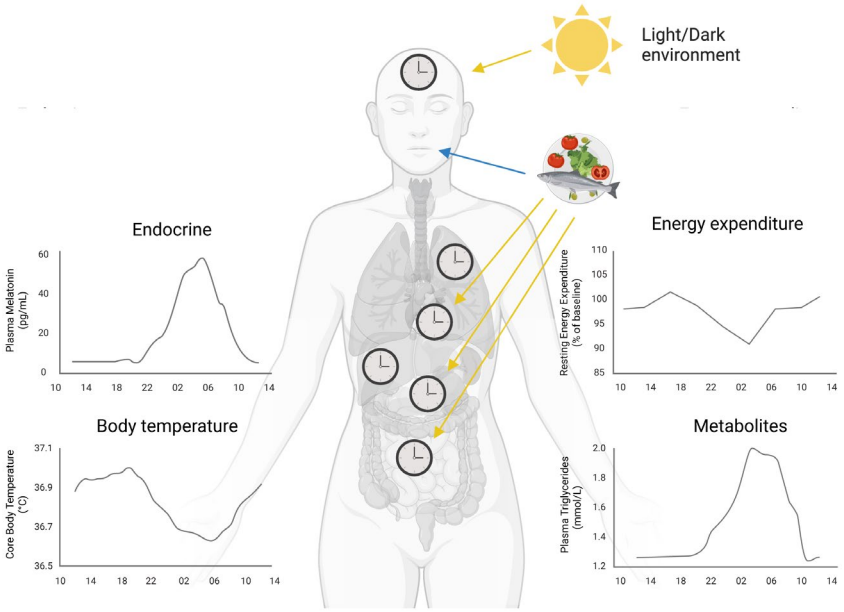

FIGURE 2 Circadian rhythms regulate multiple aspects of metabolic physiology. In conditions that control for effects of environment and behaviour, circadian rhythms persist in aspects of physiology such as: hormone secretion, core body temperature, resting metabolic rate and plasma metabolite concentration

to measure in mice (currently the dominant model in circadian research). Where it has been possible to examine the circadian underpinnings of FAA, for example using non-24-hr feeding cycles to test the limits of entrainment, important differences have emerged. Namely, while normal mice show robust limits of food entrainment (between ~22–29 hr frequencies), mice lacking a functional clock (*Bmal1*$^{-/-}$ and *Cry1*$^{-/-}$*Cry2*$^{-/-}$) will exhibit food directed behaviours in response to RFS at frequencies well beyond those limits (Hamaguchi et al., 2015; Takasu et al., 2012). Moreover mice lacking the clock gene *Reverbα* either globally or within the brain do not show FAA under RFS (Challet, 2019; Mistlberger & Antle, 2011), and similarly deletion of *Bmal1* from the nervous system also impairs entrainment to restricted feeding (Mieda & Sakurai, 2001). Thus, it seems most likely that behavioural entrainment to RFS is governed by the circadian clock, which imposes temporal aspects to feeding related behaviours; however, when normal clock function is lost, behavioural responses to feeding/fasting cycles remain albeit without robust underpinning clock characteristics. This may reflect that it is unlikely a single FEO exists, or should one exist, it would be impossible to demonstrate it because so many neural sites and pathways will drive behaviour in response to fasting/feeding cycles. Despite numerous attempts, lesioning studies and targeted genetic manipulations have failed to reveal a unique FEO structure solely responsible for driving FAA (Pendergast et al., 2018).

Beyond behavioural responses to RFS, timing of food intake exerts a powerful influence over functioning of molecular clocks outside the SCN, with meal timing representing an important *zeitgeber* for circadian entrainment of peripheral tissues (Figure 2). Mice fed exclusively during the day exhibit a relatively rapid shift in the phase of clock gene rhythms in peripheral tissues to match the new feeding regimen, while SCN clock gene rhythms remaining phase aligned to the prevailing light/dark cycle (Damiola et al., 2000; Tahara et al., 2010). Widespread entrainment of peripheral tissue clock gene rhythms to altered feeding schedules has been reported (Damiola et al., 2000), nevertheless the speed and extend of peripheral tissue response will be dependent on the specific RFS design and severity of caloric restriction. Similar to the entrainment of behavioural rhythms to repetitive feeding schedules, numerous feeding-associated factors, nutrients, and hormones have been implicated in the entrainment of peripheral gene rhythms to RFS. For example, increased levels of glucagon, insulin, and IGF-1 are all capable of modulating clock gene and or protein expression, an effect which is heightened when animals are in a fasted state (Crosby et al., 2019; Ikeda et al., 2018; Mukherji et al., 2015; Sun et al., 2014; Tahara et al., 2010). With regards to insulin, in vitro and in vivo evidence demonstrates a pronounced influence of insulin over clock gene and protein expression in many cell and tissue types (Crosby et al., 2019; Yamajuku et al., 2012). Recently, Crosby et al. (2019) demonstrated that administration of insulin or IGF-1 drives a pronounced induction of PER2 in numerous cell and tissue types, as well as in vivo in mice. Here, pharmacological attenuation of insulin/IGF-1 signalling was capable of delaying entrainment of PER2::Luc rhythms to changes in the timing of food availability. This work suggests that insulin can serve as a post-prandial signal which communicates meal timing to circadian clocks across the body (Figure 2). In addition to insulin, numerous meal-related factors have been implicate in food-related entrainment of the clock. These include both nutrient (e.g., glucose, fatty acids) and endocrine (e.g., corticosterone, ghrelin, oxyntomodulin, leptin, glucagon) signals (Landgraf et al., 2015; Patton & Mistlberger, 2013). Therefore, the potent effect of meal timing on the peripheral clock likely reflects the action of multiple reinforcing signals which serve to coordinate rhythmic metabolic activity across the body (Figure 2).

Just as timed feeding can entrain the circadian system and improve metabolic outcomes, disordered feeding, provision of diets high in fat, and diet-induced obesity have been shown to disrupt robust circadian rhythms in mice (Kohsaka et al., 2007). For example, shifting mice onto diets high in fat (HFD) rapidly causes a weakening of the circadian/diurnal rhythm in food intake, with increased calorie consumption during the daytime (when food intake is normally low) (Cunningham et al., 2016; Kohsaka et al., 2007; Sherman et al., 2012). Diet-induced obesity in mice has also been associated with tissue specific deterioration in clock gene rhythms, with white adipose tissue being particularly susceptible (Eckel-Mahan et al., 2013; Scott, 2015). The cause of clock disruption is not yet clear, but may be because of increased tissue inflammation during obesity (Cunningham et al., 2016). Importantly, high-fat diet feeding has also been shown to cause substantial disruption of rhythmic processes within the liver, which included not only the loss of certain metabolite and transcript oscillations, but also an emergence of newly oscillating transcripts and metabolites (Eckel-Mahan et al., 2013).

The strength of interconnection between circadian timing and feeding behaviour has been made eminently clear through these animal studies, demonstrating how patterns in feeding can have positive or particularly harmful impact on metabolic health. As a simple, yet powerful demonstration—the metabolic consequences of high-fat feeding can be mitigated by time restricting the access to food, despite the fact that the animals consume similar calorie (Chaix et al., 2014; Haraguchi et al., 2014; Hatori et al., 2012; Sherman et al., 2012). In the following sections, we explore the evidence in humans, including temporal eating patterns in epidemiology, and the potential for time-restricted feeding and chrono-nutrition to improve our health and wellbeing.

3 | Meal timing and patterns of energy intake in humans

3.1 | Temporal eating patterns in epidemiology

Elucidating meal patterns in humans presents challenges for nutritional epidemiology. Food frequency questionnaires (FFQs) are generally designed to capture average intakes over a specific reference period, rather than meal timing (Leech et al., 2015). Most studies analysing meal patterns have utilised multiple 24-hr dietary recalls, or

repeated food records, sometimes including pre-defined meal labels (Almoosawi et al., 2016; Eicher-Miller et al., 2016; Pot et al., 2016). However, there remains a lack of standardised operational definition for 'meals', 'snacks', which may result in discordant findings when timing of food intake, frequency and (ir)regularity are the outcomes of interest (Eicher-Miller et al., 2016; Leech, Timperio, et al., 2017; Leech et al., 2016). While some researchers apply a minimum energy criterion (i.e., >50 kcal (210 kJ)) to snacks (Leech, Timperio, et al., 2017), meals remain largely characterised by pre-defined, culturally, and socially-driven labels of 'breakfast', 'lunch', and 'dinner', which differ cross-culturally (Mäkalä et al., 1999). The term 'eating occasion' (EO), encompassing any occasion at which calories are ingested, has been proposed as a neutral descriptor which captures all culturally laden labels for meals or snacks (Mäkalä et al., 1999). Characterising EO based on the time-period between respective EO may also influence any analysis of EO frequency, distribution, and/or total energy intake, with some researchers applying a 15-min minimum period to distinguish between EO (Leech, Timperio, et al., 2017). A final challenge has been failure to adjust for energy misreporting in many studies, as computations of energy intake by FFQ are more accurate for group level, rather than individual intake, and given that underreporting of energy intake correlates with underreporting of EO (Bellisle et al., 1997).

A number of recent analyses have attempted to account for these methodological challenges. In a meal pattern analysis in Australian adults, meal frequency, but not snack frequency, was associated with higher diet-quality indices (DQI) (Leech et al., 2016). In a cluster analysis (CA) of the US NHANES III (1994–2004) data, which defined groups based on similar temporal characteristics, 4 distinct clusters, that is, patterns of temporal distribution of energy intake, were identified. 'Cluster 1', characterised by lower proportional energy consumed relative to frequency, displayed peak energy intake earlier in the day, with the largest intake EO at midday, and was associated with the highest DQI (Eicher-Miller et al., 2016). Conversely, 'Cluster 4' was characterised by more frequent EO, lower peak energy intake at each EO, extended duration of EO into the biological evening, and was associated with the lowest DQI (Eicher-Miller et al., 2016). Using latent-class analysis (LCA), a statistical technique to identify different classifications based on observed categorical variables (i.e., whether or not a EO took place), Leech, Timperio, et al., 2017 identified three temporal patterns in Australian adults; a 'conventional pattern', with probability of an EO at 12.00 hr and 18.00 hr; 'later lunch', with probability of an EO at 13.00 hr; peak total daily energy intake in both patterns was similar, occurring between 10.00–15.00 hr. Finally, a 'grazing' pattern, defined as having no distinct peaks but frequent EO, later initiation of eating, and EOs occurring after 20.00 hr, similar in characteristics with the 'Cluster 4' pattern identified in the US population (Eicher-Miller et al., 2016; Leech et al., 2017). A multilevel latent class analysis, an extension of LCA which allows for the repeated measurement of categorical variables within individuals, analysed temporal patterns of carbohydrate intake in the UK population and highlighted day-to-day within-person variance, indicating that temporal eating patterns are not necessarily a fixed behavioural trait in individuals (Wang et al., 2019). A principle components analysis using UK National Diet and Nutrition Survey data in adolescents indicated three diurnal eating patterns, characterised by earlier distribution, grazing, or later distribution of meals and snacks (Palla & Almoosawi, 2019). Thus, temporal eating patterns in humans exhibit between-society, within-society, and within-person variance.

In addition to meals being largely defined by culturally-driven labels of 'breakfast', 'lunch', and 'dinner', the use of broad, time-insensitive definitions for time-of-day, such as 'morning' or 'evening', may further render capturing a true interaction between energy intake, clock time, and biological time, more ambiguous. The definition of a 'late lunch' pattern in Australian adults was lunch occurring at 13.00 hr (Leech et al., 2017b); in contrast to analysis in a Spanish population, where 'late lunch' was defined as occurring after 15.00 hr (Garaulet et al., 2013). Thus, the operational definition issues with regard to eating occasions also have an inherent time component, and more objective quantification of clock time would be a useful standardisation. One definition that appears uniform is that of the 'main meal', defined as the EO with the greatest energy intake (Garaulet et al., 2013; Leech, Timperio, et al., 2017). In the US Adventist Health Study 2 (AHS-2), participants who consumed breakfast (0500–1100 hr) as the largest meal of the day decreased their BMI (−0.038, 95% CI −0.048 to −0.028) compared with those who had their largest meal at dinner, while consuming the largest meal at lunch (1200–1600 hrs) was also associated with decreased BMI (−0.02, 95% CI −0.03 to −0.01 compared to dinner (Kahleova et al., 2017). Garaulet et al. (2013) found that consumption of the main daily meal after 15.00 hr was associated with significantly less weight lost over a 20-week intervention, compared to participants consuming the main meal before 15.00 hr, in 420 women with obesity. Generally, analyses which find peak energy intake earlier in the clock time of day, before 15.00 hr, are associated with lower total daily energy intake, higher DQI, lower dietary energy density and more structured meal patterns (Figure 3) (Aljuraiban et al., 2015; Eicher-Miller et al., 2016; Garaulet et al., 2013; Kahleova et al., 2017; Leech et al., 2016, 2017).

3.2 | Associations with health outcomes

The associations between various temporal patterns and adiposity, defined by body mass index (BMI), are more ambiguous (Almoosawi et al., 2016). Leech et al. (2017b) found that the associations between temporal eating patterns and BMI were rendered null after adjusting for total daily energy intake and energy misreporting. In UK children and adolescents, there was no increased risk for obesity consuming the main evening meal between 20.00 and 21.59 hr, compared to consumption between 14.00–19.59 hr (Coulthard & Pot, 2016). However, total daily energy intake in this cohort was relatively low (1524–1768kcal/d), and the majority of children (71.5%) and adolescents (64.9%) were normal weight. Conversely, the proportion of energy intake in the evening has been positively associated with total daily energy intake (Datillo et al., 2011; Reid et al., 2014), reflecting

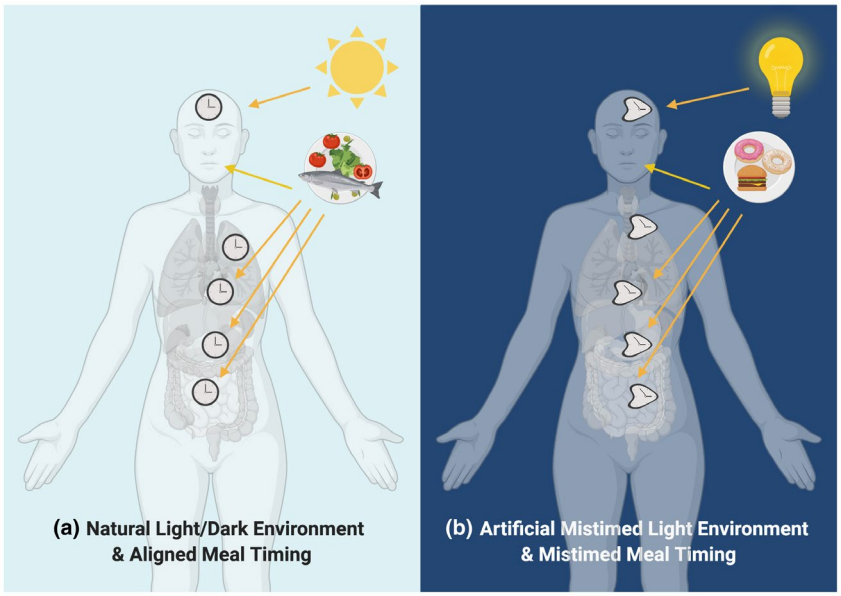

FIGURE 3 Relationship between external time cues (zeitgebers) and the circadian timing system. (a) Alignment of light and energy intake to the solar day results in a well-synchronised circadian system. (b) Mistimed environmental cues, including artificial light and food timing during the biological night, contribute to circadian desynchrony. Nocturnal eating is also associated with consumption of energy dense food

increasing meal size over the course of the day, and shorter duration between meals as the day progresses (de Castro et al., 2004). A high ratio of evening-to-morning energy, and energy intake after 20.00 hr, have been positively associated with an increase in BMI, while inversely, high morning energy associated with reduced BMI longitudinally (Aljuraiban et al., 2015; Baron et al., 2013; Kahleova et al., 2017) (Figure 3). Consuming >33% of total daily energy between 17.00–00.00 hr has been associated with a 2-fold odds ratio increase (OR 2.00, 95% confidence interval (CI) 1.03–3.89) in risk for overweight/obesity compared to those consuming <33% (Wang et al., 2013). Proximity of food intake to the nocturnal rise in melatonin, measured by 'dim light melatonin onset' (DLMO), a robust marker of circadian phase, may explain this relationship, as several recent analyses have shown that calorie intake closer to DLMO was associated with increased adiposity and impaired glucose homeostasis (McHill et al., 2017, 2019). Therefore, the extent to which a later temporal pattern of energy intake is associated with adverse metabolic health outcomes may depend on the influence on overall energy balance, the magnitude of energy consumed in evening period, the actual clock time within the definition of 'evening' at which EO occur, and the relationship between this clock time and internal biological time.

Meal regularity is a key factor within temporal patterns of energy intake, which may influence health outcomes. Meal irregularity has been defined as the consumption of food in varying amounts throughout the day, and at different times from one day to the next (Pot et al., 2016). In the UK diet, the pattern of energy intake across meals was found to be relatively consistent across a 17 year follow-up period, with energy linearly increasing across daily meals and peaking in the evening (Almoosawi et al., 2011). However, irregularity of breakfast and between-meal snack consumption were both significantly associated with increased odds for metabolic syndrome (OR for breakfast 1.34, 95% CI 0.99–1.81; OR for between meals 1.36, 95% CI 1.01–1.85) (Pot et al., 2014). A longitudinal investigation study in the UK population found changing associations over time, with irregular lunchtime energy intake at baseline significantly associated with odds (OR 1.43, 95% CI 1.05–1.91) of metabolic syndrome 17-years later, while irregular breakfast intake was associated with increased odds (OR 1.54, 95% CI 1.14–2.04) of metabolic syndrome 10-years later (Pot et al., 2015). Taken together, these observational data reveals that overall irregularity in meal patterns and energy intake is associated with increased risk of metabolic syndrome (Pot et al., 2014, 2015, 2016). Controlled interventions, however, shed little light on the mechanisms underpinning the relationship between meal regularity and metabolic health. The best controlled dietary intervention to date found no significant difference in anthropometric measures or 24-hr mean glucose levels (Alhussain et al., 2016). The irregular meal pattern displayed higher post-prandial glucose after breakfast and lunch, while the regular meal pattern resulted in increased 3 hr thermic effect of feeding (TEF) between pre and post intervention tests. However, the difference of in TEF of 11kcal ± 15kcal indicates a miniscule effect size and large margin of error, and it is difficult to attribute any clinical meaningfulness to the result, particularly given the short-term effects in these interventions relative to longer-term prospective cohort studies.

A distinct concept to meal regularity is that of meal frequency. In the INTERMAP study, participants with an average of 6 EO had higher DQI and lower BMI compared to those with <4 EO (Aljuraiban et al., 2015). However, no minimum energy criteria was applied to the definition of snacks, potentially influencing the finding in relation to total energy intake (Leech, Timperio, et al., 2017). Those with a frequency of 6 EO also had lower BMI, lower dietary energy density, lower alcohol intake, and higher fruit intake, indicating that frequency reflected of a pattern of overall health-promoting behaviours (Aljuraiban et al., 2015). Conversely, in the AHS-2 cohort, there was a positive association between increasing EO and BMI, with a pattern of >3–6 EO linearly associated with increased adiposity, with a relative risk increase in BMI per year of 0.04 (95% CI 0.02–0.06),

implying that increased EO was associated with increased energy intake (Kahleova et al., 2017). However, two main meals per day, a dietary characteristics reflecting traditional Adventist meal patterns, was associated with significant protective effects and relative reduction in BMI per year of −0.03 (95% CI −0.04 to −0.02) (Kahleova et al., 2017). It would appear that eating frequency is a secondary factor to the context of energy balance and wider health-promoting behavioural patterns. Both higher (>4) and lower (<3) meal frequencies may be associated with positive or negative health outcomes, depending on the wider characteristics associated with the eating frequency pattern (Aljuraiban et al., 2015; Kahleova et al., 2017). The role of eating frequency, therefore, appears to hinge on the relationship between eating occasions and energy excess.

The role of breakfast in the context of temporal eating patterns in humans is complex. While the weight of observational evidence suggests a protective effect of regular breakfast consumption against increasing adiposity (Gibney et al., 2018), the hypothesis that breakfast skipping influences positive energy balance and subsequent compensatory energy intake is unsupported by controlled interventions (Chowdhury et al., 2016; Levitsky et al.,, 2013; Sievert et al., 2019). The concept of 'breakfast' lacks a consensus for an operational definition that reflects the varying dietary assessment methods used in different countries, in addition to cross-cultural differences in the constitution and timing of that initial meal (Gibney et al., 2018; Leech, Timperio, et al., 2017). The totality of evidence suggests that regular breakfast consumption is associated with improved nutritional status, in children and adolescents (Gaal et al., 2018), and in adults (Fayet-Moore et al., 2019). However, it is difficult to tease apart the role of breakfast per se in bolstering nutritional status from the wider behavioural correlates of breakfast consumption, with regular breakfast intake associated with health-promoting behaviours and attitudes, implying that breakfast consumption may be a proxy for health-promoting behaviours, and the associations in observational research may reflect a 'healthy user bias' (Reeves et al., 2013). Breakfast may also reflect a relationship between time-of-day preference and behavioural attitudes to breakfast consumption (Walker & Christopher, 2016). Indeed chronotype, a behavioural preference for time-of-day reflecting an individual's internal biological time, has been shown to mediate the relationship between personality traits and attitudes towards breakfast consumption (Walker & Christopher, 2016). Whether this relates to biological factors (i.e., rhythms in appetite) or social factors (i.e., lack of time from sleeping later), is unclear, however, it indicates that behavioural influences on breakfast consumption may have an inherent time-of-day preference component (Reeves et al., 2013; Walker & Christopher, 2016). In support of this relationship, Xiao et al. (2019) found that the protective effect of breakfast and increasing quintiles of energy intake in the morning was only observed in chronotypes with a morning preference. However, consumption of either high or low levels of energy at breakfast did not attenuate the risk of obesity in evening chronotypes, while greater evening energy was associated with profound increases in odds (OR 4.94, 95% CI 1.61–15.14) for overweight and obesity only in evening chronotypes, and not in morning chronotypes (OR 1.36, 95% CI 0.69–2.67) (Xiao et al., 2019). In addition, Lopez-Minguez et al. (2019) investigated genetic influence on food timing by comparing 56 pairs of monozygotic and dizygotic female twins, and found heritability for the timing of breakfast of 56%, compared to 38% for lunch, while the timing of dinner was not determined to be heritable. Food timing and chronotype were highly genetically correlated. Thus, considering breakfast as a characteristic of temporal eating patterns with ubiquitous benefit may be insufficient to account for the complex relationship between behavioural preferences and internal biological timekeeping influencing breakfast consumption and daily energy distribution (Reeves et al., 2013; Walker & Christopher, 2016; Xiao et al., 2019). Nonetheless, there remain strong associations with reduced risk of type-2 diabetes (T2DM) from regular breakfast consumption, which may relate to the impact of breakfast compared to delayed meals on glycaemic control (discussed in more detail below). In the US Health Professionals Follow-Up Study cohort, men who did not eat before lunchtime exhibited a 23% relative risk increase (RR 1.23, 95% CI 1.08–1.39) for T2DM, compared to men who ate at least once, after adjustment for diet and BMI (Mekary et al., 2012). Ballon et al. (2018) conducted a recent meta-analysis of prospective cohort studies, demonstrating (from 4 cohorts, adjusted for BMI) a similar 22% (RR 1.22, 95% CI 1.12–1.3) relative increase in risk for T2DM. In a prospective analysis of participants with haemoglobin-A1c (HbA1c) data available, breakfast skipping was associated with an increase in HbA1c of 10.8% above baseline values (Reutrakul et al., 2013a). Analysis of the relationship with chronotype indicated that each hour delay in the mid-point of sleep was associated with a 2.5% increase in HbA1c (Reutrakul et al., 2013b). However, both chronotype and breakfast skipping were independently associated with impaired glycaemic control (Reutrakul et al., 2013a, 2013b).

Finally, the duration of the daily eating window may be an important determinant of health outcomes. Gill & Panda (2015) demonstrated an average daily eating duration of 14hrs 45mins in a US population, with a tendency towards later distribution of energy intake to the later afternoon and evening. This bias towards extended evening eating duration may predispose to overweight and obesity, given the tendency for energy intake in the later evening to exceed energy requirements (Baron et al., 2013; Gill & Panda, 2015). Independent of evening timing, extended duration in a post-prandial state may impair metabolism, with post-prandial glycaemia and post-prandial lipaemia contributing to cardiometabolic disease risk (Pappas et al., 2016). It may be beneficial to think about temporal eating patterns in terms of overall energy load and how that is distributed across the day, with evidence that the main meal and majority of daily energy occurring across the first two meals of the day (i.e., <16.00 hr) may result in favourable health outcomes (Garaulet et al., 2013; Kahleova et al., 2017), particularly given evidence at the population level indicating less than 25% of daily energy is consumed before noon (Gill & Panda, 2015). These associations indicate the potential benefit for timed dietary manipulations that reduce the daily duration of eating and/or manipulate distribution of energy, discussed further in Sections 3 and 4, below.

4 | Effect of time of day on post-prandial responses and metabolic physiology in humans

4.1 | Circadian Phase of Energy Intake Correlates with Body Weight and Adiposity

The intrinsic circadian variance in metabolism across the day indicates that the most significant contrast for human metabolic health may be between morning vs. evening energy distribution (Ruddick-Collins et al., 2018). Higher levels of adiposity have been shown cross-sectionally to be associated with a mid-point of calorie intake, defined as the time at which consumption 50% of total daily energy was reached, occurring closer to measured dim-light melatonin onset (DLMO), and with consuming a greater proportion of total daily energy intake at a later circadian phase, when compared to lean participants (McHill et al., 2017, 2019) (Figure 4). Neither calorie midpoint nor last calorie intake differed when measured by clock time, indicating that internal biological time was the primary mediating factor associated with increased adiposity (McHill et al., 2017, 2019). Finally, although circadian phase was assessed by proxy of habitual bedtime, not direct measures of DLMO, Xiao et al. (2019) found that greater distribution of energy in closer proximity to bedtime dramatically increased risk for overweight and obesity, a relationship which again was not evident when assessing energy intake relative to clock time. Thus, several recent observational studies have indicated food intake in close proximity to later biological timing is associated with increased adiposity and metabolic risk, a relationship which may not be evident if assessing energy intake in relation to clock time (McHill et al., 2017, 2019; Xiao et al., 2019).

4.2 | Diurnal variation in glycaemic control

The well-established diurnal variation in glucose tolerance is characterised by amplified glucose tolerance during the early part of the day, and diminished responses by the evening (van Cauter et al., 1989). A controlled intervention comparing the glycaemic responses to a 2 hr oral glucose tolerance test (OGTT) at 08.00 hr and 20.00 hr, found that the post-prandial glucose excursion was significantly greater at 20.00 hr compared to 08.00 hr (Leung et al., 2019). Comparing low-GI meals consumed at 08.00 hr, 20.00 hr, and 00.00 hr, post-prandial glucose was significantly greater after the 20.00 hr and 00.00 hr meals compared to the 08.00 hr meal (Leung

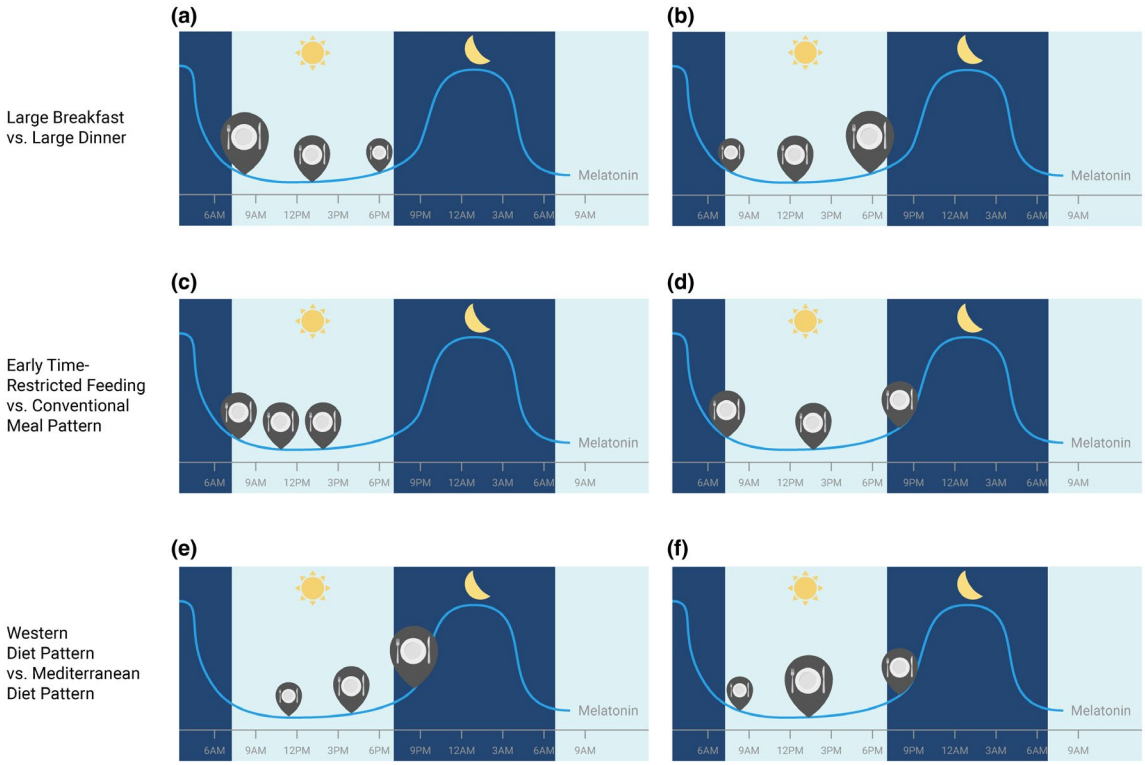

FIGURE 4 Temporal eating patterns in humans. (a) High-energy breakfasts with low-energy dinners have been demonstrated to result in favourable metabolic responses compared to the inverse energy sequence depicted in (b). Time-restricted feeding interventions include (c) an 'early time-restricted feeding' (eTRF), which aligns all meals in a 6–8 hr window early in the day, compared to (d) a more conventional meal pattern. (e) A typical diurnal distribution of energy in a 'Western' style dietary pattern, with delayed initiation of eating (or omitted breakfast), and increasing energy intake across subsequent meals with peak energy intake during the biological night, a pattern associated with adverse health outcomes. (f) A pattern of energy distribution observed in certain Mediterranean countries; peak energy intake occurs in the middle of the day, with evidence suggesting that earlier timing of this main meal results in more favourable metabolic responses compared to later afternoon timing

et al., 2019). Glucose concentrations remained elevated above baseline 3 hr after the 00.00 hr meal, while after 3 hr in the 08.00 hr and 20.00 hr meals glucose had returned to baseline concentrations (Leung et al., 2019). Controlled interventions shed additional light on the metabolic physiology underpinning the relationship between time-of-day and food intake. Nutrient intake during the biological night have been shown to correspond to impaired insulin sensitivity and exaggerated pancreatic beta-cell insulin secretion (Eckel et al., 2015). The diurnal variation in insulin sensitivity mirrors the diurnal variation in circulating free-fatty acids, which are elevated in the biological evening, contributing to a state of impaired insulin sensitivity (Morgan et al., 1999). In an isocaloric intervention in lean young women with breakfast (08.00 hr) and dinner (20.00 hr) consumed at the same times in both groups, varying the timing of lunch between earlier (13.00 hr) and later (16.30 hr) timing resulted in a 46% increase in post-prandial glucose area-under-curve (AUC) after late timed lunch compared to early lunch, decreased carbohydrate oxidation, and a blunted cortisol profile (a marker of circadian phase) (Bandín et al., 2014). Comparing morning (60% breakfast vs. 20% dinner) versus. evening (20% breakfast vs. 60% dinner) energy loads, and either a high-glycaemic index (GI) or low-GI meals, the high-energy/high-GI evening meal resulted in significantly greater post-prandial glucose and insulin, compared to the other meal interventions (Morgan et al., 2011). Cumulatively, these studies indicate a pronounced difference in evening metabolic physiology, with impaired glycaemic control in response to the timing, size, and composition of meals in the biological evening (Figure 4).

Incretin hormones, in particular glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinoptropic polypeptide (GIP), exhibit diurnal variation and are amplified in the early part of the day, resulting in more rapid insulin responses to nutrient intake in the morning (Lindgren et al., 2009). Comparing isocaloric meals of identical macronutrient composition consumed at 08.00 hr and 17.00 hr, the morning meal resulted in rapid elevations in GLP-1 and GIP, corresponding to a rapid insulin response and lower post-prandial total and peak glucose levels (Lindgren et al., 2009). These variations in morning metabolic physiology may contribute to the 'second meal phenomenon', which is characterised by an attenuated elevation in blood glucose levels in response to a second meal, when preceded by a prior meal earlier in the day (Jovanovic, Leverton, et al., 2009; Lindgren et al., 2009). Two factors appear to mediate this effect, namely suppression of FFA and enhanced skeletal muscle glycogen synthesis. Using ^{13}C magnetic resonance spectroscopy to investigate muscle glycogen storage, Jovanovic et al. demonstrated that compared to fasting until lunch, the plasma glucose response to lunch following breakfast was significantly attenuated, while muscle glycogen uptake signalling increased significantly (Jovanovic, Leverton, et al., 2009). Both effects correlated with pre-lunch NEFA levels, which were significantly reduced following breakfast (Jovanovic, Leverton, et al., 2009). Comparing the metabolic effects of standardised meals consumed at 08.00hr versus 17.00hr, Lindgren et al. showed that NEFA levels were higher at baseline before the 17.00 hr meal, while the 08.00 hr meal resulted in significantly lower nadir NEFA levels (Lindgren et al., 2009). Lee et al. (2011) found that, in participants with type-2 diabetes, ingestion of breakfast resulted in a rapid suppression of NEFA and nadir 90-min post-breakfast, which remained low and elevated only slightly in response to lunch. Thus, the rapid suppression of NEFA following morning energy intake appears to have a legacy effect over the course of the remainder of the day, and lower pre-meal NEFA levels associated with attenuated the magnitude of glycaemic responses to subsequent meals (Jovanovic, Leverton, et al., 2009; Lee et al., 2011; Lindgren et al., 2009). Conversely, extended morning fasting has been shown to result in elevated NEFA in the afternoon, and a lesser degree of NEFA suppression over the course of the day, which may contribute to elevated post-prandial glucose concentrations in response to both lunch and dinner (Jakubowicz, Wainstein, Ahren, et al., 2015; Jovanovic, Leverton, et al., 2009). In addition, following breakfast the uptake of glucose ingested at lunch into muscle glycogen occurs at a 50% greater rate in the 2 hr post-prandial period compared to when breakfast is omitted, an effect which is inversely correlated with NEFA concentrations before lunch (Jovanovic, Leverton, et al., 2009). Although some studies have found no difference in overall insulin concentrations after lunch with or without a preceding meal, (Jovanovic, Leverton, et al., 2009; Jovanovic et al., 2017), there is evidence to suggest that the first-phase insulin response may be enhanced at lunch following consumption of a prior breakfast, resulting in reduced post-prandial glycemia (Lee et al., 2011).

The second meal effect has also been shown to occur in persons with type-2 diabetes in a number of intervention studies. Jovanovic, Gerrard, et al., 2009 demonstrated that post-prandial blood glucose elevations in response to lunch were 95% less when breakfast preceded lunch (0.68 ± 1.47mmol/L), compared to fasting until lunch (12.32 ± 1.73mmol/L). In a controlled feeding study of patients with type-2 diabetes that tested the difference between two acute one-day interventions, one with breakfast consumed and the other fasting until lunchtime, Jakubowicz, Wainstein, Ahrén, et al., 2015 found that peaks in blood glucose in response to lunch and dinner were 39.8% and 24.9% higher, respectively, when breakfast was omitted. The 3 hr glucose area under the curve (AUC) was shown to be 36.8% and 26.6% higher after lunch and dinner, respectively, with breakfast omission. The meals in this study were isocaloric, such that energy was not compensated for on the breakfast omission test day and lunch and dinner on both days contained the same absolute energy content, minimising any effect of increased energy at those meals on the breakfast omission day. The same group also demonstrated that distribution of energy across the day in type-2 diabetes was an important factor in overall 24 hr glycaemic control (Jakubowicz et al., 2015b). Comparing two dietary regimens, one with 700 kcal at breakfast, 600 kcal at lunch, and 200 kcal at dinner, against the reverse (200 kcal breakfast, 600 kcal at lunch, and 700 kcal dinner), the high-energy breakfast intervention resulted in a 20% lower whole-day glucose AUC, and post-prandial glucose AUC was 24% lower after the 700 kcal meal at breakfast compared to the 700 kcal meal at dinner (Jakubowicz et al., 2015b). In addition, the timing of the peak in insulin secretion, the magnitude of the peak in insulin, and

the post-prandial AUC for insulin were all impaired in response to the high-energy dinner, compared to high-energy breakfast (Jakubowicz et al., 2015b).

4.3 | Effect of energy distribution on bodyweight regulation and metabolism

The role of morning metabolism on body weight and obesity energetics has been the subject of multiple intervention studies. A secondary analysis of a 20-week weight loss intervention found that participants who consumed their largest energy meal before 15.00 hr lost twice as much weight than participants consuming their largest meal after 15.00 hr (Garaulet et al., 2013). Similarly, an intervention trial comparing high-energy breakfast/low-energy dinner (700 kcal breakfast, 500 kcal lunch. 200 kcal dinner) to low-energy breakfast/high-energy dinner (200 kcal breakfast, 500 kcal lunch, 700 kcal dinner), found a 2.5-fold greater weight loss in the high-energy breakfast group after 12 weeks (Jakubowicz, Wainstein, Ahrén, et al., 2015). It should be noted, however, that diets were consumed under free-living conditions and intake was self-reported. It is difficult to attribute the difference between groups to a thermodynamic advantage conferred by a higher energy breakfast. It has been suggested that the circadian variance in diet-induced thermogenesis (DIT) may explain the difference in weight loss (Jakubowicz, Wainstein, Ahrén, et al., 2015). While there may be a diurnal variance in DIT that is higher in the morning and reduced in the evening, the magnitude of difference between 'early DIT' (i.e., up to 120 mins post-prandial) in response to isocaloric meals in the morning and in the evening has been shown to be 0.11 kcal/min (Morris et al., 2015). A recent tightly controlled study found that consuming 69% of daily energy (weight maintenance level) at breakfast resulted in twice as high DIT compared to 69% at dinner, although the magnitude of difference was again small, 0.17 kcal/min, and extrapolating the per minute energy expenditure to the entire 3.5 hr post-prandial period measured, the difference was 15 kcal (Richter et al., 2020). Similarly, in a metabolic ward study conducted at maintenance level energy intake, Ravussin et al. (2019) found that the increase in DIT in response to consuming 100% of total daily energy between 08.00 hr and 14.00 hr amounted to 56 kcal energy expenditure during the daytime, however, this was negated by the extended fasting period, such that total 24 hr energy expenditure was unchanged. Taken together, the absolute caloric value of variance in DIT seems insufficient to explain the energetic imbalance required to produce the 5.1 kg difference in weight loss observed over 12 weeks by Jakubowicz et al. (2013). Controlled interventions also do not support the hypothesis that breakfast skipping leads to compensatory increases in energy intake (Levitsky et al.,, 2013; Sievert et al., 2019).

Other components of energy balance, specifically physical activity thermogenesis, have been investigated for their potential to influence energy expenditure in response to breakfast. In the Bath Breakfast Project (BBP), consumption of >700kcal before 11.00 hr, with at least 50% within 2 hr of waking, resulted in increased physical activity thermogenesis (PAT), compared to extended morning fasting until 12.00 hr daily (Betts et al., 2014). However, the additional energy expenditure was equivocal to the extra calorie intake consumed in the breakfast groups, such that energy balance was maintained (Betts et al., 2014; Chowdhury et al., 2016). The small but consistent increase in DIT in response to breakfast was proportionate to the additional morning energy consumed compared to extended fasting, conferring no additional metabolic advantage in the context of the breakfast group consuming more total daily energy (Betts et al., 2014; Chowdhury et al., 2016). In addition, in the participants with obesity, the extra PAT in response to breakfast intake was accumulated primarily before 12.00 hr, but no difference was observed beyond that time, and thus whole-day PAT did not differ significantly between groups (Chowdhury et al., 2016). Consumption or omission of breakfast for six weeks did not result in any compensatory or adaptive effect on energy regulatory hormones and acute energy intake in either lean (Chowdhury et al., 2018) and obese participants (Chowdhury et al., 2019). However, in the BBP, metabolic control was improved in the breakfast group compared to morning fasting, with improved insulin sensitivity in the breakfast group in both lean participants and participants with obesity, lower nocturnal blood glucose levels in participants with obesity (Chowdhury et al., 2019), and higher blood glucose variability in the afternoon/evening in lean participants in the fasting group (Chowdhury et al., 2018). Consistent with this finding, in a metabolic chamber study comparing breakfast skipping to dinner skipping under energy balance conditions, breakfast skipping resulted in significantly higher incremental AUC for both glucose and insulin following lunch, higher HOMA-IR, and overall 24-hr glucose AUC, compared to dinner skipping (Nas et al., 2017).

Temporal distribution of macronutrients may also influence metabolic outcomes. Using an intervention in participants with poorly controlled type-2 diabetes, Pearce et al. (2008) demonstrated that distributing the majority of carbohydrate to lunch or breakfast resulted in significantly lower overall daily glycaemic excursions, compared to carbohydrate evenly distributed across the day or majority at dinner. Another intervention comparing the effect of diurnal distribution of carbohydrates and fats, with carbohydrate-rich meals consumed until 13.30 hr followed by fat-rich meals consumed between 16.30–22.00 hr (HC/HF), compared to the inverse of this meal sequence (HF/HC), the HF/HC sequence resulted in impaired glycaemic control in participants with impaired glucose tolerance (IGT), but not in normoglycaemic participants (Kessler et al., 2017). The distribution of carbohydrate to the afternoon resulted in significantly higher post-prandial glucose and insulin peaks in participants with IGT. High-energy, protein and carbohydrate-rich breakfasts have been shown to result in persistent suppression of the appetite hormone ghrelin, an effect which extended beyond the period of weight loss (Jakubowicz et al., 2012). Given the circadian clock-driven peak in hunger has been shown to occur in the biological evening within both forced desynchrony (Scheer et al., 2013) and constant routine (Wehrens et al., 2017) protocols, the potential for morning energy intake to suppress ghrelin levels both acutely and

persistently suggests that the impact of morning energy intake on parameters like hunger and appetite may be important characteristic of circadian metabolism.

To conclude, while there is conflicting evidence regarding an energetic advantage to morning energy intake in the context of energy expenditure and weight loss, diurnal distribution of energy may have profound impacts on post-prandial metabolism, with particular importance for post-prandial glycaemia in the management of T2DM.

5 | Time-restricted feeding

Time restricted feeding (TRF), sometimes referred to as time restricted eating (TRE) in humans, is an intervention that restricts the time between first and last energy intake each day, and therefore lengthens the daily fasting period (Longo & Panda, 2017; Melkani et al., 2017; Rothschild et al., 2014). It is currently unclear whether TRF acts via temporal restriction of energy intake and/or the increased daily fasting period. Nonetheless, available evidence indicates that it is a potentially effective behavioural intervention within patient groups and the wider population. A novel aspect of TRF that may help its adoption by many people is that it primarily focuses on timing of energy intake, rather than seeking to change dietary preferences. A survey of 156 adults in the USA revealed that the median time between first and last energy intake each day is nearly 15hr (Gill & Panda, 2015), indicating that there is considerable scope for many people to adopt TRF within their daily routines.

Until recently, most studies of TRF had been conducted in animal models. Early research using mice revealed that TRF reduces weight gain in response to a high-fat diet (Hatori et al., 2012; Sherman et al., 2012). These effects occurred irrespective of whether the restricted feeding opportunity came during the light or dark phase of the light-dark cycle and despite equivalent energy consumption in the TRF and ad libitum feeding groups. Later rodent research suggested that TRF can reverse the progression of metabolic diseases, with metabolic physiology improved in multiple ways including: lowered fat mass, lowered serum cholesterol, improved glucose tolerance (Chaix et al., 2014). The potential for TRF to be an effective intervention across species was highlighted when TRF was shown to prevent body weight gain and decelerate cardiac aging in *Drosophila* (Gill et al., 2015). A restricted daily duration of energy consumption may therefore represent a beneficial intervention of use in humans.

The effects of TRF in humans remain poorly understood, although an increasing number of small-scale studies are providing evidence in favour of TRF's efficacy. Early research related to TRF included studies of participants during Ramadan. As reviewed elsewhere (Rothschild et al., 2014), Ramadan has been associated in many studies with metabolic benefits, including reduced body weight, improved lipid profile and reduced blood glucose concentration. However, Ramadan involves a shift from daytime to nighttime feeding, in addition to cultural changes, making it difficult to interpret data purely in terms of TRF. More controlled human interventions, specifically related to TRF, have taken multiple forms. Studies have typically restricted daily energy intake to windows of 4–12 hr; they have been performed in participants who are athletes, healthy non-athletes, overweight/obese, and overweight individuals identified as having pre-diabetes. From a circadian perspective, it is also noteworthy that the temporal nature by which feeding windows have been reduced also exhibits great variation.

One of the more commonly published TRF interventions has been to bring forward the evening meal by around 6 hr in a so-called 'early TRF' (eTRF) protocol (Ravussin et al., 2018; Sutton et al., 2018; Jamshed et al., 2019). In these studies, participants consumed the same amount of daily energy in the control and eTRF groups. A 5-week eTRF intervention resulted in improved insulin sensitivity, blood pressure and oxidative stress in men with prediabetes (Sutton et al., 2018). In a group of overweight men and women, eTRF for 4 days had various effects including reduced appetite and increased fat oxidation (Ravussin et al., 2019), together with decreased 24-hr glucose levels and glycaemic excursions (Jamshed et al., 2019) compared to control. A similar 'night eating restriction' study eliminated energy intake from 19:00 to 06:00 each day for 2 weeks in healthy men (LeCheminant et al., 2013). There was no control placed on total daily energy intake. During the restricted night eating leg, participants consumed less daily energy and exhibited a significant difference in weight change compared to the control leg (LeCheminant et al., 2013). However, the fact that the restricted feeding window is purely because of an earlier end to daily energy consumption may reflect in part the benefits of lower evening energy intake, as described in Section 3.

Other studies have implemented TRF in different ways. In order to remove bias between morning and evening restriction, one study employed symmetrical compression of daily feeding by 3-hr compared to habitual over a 10-week period, with ad libitum feeding allowed within the allocated daily window (Antoni et al., 2018). The TRF condition reduced daily energy intake and body fat; there was also a significant difference in fasting plasma glucose concentration, although this was primarily caused by an increase in the control group over the 10-week period. Symmetrical compression of the daily feeding window was also employed in a later study of overweight/obese men (Parr et al., 2020). Here, participants completed two 5-day isoenergetic legs, one adopting an 8-hr (TRF) window and the other with a 15-hr window. The TRF condition decreased nocturnal glucose concentration and improved feelings of well-being (Parr et al., 2020). Another study recruited overweight individuals with a habitual daily eating window of > 14 hr (Chow et al., 2020). All participants were allowed ad libitum feeding with the TRF group restricted to a self-selected 8-hr window. The TRF group resulted in fewer eating occasions, weight loss, reduced visceral fat, and reduced lean mass (Chow et al., 2020). Finally, a recent study has restricted early energy intake in obese individuals to either a 4-hr (15:00–19:00) or 6-hr (13:00–19:00) daily window for 8 weeks (Cienfuegos et al., 2020). Both TRF groups reduced daily energy intake and exhibited reductions in body weight, insulin resistance, and oxidative stress.

To date there is limited data comparing the effects of TRF in a feeding window aligned to the early or late part of the day. One study using a 7-day TRF intervention found a beneficial effect of TRF on glucose and triglyceride concentration, but no interactions between TRF and mealtime (Hutchinson et al., 2019). In summary, initial evidence suggests that adoption of TRF in humans may lead to important health benefits. From a public health perspective, the potential ability of TRF to induce health benefits is extremely encouraging. Whether TRF works by reduction in energy intake, increased daily fasting and/or circadian regulation of energy consumption is to be determined by future research. It will also be essential to identify sociological factors that determine whether or not a given individual is able to incorporate TRF principles into their regular lifestyle.

6 | Areas for future research

The literature remains nascent on the relationship between chronotype, social jetlag, and cardiometabolic health. To date, an evening chronotype has been associated with lower diet quality, and a redistribution of energy of energy and macronutrient intake to later in the wake cycle (Kanerva et al., 2012). A recent pilot study found that adjusting energy intake relative to chronotype, with 'early' chronotypes consuming higher energy breakfast and lower energy dinner, and 'late' chronotypes consuming the inverse, led to 1.4 kg greater weight loss over the course of a 12-week weight-loss intervention in the chronotype-adjusted diets, compared to a usual hypocaloric diet (Galindo Muñoz et al., 2019). However, there was no objective measure of circadian phase and no data is presented in relation to the clock time at which meals were consumed, thus this study remains exploratory. However, interventions addressing chronotype would be a valuable addition to the evidence-base, given the higher risk of adverse cardiometabolic health in this population group as a result of discord between their biological time-of-day preferences and social timing in society (Reutrakul et al., 2013b).

Social jetlag is another important environmental risk factor which observational research suggests a relationship between social jetlag, increased adiposity, and metabolic disease risk factors (Parsons et al., 2014). Social jetlag describes the differences between sleep timing and duration on work days, with enforced wake times, and free days or weekends, creating a discordance between internal biological time and social timing that can lead to a chronic form of jetlag (Wittman et al., 2006). Several authors have posited that the relationship between chronotype, social behaviours, and timing of food intake may be mediated by social jetlag (Walker & Christopher, 2016; Wittman et al., 2006). In addition, social jetlag may exert negative influences on self-regulation and health-promoting behaviours, influencing dietary intake and health status (Walker & Christopher, 2016). Many studies to date on the relationship between social jetlag and metabolic health are cross-sectional, and more longitudinal studies would add to the understanding of the interaction between biological and societal clocks, and accumulated social jetlag, on health outcomes.

7 | CONCLUSIONS

A substantial body of evidence from converging lines of research demonstrates clear links between circadian rhythms in metabolism, nutrition, and metabolic health. Epidemiological associations between temporal eating patterns, obesity, and metabolic health in humans are supported by from animal models and human intervention studies investigating the intimate links between metabolic clocks and nutrition, and temporal distribution of energy intake. The modern environment, with exposures such as artificial light, shift-work, and ubiquitous food availability, predisposes individuals to circadian dysregulation and dysmetabolism. The evidence to date indicates that chrononutrition may provide accessible approach to improving population health, and effective strategies for targeted population subgroups, in particular metabolic diseases like Type-2 Diabetes.

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CONFLICT OF INTERESTS

The authors declare no competing interests.

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