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SPECIAL REPORT

Advancing Chrononutrition for Cardiometabolic Health: A 2023 National Heart, Lung, and Blood Institute Workshop Report

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ABSTRACT: The circadian system maintains optimal biological functions at the appropriate time of day, and the disruption of this organization can contribute to the pathogenesis of cardiometabolic disorders. The timing of eating is a prominent external time cue that influences the circadian system. "Chrononutrition" is an emerging dimension of nutrition and active area of research that examines how timing-related aspects of eating and nutrition impact circadian rhythms, biological processes, and disease pathogenesis. There is evidence to support chrononutrition as a form of chronotherapy, such that optimizing the timing of eating may serve as an actionable strategy to improve cardiometabolic health. This report summarizes key information from the National Heart, Lung, and Blood Institute's virtual workshop entitled "Chrononutrition: Elucidating the Role of Circadian Biology and Meal Timing in Cardiometabolic Health," which convened on May 2 to 3, 2023, to review current literature and identify critical knowledge gaps and research opportunities. The speakers presented evidence highlighting the impact on cardiometabolic health of earlier and shorter eating windows and more consistent day-to-day eating patterns. The multidimensionality of chrononutrition was a common theme, as it encompasses multiple facets of eating along with the timing of other behaviors including sleep and physical activity. Advancing the emerging field of chrononutrition will require: (1) standardization of terminology and metrics; (2) scalable and precise tools for real-world settings; (3) consideration of individual differences that may act as effect modifiers; and (4) deeper understanding of social, behavioral, and cultural influences. Ultimately, there is great potential for circadian-based dietary interventions to improve cardiometabolic health.

Key Words: chrononutrition ■ circadian rhythms ■ eating timing ■ eating variability ■ exercise timing ■ shift work ■ time-restricted eating

The discovery of the molecular machinery underlying circadian rhythms was recognized with the Nobel Prize in Physiology or Medicine in 2017.[1] This research described an intricate endogenous system that evolved to synchronize biological activity and behavior with the 24-hour light–dark cycle of the Earth.[2–5] At the cellular level, a collection of clock genes and proteins oscillate through a transcriptional–translational

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Nonstandard Abbreviations and Acronyms

TRE	time-restricted eating

negative feedback loop, generating 24-hour endogenous rhythms. The timing of these cellular rhythms is orchestrated by a primary, central circadian clock in the suprachiasmatic nucleus of the anterior hypothalamus and a series of secondary clocks throughout the brain and periphery, in nearly every other organ and tissue.

The internal circadian system governs a spectrum of human physiology and behavior, including sleep–wake cycles, core body temperature, immune system activity, appetite, and metabolism to promote optimal biological function at the appropriate time of day.[4,6] Under normal conditions, the central and peripheral oscillators are synchronized, and work together to orchestrate these cycles.[7] However, external cues, behaviors, and underlying circadian rhythms can disrupt this synchrony; common examples include eating and activity during the night, which are pervasive in the general population and, more markedly, in shift work.[8] Misalignment between the timing of different behaviors or between the clocks and behavioral or environmental cycles, can disrupt the coordination of clocks in the body, potentially driving the pathogenesis of cardiometabolic disorders.[9–12] Conversely, aligning internally driven circadian rhythms, behavioral cycles, and physiological function may prevent chronic pathological conditions and support optimal health, including the reversal or improvement of existing metabolic conditions.[13]

Several lifestyle and environmental factors affect the circadian system. Exposure to light is the predominant "zeitgeber," or time giver, entraining the circadian system to the external environment. In humans, a primary biomarker of the timing of the central circadian clock is the suprachiasmatic nucleus–driven production of melatonin, which reflects the biological night.[14,15] Light exposure in the early morning hours advances the rhythm of melatonin (ie, *phase advance*), along with other biological markers, whereas light exposure in the evening delays the biological rhythms (ie, *phase delay*). In addition, other external cues, such as patterns of fasting–feeding[16,17] and rest–activity,[18,19] act as zeitgebers for peripheral clocks. In recent years, it was demonstrated that the timing of eating is such a robust entrainer of peripheral oscillators that misalignment between eating and light exposure can uncouple peripheral clocks from the central clock.[20] This is particularly relevant in the context of the current 24-hour environment, in which energy-dense, palatable foods are available at all hours, promoting eating at inappropriate times.

As an important zeitgeber for the circadian system, eating timing (see Figure 1 for an overview of eating timing-related variables) has emerged as a novel factor affecting multiple aspects of cardiometabolic health. Traditionally, nutrition research has emphasized *what* and *how much* to eat. Indeed, healthy diets composed of nutrient-rich foods and beverages in moderate amounts are central to promoting cardiometabolic health and constitute the core themes of the Dietary Guidelines for Americans.[21] However, new evidence strongly supports a key influence of *when* one eats on cardiometabolic health. "Chrononutrition" is an emerging dimension of nutrition and an active area of research that examines how timing-related aspects of nutrition impact circadian rhythms, biological processes, the pathogenesis of diseases, and its potential as a form of chronotherapy.

Given that chrononutrition represents an emerging modifiable behavior that could promote cardiometabolic health, the National Heart, Lung, and Blood Institute hosted a virtual workshop entitled "Chrononutrition: Elucidating the Role of Circadian Biology and Meal Timing in Cardiometabolic Health" on May 2 and 3, 2023. The workshop was chaired by Drs Karen Gamble and Marie-Pierre St-Onge and featured a multidisciplinary group of investigators who presented emerging research on the relationships of timing-related aspects of eating and physical activity with cardiometabolic health and relevant underlying biological mechanisms (Table 1). Participants highlighted opportunities to apply these novel discoveries to clinical practice to prevent and treat cardiometabolic diseases. The workshop also identified critical knowledge gaps and barriers in this emerging area that must be addressed to advance the field. The National Heart, Lung, and Blood Institute–wide workshop was aligned with the goals of the National Institutes of Health Common Fund's Nutrition for Precision Health powered by the All of Us Research Program[22]; the National Heart, Lung, and Blood Institute Nutrition Research Implementation Plan[23]; and the new National Institutes of Health Sleep Research Plan.[24] The goal of this workshop report is to summarize current understanding of the role of chrononutrition in cardiometabolic health and to convey the critical knowledge gaps highlighted by the expert panel. It is important to note that the purpose of this report is to summarize specific discussions and themes that emerged from the workshop and to describe related opportunities. Thus, the content of this report does not reflect all research conducted or anticipated in the field of chrononutrition and certainly does not imply that there are no other rich areas of exploration and future discovery within this field.

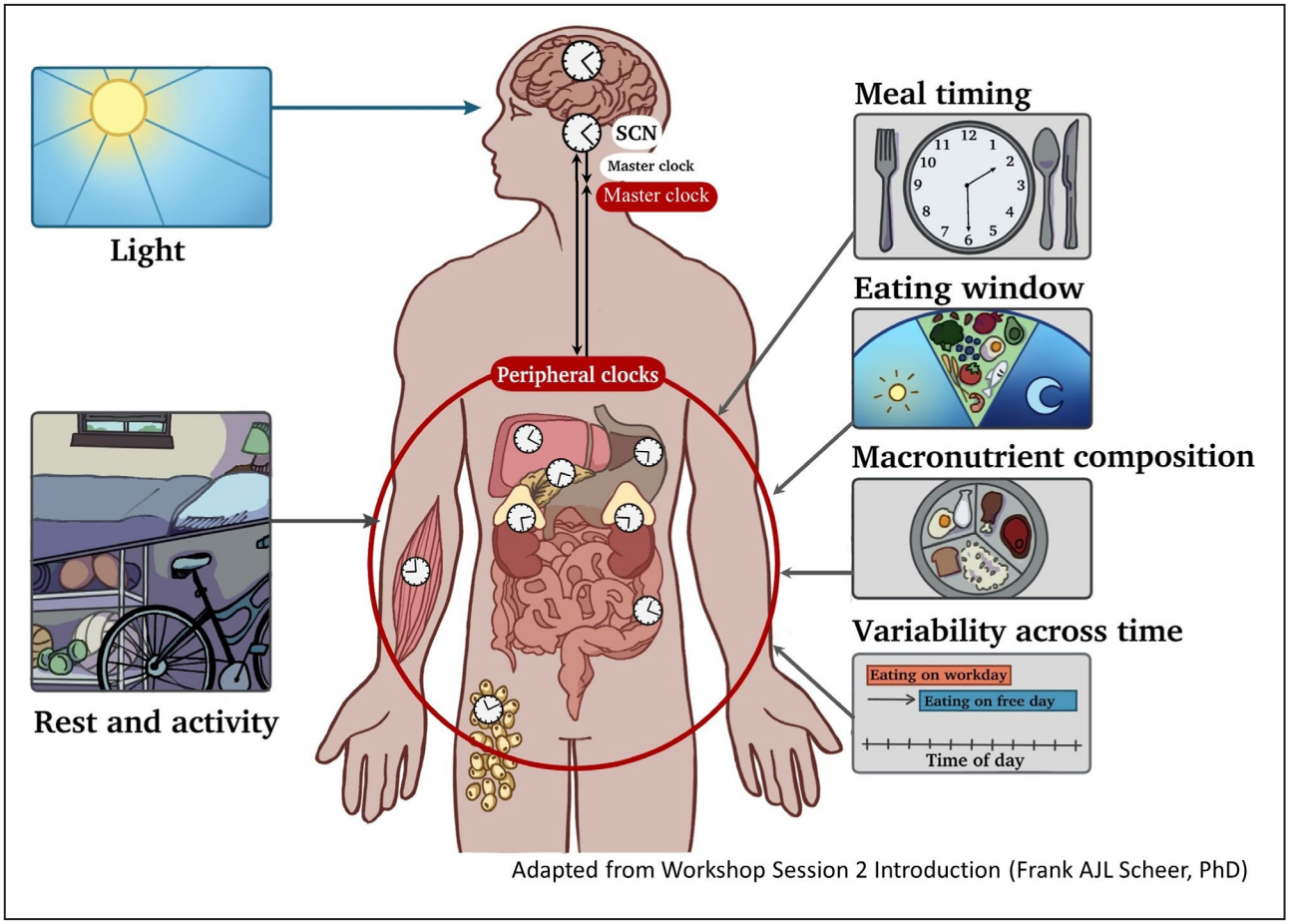

Figure 1. Overview of zeitgebers and the role of diet.
Adapted from Workshop Session 2 Introduction presented by Dr Frank A. J. L. Scheer.

ESTABLISHING THE INTERPLAY OF EATING AND CIRCADIAN RHYTHMS AND THEIR PHYSIOLOGICAL CONSEQUENCES

There is a strong biological basis for the influence of the timing of eating on cardiometabolic health.[13,25–29] As a synchronizing time cue for peripheral tissues, the timing of eating can alter the phase of molecular clocks in peripheral tissues.[26] These phase shifts, in turn, influence cellular and metabolic functions in peripheral tissues. Indeed, several metabolic processes are at least partially regulated by the clock, including insulin secretion, insulin sensitivity, the thermic effect of food, lipogenesis, and lipolysis.[25,30] Insulin secretion in response to a nutrient (glucose) load represents a key pathway by which the timing of intake can impact circadian rhythms; insulin release acts as a systemic signal entraining circadian clocks across multiple organ systems.[31,32] Because timing of eating is a more potent zeitgeber for peripheral clocks than for the central clock, mistimed food intake can result in internal misalignment (internal desynchrony) between these internal clocks and their biological rhythms.[13,29] Interestingly, the impact of eating on circadian rhythms is not isolated to the timing of intake but also extends to the nutrient composition of the diet. For example, there is evidence of nutrient sensing by the circadian system; consuming a high-fat diet has been shown to disrupt circadian rhythms in peripheral tissues under appropriate eating timing conditions (ie, aligned).[33–35] Given the emphasis of this workshop on chrononutrition, however, the remaining discussion will focus on the timing of food intake, rather than specific nutrients, as a modulator of circadian rhythms and health. Detailed description of molecular mechanisms underlying nutrient sensing of the circadian system, and downstream consequences, has been described elsewhere.[25,26,36]

Some of the earliest evidence in humans of a role for the timing of eating in cardiometabolic health came

Table 1. List of Speakers for the NHLBI-Sponsored Chrononutrition Workshop Held on May 2 to 3, 2023, Titled "Chrononutrition: Elucidating the Role of Circadian Biology and Meal Timing in Cardiometabolic Health"

Role	Speaker	Academic title and primary institution (country)	Presentation title
Workshop co-chair	Karen Gamble, PhD	Professor and Vice Chair (Basic Research), University of Alabama at Birmingham (USA)	Workshop introductions and discussions: Chrononutrition in the basic sciences
Workshop co-chair	Marie-Pierre St-Onge, PhD	Associate Professor, Columbia University Irving Medical Center (USA)	Workshop introductions and discussions: Chrononutrition in the clinical and population sciences
Keynote speaker	Marta Garaulet, PhD	Professor, University of Murcia (Spain)	State of chrononutrition science and opportunities to advance the field
Session 1 chair	Matthew P. Butler, PhD	Associate Professor, Oregon Health & Science University (USA)	Introduction: The timing and salience of nutrient cues in circadian physiology
Speaker	Josiane L. Broussard, PhD	Associate Professor, Colorado State University (USA)	Impact of circadian misalignment and timing of eating on whole-body and tissue-specific metabolic homeostasis
Speaker	Erin C. Hanlon, PhD	Research Associate Professor, University of Chicago (USA)	Sleep deficiency and food Intake: Pathway to obesity
Speaker	Karyn A. Esser, PhD	Professor and Chair (Physiology & Aging), University of Florida (USA)	Exercise as a peripheral clock time cue: Links to muscle metabolism
Session 2 chair	Frank A. J. L. Scheer, PhD	Professor, Harvard Medical School & Brigham & Women's Hospital (USA)	Introduction: The human circadian system, meal timing, and cardiometabolic consequences
Speaker	Nour Makarem, PhD	Assistant Professor, Columbia University Irving Medical Center (USA)	Temporal eating patterns and cardiometabolic risk: Epidemiological evidence and research opportunities
Speaker	Christopher M. Depner, PhD	Assistant Professor, University of Utah (USA)	Timing of food intake, eating patterns, and links to cardiometabolic health outcomes
Speaker	Emily N. Manoogian, PhD	Staff Scientist, Salk Institute for Biological Sciences (USA)	Methods for assessing eating patterns and evaluating circadian-cardiometabolic interactions
Session 3 chair	Kenneth P. Wright, PhD	Professor, University of Colorado Boulder & Denver Anschutz School of Medicine (USA)	Introduction: State of the science on circadian and meal timing interventions for cardiometabolic health
Speaker	Courtney M. Peterson, PhD	Associate Professor, University of Alabama at Birmingham (USA)	Clinical trials of meal timing
Speaker	Cibele A. Crispim, PhD	Associate Professor, Federal University of Uberlândia (Brazil)	The role of circadian misalignment and meal timing in public health: Shift working populations
Speaker	Seth A. Creasy, PhD	Assistant Professor, University of Colorado & Anschutz School of Medicine (USA)	Examining the clinical implications of exercising at different times of the day

from a series of experiments conducted on volunteers at the University of Minnesota.[37] In 1 of these studies, participants were restricted to eat only in the morning (breakfast) or the evening (dinner), and physiological parameters were measured throughout the day. Results demonstrated that shifting the timing of eating impacted diurnal patterns of blood pressure, temperature, and circulating levels of immune cells. Most notably, restricting eating to the evening delayed the acrophases of growth hormone and insulin and advanced the timing of peak cortisol levels, suggesting that later eating could adversely impact glucose homeostasis. Furthermore, a lesser reduction in body weight was observed when participants' only meal was in the evening versus the morning.[37] Subsequent animal experiments also reported differential effects of early versus late food availability on physiological outcomes, including body weight regulation; some of the key studies have been highlighted in previous reviews.[38,39] A study that is largely credited with returning public attention to a potential independent impact of meal timing on cardiometabolic function was published in 2009 and demonstrated that mice fed a high-fat diet exclusively during their typical active/feeding period (ie, the dark phase for nocturnal animals) gained significantly less weight than mice fed exclusively during their typical rest/fasting period (ie, the light phase).[40] The misaligned timing of feeding resulted in larger increases in total weight and fat mass despite similar levels of energy intake and activity. That same year, a study in humans found that circadian misalignment from eating at times that did not align with the day–night cycle worsened glycemic control and elevated blood pressure in healthy humans.[41] These findings helped to catalyze substantial growth in the study of 24-hour diurnal patterns in the timing of eating in humans, that is, rhythmic behavior in food intake.[42]

Key human studies more than a decade ago reinforced that the timing of eating is an important cardiometabolic factor. In a randomized controlled trial from 2013 conducted in 96 women with overweight, eating

a large breakfast and light dinner increased weight loss and reduced mean glucose and insulin levels relative to eating a large dinner.[43] That same year, a study in a Spanish cohort of 420 adults found that the timing of food intake differentially influenced weight loss achieved during a dietary intervention.[44] In both that study and a subsequent, larger study of >3000 adults, late eating was associated with a reduced efficacy of weight loss interventions.[44,45] These findings align closely with those of the seminal Minnesota studies[37] and suggest that eating timing may influence the types and amounts of foods consumed. In partial support of this postulation, later eaters in the Spanish cohort, who had a poorer weight loss response, had lower serum levels of the satiety hormone leptin during the morning as they were waking up.[45] However, more research into the impact of meal timing on the homeostatic and hedonic pathways regulating food intake in humans is needed to elucidate mechanisms underlying effects on body weight. Notably, clinical trials have since shown that the effects of timing of eating on cardiometabolic health can occur independently of changes in energy intake. In 2015, an isocaloric controlled feeding study in adults with type 2 diabetes found that eating a large breakfast increased insulin secretion and lowered mean glucose levels across the day relative to eating a large dinner.[46] Similarly, another randomized controlled trial reported that skipping breakfast and fasting until noon increased postprandial glucose levels and impaired insulin secretion.[47] Finally, an early multicomponent crossover study among women demonstrated that consuming the same meal late in the afternoon, relative to early in the afternoon, resulted in impaired glucose tolerance and pancreatic β-cell function as well as reduced energy expenditure.[48]

Subsequent studies further examined eating timing relative to endogenous circadian rhythms rather than the 24-hour societal clock. In a 2017 cross-sectional analysis, late eating relative to the internal phase of the central circadian clock (defined by dim light melatonin onset) and not the local clock time was found to be associated with higher body mass index and body fat.[49] Mechanistic trials in humans confirmed that the impact of food intake on cardiometabolic health is, in part, determined by its timing relative to the endogenous circadian clock. For example, a randomized, crossover study using both simulated day and night shift protocols, demonstrated a dominating effect of the endogenous circadian system on glucose tolerance and pancreatic β-cell function, with much higher glucose tolerance and β-cell function in the biological morning as compared with the biological evening, and a circadian effect that was larger than the combined effects of all behavioral and environmental factors combined.[50] Collectively, these results suggest that limiting circadian misalignment by aligning food intake with the active phase of the biological clock is expected to yield cardiometabolic benefits. To examine the health benefits of earlier eating times, recent crossover trials compared metabolic outcomes in response to consuming a controlled diet earlier in the day (first eating occasion within 1 hour of waking) versus later in the day (first eating occasion ≈4–5 hours after waking). In the context of identical duration of the eating window, early eating led to more favorable outcomes.[51–53] One study observed higher waking energy expenditure, higher 24-hour core body temperature, improved appetite regulation, and decreased expression of genes involved in lipogenic pathways within adipocytes in response to early versus later eating.[51] Another study found that early compared with late eating increased fat oxidation.[52] Finally, improved insulin sensitivity and body composition are found with early versus late eating.[53]

Melatonin plays a pivotal role in modifying the cardiometabolic response to food intake. Melatonin is secreted from the pineal gland and is a biomarker for the circadian phase of the central clock.[54,55] Exogenous melatonin administration (both at pharmacological and physiological concentrations) reduces glucose tolerance[56] as the body anticipates sleep and the onset of fasting. Correspondingly, melatonin receptors are found in pancreatic islets.[57] A crossover study in women with overweight or obesity showed that late dinner eating in the presence of high endogenous melatonin decreased glucose tolerance compared with early dinner eating.[58] Recently, a large study reported that carbohydrate intake at a time when endogenous melatonin is high, as is typical for late eaters, impairs glucose tolerance, particularly among those with a common melatonin receptor 1B gene (*MTNR1B*) G risk allele robustly associated with diabetes.[59] This deficit is attributed to a decrease in β-cell function and insulin secretion defects. Other physiological mechanisms in addition to melatonin are likely to play a role and have yet to be fully elucidated.

KEY THEMES IN CHRONONUTRITION RESEARCH AND CRITICAL KNOWLEDGE GAPS

Several key themes in chrononutrition emerged over the course of the workshop (summarized in Figure 2). We highlight existing knowledge gaps and opportunities for future research for these themes.

Multidimensional Chrononutrition for Cardiometabolic Health

While experimental studies have established mechanisms by which suboptimal chrononutrition could ultimately lead to cardiometabolic disorders, longer-term studies among large samples of free-living populations are needed to establish relationships between chrononutrition and cardiometabolic outcomes. These studies are just starting to emerge. Findings from population- or community-based cohorts highlighted several

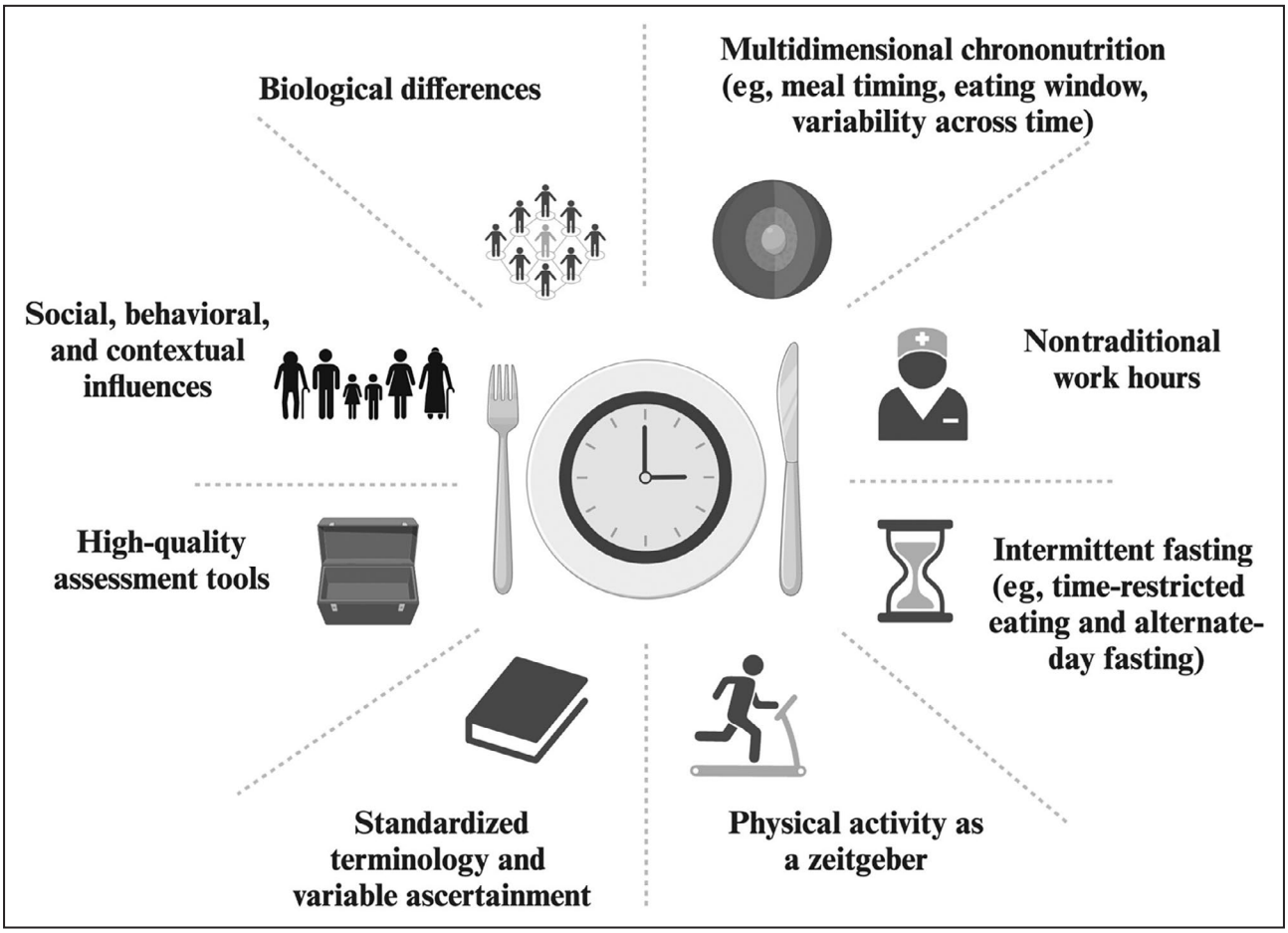

Figure 2. **Key themes in chrononutrition research and critical knowledge gaps.**

dimensions of chrononutrition as potential determinants of cardiometabolic health. Relevant dimensions include the timing of the first or last eating occasion, the daily eating window, the distribution of food intake across the day, and the variability in eating times. There is strong biological data indicating that later eating start and end times as well as greater caloric intake coinciding with the circadian evening relate to worse cardiometabolic health outcomes, including poorer glycemic control and elevated weight status, lipids, blood pressure, and inflammation.[45,49,60–62] However, later eating is likely not the only chrononutrition dimension linked to adverse cardiometabolic consequences. The distribution of calories and macronutrients consumed across the day has emerged as another meaningful dimension, as well as the timing of the largest caloric load, which was demonstrated by a recent meta-analysis.[63] The consumption of a larger proportion of energy early versus late in the day leads to greater improvements in body weight and glycemic control among adults at elevated cardiometabolic risk. Thus, common patterns of skipping breakfast paired with evening eating are expected to be deleterious to health.

Emerging observational studies show that the degree of day-to-day and weekday–weekend variability in eating timing patterns may also predict cardiometabolic risk. Among a community sample of US women, greater interdaily variability in extent of evening eating, including eating jetlag (weekday versus weekend difference), predicts greater weight status and waist circumference as well as higher blood pressure after 1 year.[64] In addition, greater variability in the eating start time was related to higher body mass index and waist circumference and poorer glycemic control. A separate investigation observed higher levels of C-reactive protein, a marker of systemic inflammation, among women with more variable eating patterns.[65] Nonetheless, prior observational studies were hindered by a limited ability to parse out effects due to variations in interdaily eating timing from those due to differences in sleep timing (ie, social jetlag). Moreover, the few studies that have examined regularity in the timing of eating in relation to health outcomes were conducted predominantly in adult women. There is a need for more studies across the life span and among

diverse populations, including older adults and those with cardiometabolic disorders. Furthermore, the circadian underpinnings of the relationship between interdaily variability in eating timing and cardiometabolic outcomes remain to be elucidated.

Nontraditional Work Hours and Risk of Cardiometabolic Disease

Observational studies support the notion that working rotating or night shifts is associated with higher incidence of cardiometabolic diseases versus working only during the day, and risk estimates increase as a function of the length and frequency of occupation as a shift worker.[66–69] These associations may be explained, at least in part, by repeated exposure to circadian misalignment. Occupations requiring irregular or nighttime work hours induce misalignment between behavioral schedules and the solar light–dark cycle, thereby disrupting circadian rhythms.[70,71]

The causal effects of circadian misalignment on cardiometabolic health when working nontraditional hours were confirmed through a controlled inpatient trial that applied a forced desynchrony protocol. The forced desynchrony protocol allows for the uncoupling of endogenous circadian rhythms from external time cues provided through rest and activity patterns, thereby allowing the evaluation of the direct effects of meal timing interventions on metabolic outcomes, independent of endogenous rhythms.[72] Systematically imposing delays to eating and sleeping hours, to the degrees that may be observed in night workers, impaired glucose tolerance and elevated blood pressure.[41] Three nights of simulated shift work, with healthy adults consuming an energy-balanced diet during the night and sleeping during the day, resulted in reduced total daily energy expenditure[73] and elevated glucose, insulin, and glucagon levels.[74] Furthermore, a recent trial using a similar experimental shift work protocol showed that 2 days of simulated night shift significantly impaired glucose metabolism, including by elevating postprandial glucose levels and increased diastolic blood pressure relative to the simulated day shift (control) condition.[75] These results underscore potential mechanisms by which inverted behavioral cycles could contribute to adverse cardiometabolic outcomes.

Studies have also assessed eating patterns among habitual shift workers.[76] Overall, several factors have been identified that may contribute to adverse health outcomes among shift-working populations, with frequent nighttime eating likely 1 of the primary contributors. In 2 separate studies, night work was associated with longer eating windows,[77,78] which are linked with greater energy intakes in both day and night workers.[77] However, there remain significant gaps in our knowledge of how exposure to irregular and inappropriate (not primarily day) work hours shapes eating behaviors in free-living environments. This is underscored by key methodological limitations of existing studies, including the lack of objective measures of food intake and detailed assessment of timing of eating. There is a need to address these gaps and characterize eating patterns of nightshift workers using rigorous approaches. It will be critical to expand upon this research among larger samples, with longer durations of dietary intake assessment. Additionally, detailed assessment of appetite-regulating hormones in day versus night workers would provide mechanistic insights into the effects of shift work on energy balance regulation, since circadian misalignment and sleep perturbations, common among night workers, can impact hormones involved in the control of food intake.[79–81] Determining effective countermeasures to the cardiometabolic consequences of habitual shift work is necessary particularly in long-term night workers, as habitual nightshift workers often have phase-shifted and attenuated rhythms.[70]

Time-Restricted Eating to Improve Cardiometabolic Health and Mitigate Circadian Misalignment

The association of the eating window with cardiometabolic health outcomes indicates that limiting this window and shifting it to earlier in the day may be an effective strategy to improve health. This intervention of curtailing eating to a consistent ≤8- to 10-hour window, termed time-restricted eating (TRE), has been evaluated.

TRE has generated much excitement as a potential treatment for obesity. A seminal experiment in mice reported improvements on cardiometabolic profiles, independent of caloric intake, when feeding intervals were shortened.[82] To date, there have been dozens of clinical trials of TRE, albeit most have small sample sizes largely composed of individuals without obesity comorbidities or use short-term or single-arm interventions. A recent systematic review found that about 80% of studies testing eating windows of ≤8 hours reported reductions in body weight relative to unrestricted eating,[83] and several meta-analyses conclude that TRE reduces body weight.[84–92] Mechanistic evaluations suggest that weight-reducing effects of TRE in humans are at least partially mediated by reduced energy intake, leading to a negative energy balance.[93,94] In addition to reductions in energy intake, another plausible mechanism by which TRE could facilitate improvements in body weight or composition is by increasing energy expenditure or favorable alterations in its components (eg, elevated basal metabolic rate, reduced respiratory quotient). Whether restricting the duration of the eating window in humans impacts

energy balance independently of reducing caloric intake, however, remains to be determined. The timing of the eating window is likely to be an important factor in whether TRE leads to favorable effects on energy expenditure.[51 52]

TRE has also been found to improve glycemic control in adults with type 2 diabetes[95–99] or prediabetes[100,101] and to lower blood pressure.[88,91] Interestingly, studies reporting such positive findings nearly all had eating windows that ended by 6:00 PM. Indeed, early TRE interventions (eg, 7:00 AM to 3:00 PM; 8:00 AM to 6:00 PM) support cardiometabolic health relative to unrestricted eating,[100,102–107] whereas restricting the eating window to late in the day has been shown to have no effect.[108] Overall, other than body weight, data on cardiometabolic outcomes are somewhat mixed. The mixed findings may be related to differences in TRE protocols across studies. This includes heterogeneity across studies in the duration and timing of the eating window as well as the study population and whether the intervention is paired with caloric restriction. Initial positive findings paired with existing questions about mechanisms and best approaches for TRE all point to the need for large-scale and longer-term studies.

TRE may also be effective in improving health among nightshift workers, as curtailing the eating window during the night shift could counter the negative cardiometabolic consequences of eating and activity during the circadian night.[13] Several studies have been designed to evaluate the efficacy of TRE in improving body weight and cardiometabolic risk profile of shift workers. For example, in a 12-week TRE protocol in firefighters working 24-hour work shifts, reducing the eating window by 2.4 hours improved very-low-density lipoprotein particle size and other metabolic parameters, including glycemic control among those with elevated cardiometabolic risk.[109] Another study applying a 6-week TRE intervention (14- versus 10-hour eating window target) among firefighters observed improvements in markers of oxidative stress.[110] These preliminary findings provide initial support for restricting the eating window of shift workers to daytime hours. Further research is warranted to examine the role of diet quality and quantity in these findings.

Physical Activity as a Zeitgeber for Cardiometabolic Health

While the large focus of the workshop was on timing of eating, the expanding chrononutrition field has resulted in increased interest in potential time-of-day effects of the other behavioral determinant of energy balance: physical activity. Similar to the time-giving signals provided by eating to tissues involved in absorption and metabolism of nutrients, the timing of exercise influences molecular clocks in the skeletal muscle and can serve as a zeitgeber[18,111,112] and impact circadian rhythms.[113,114] Yet, despite the established role of exercise on muscle-based molecular clocks,[111] only recently have the metabolic impacts of timing of activity begun to be studied in humans. Indeed, despite well-known positive effects of regular physical activity and less sedentary time on health outcomes,[115] there is a paucity of literature evaluating the influence of timing of physical activity on cardiometabolic risk profiles compared with the growing chrononutrition field.

Results of studies evaluating the role of timing of exercise in metabolic health were recently reviewed.[116,117] Most studies investigating the relationship between the timing of physical activity and health outcomes stem from observational data. Most studies suggest that earlier (ie, morning) activity is associated with lower cardiometabolic risk compared with evening activity.[118–121] However, not all studies agree; 1 recent study found that evening activity was associated with lower risk of death and cardiovascular disease compared with morning activity among adults with obesity from the UK Biobank.[122] For the outcome of body weight, a key determinant of metabolic risk, results of several observational studies suggest that morning activity may be beneficial for weight management, with greater activity earlier versus later in the day being associated with lower weight status[120,121] and greater maintenance of lost weight.[123,124] Furthermore, a secondary analysis of exercise patterns from the Midwest Exercise Trial-2 showed that completing more exercise earlier in the day resulted in greater improvements in body weight and body composition compared with individuals who completed the majority of their exercise in the evening.[125] In addition to these observational data, there have been a few small, randomized trials examining the effect of morning versus evening exercise on cardiometabolic outcomes with mixed results. Studies randomizing participants to earlier versus later exercise timing have reported greater improvements in weight-related outcomes in response to earlier exercise,[126,127] while others report no differences on the basis of exercise timing[128–130] or that later exercise timing is more effective for improving cardiometabolic health.[131–133]

Several factors may contribute to mixed findings from observational studies and clinical trials. The most notable limitations are the small sample sizes of studies, heterogenous study populations, and noncomparable study designs. The trials used different exercise stimuli and timing protocols (eg, different circadian times, pre- versus postprandial), which hinders meaningful comparisons. Addressing these limitations and reconciling these findings could determine the potential chronotherapeutic role of exercise.

Standardized Variable Ascertainment and Terminology in Chrononutrition

Within the nascent field of chrononutrition, the need for a unified framework and consistent terminology is becoming increasingly apparent. Some urgent needs are as follows:

1. *Encouraging eating relative to "biological timing."* Meals are typically eaten according to the time of day on the basis of societal or cultural norms. Optimal eating times are likely defined, however, by biological clocks and an individual's chronotype. The gold-standard approach for determining biological timing of eating is to evaluate the timing of eating relative to dim-light melatonin onset or the dim-light melatonin offset.[134] However, in recognizing that dim-light melatonin onset and dim-light melatonin offset tests are costly and laborious, examining eating time relative to sleep–wake timing (eg, sleep onset time, midpoint of sleep, wake time) may be an effective proxy.
2. *Promoting 24-hour repeated measurements of outcomes*. Beyond the assessment of diurnal patterns of eating, cardiometabolic outcomes should also be measured over the course of the 24-hour day to better characterize the effects of chrononutrition on health, as has been encouraged previously.[42] Most biomarkers of metabolic health and disease risk oscillate over the day[42,135–138] and moreover, postprandial measures of metabolic risk factors are substantially more sensitive to circadian phase, circadian misalignment, and interventions than fasting values.[50,59] If outcomes are assessed only at a single fasted time point, which most studies do, or when levels are biologically low, there is a risk of missing a relationship between dimensions of chrononutrition and outcomes.
3. *A conceptual framework for chrononutrition that delineates and standardizes each component*. There is currently no universally accepted conceptual framework for evaluating chrononutrition. A successful model to guide this effort is the "RU-SATED" framework for sleep, which parses sleep into 6 separate components: regularity, satisfaction, alertness/sleepiness, timing, efficiency, and duration.[139] For chrononutrition, various components could be defined, including the window, timing, and frequency of eating as well as interdaily consistency/variability of eating times, including the distribution of calories and individual nutrients. At present, different approaches have been used to operationalize the same variables. To illustrate this, the "eating window" has been defined as the average of eating windows across multiple days or by using the 95% CI of all daily eating events over a 2- to 3-week period.[140] Developing standardized definitions for each component of chrononutrition will facilitate this effort.

High-Quality Assessment Tools for Chrononutrition

The ideal tools for chrononutrition research have yet to be determined. To facilitate robust chrononutrition studies in real-world settings, there is an urgent need for innovative, cost-effective, scalable, and low-burden tools and assessment methods to ascertain the timing of eating and, more broadly, circadian health.

1. *Self-reported measures of eating temporality*. Growing support for a role of the timing of eating in cardiometabolic health has led to modifications to existing diet assessment measures, and the development of new tools, specifically targeting the quantification of eating timing metrics. One commonly used tool is the Automated Self-Administered 24-Hour Diet Assessment, developed by the National Cancer Institute.[141] Key strengths of the Automated Self-Administered 24-Hour Diet Assessment are its accessibility (eg, records can be accessed by hyperlink, and researchers can use the tool for free, including free access to nutrient assessments), and it captures *when* food is eaten in addition to *what, where*, and *how much* is consumed. An additional strength of the tool is that eating times can now also be quantified in relation to sleep timing, given the recent inclusion of a sleep module. Despite these strengths, it is notable that the tool was not originally designed for chrononutrition and is prone to recall error and reporting biases. An alternative, low-burden alternative is recall-based survey questionnaires on food timing (eg, "At what time do you first start/stop eating?"). These tend to show modest agreements with prospectively collected food timing via food records and may be considered as a simple, crude assessment method for assessment of the timing of eating.[142] The My Circadian Clock phone application was developed for the purpose of capturing diurnal patterns of eating and drinking.[143,144] The application offers a user-friendly interface and low logging burden to track food timing data over longer periods of time but does not assess calorie or nutrient intakes. Ideally, food timing tools should comprehensively capture all aspects

of eating with high reliability and validity; this includes information on the start and end of all eating episodes including meals, snacks, and beverages; day-to-day variability in eating times; and circadian phase (ie, eating episode relative to melatonin rhythms, circadian cycle, or sleep–wake cycles).

2. *Wearable devices for the assessment of the timing of eating and diurnal rhythms*. Data collected from wearable devices may provide robust measures of circadian health. Noninvasive wearable technologies make it possible to passively track and monitor 24-hour human physiology including heart rate, sleep–wake and rest–activity cycles, body temperature, blood pressure, glucose, and other vital signs in real-world settings. Devices such as wrist accelerometers equipped with light sensors, continuous glucose monitors, and out-of-office blood pressure monitors are still being investigated as possible methods to ascertain objective data on the timing of eating and, more generally, circadian rhythms.[145]
3. *Measuring suprachiasmatic nucleus and peripheral clock rhythms*. The central suprachiasmatic nucleus clock rhythm is typically measured via frequent sampling of either (1) cortisol and melatonin in blood or saliva over a 24-hour period in dim-light conditions, or (2) core body temperature under constant routine conditions. Because of the frequent sampling, the controlled environment needed, and cost, it is difficult to measure central clock rhythms in a real-world setting. For free-living studies, there is a need for alternative methods or novel techniques using single time point blood draws to estimate circadian phase.[146–148] Peripheral clock rhythms are also challenging to measure, as serial biopsies and measurements of gene and protein expression from relevant tissues over a 24-hour period are rarely feasible. Frequent sampling of blood- or urine-based biomarkers could provide information related to peripheral clock rhythms and the timing of eating.[74,149] While not yet applied to the field of chrononutrition, it is worth investigating whether recently established biomarkers determined from global metabolomics studies can be used to capture information on peripheral rhythms or eating rhythms.[150]
4. *Integrating multiple sources of data, including those described herein, with genetic variation in clock genes*. Combining multiple sources of behavioral and biological data, including genetic information, could generate a multidimensional "circadian health score." Artificial intelligence can facilitate the development of a multidimensional circadian health score that also incorporates genetics with timing and quality of dietary intake along with sleep and physical activity derived from multiple sources.

For any timing biomarker to be successful, measurements should be precise and scalable. Passively collected data using scalable approaches with minimal participant burden should be prioritized. Complementing eating timing information with sleep and physical activity and endogenous rhythms would provide the most comprehensive understanding of circadian alignment/misalignment. However, it is important to distinguish whether cyclical data reflect endogenous circadian rhythms or 24-hour diurnal behavioral rhythms. The ideal length of the assessment period also remains to be determined to reliably capture habitual food timing, various diurnal rhythms, and their variability. Whereas 7 days of data provide information on all days of the week, 14 days of data are often preferred to measure behavioral rhythms. There is a need for consensus on what is the optimal duration of data collection for free-living assessment of interdaily variability in behavioral rhythms.

Assessing Potential Biological Differences in Chrononutrition Research

Several key effect modifiers, including biological demographic factors, genetic variation, chronotype, and health status may influence findings in chrononutrition and explain heterogeneous results. These factors may be leveraged to advance precision nutrition approaches.

1. *Biological demographic factors*. There are known sex and age differences in circadian rhythms and the responsiveness of the circadian system to light. Therefore, it is also likely that the associations of chrononutrition metrics on cardiometabolic health vary by biological sex and age group, and their consideration in future studies is imperative.
2. *Genetic variation in clock genes*. There is increasing evidence that genetic variation in clock-related genes could modify findings in chrononutrition. For example, in a Spanish randomized crossover study, late eating was associated with impaired glucose tolerance to a larger degree among carriers of the type 2 diabetes gene *MTNR1B* G-allele carriers.[59] Another Spanish study found that eating a late lunch is associated with less weight loss only among carriers of a *PLIN1* variant, a gene coding for a circadian lipid-stabilizing protein.[151] These findings provide evidence that timing interventions may need to be personalized on the basis of genetic background, as they may be relevant

or more impactful in a subgroup of people with specific genetic profiles.

3. *Chronotype*. Recent evidence suggests that associations between eating timing and poor health outcomes may be particularly evident among individuals with late chronotype.[152–154] As a result, individuals with a late or evening chronotype may constitute a high-risk population. Having a late chronotype has been consistently observed to associate with later eating times, breakfast skipping, and poor dietary intake.[152] All of this seems to justify the association between late chronotype, obesity, and metabolic diseases.[138,139] In light of these, it is relevant to evaluate whether food timing interventions promoting earlier intake may be more advantageous for those with late chronotypes.
4. *Health status*. While not strictly biological, findings regarding chrononutrition and cardiometabolic health may also differ based on the health status and comorbidities of the study participants. To date, most studies on chrononutrition have been conducted in adults with overweight or in young, healthy, lean adults. Thus, there is a critical gap in knowledge for many clinical populations including hospitalized patients receiving enteral or parenteral nutrition at night,[155,156] and those living with chronic conditions including cardiovascular disease, diabetes, hypertension, and dyslipidemia.

Social, Behavioral, and Contextual Influences on Chrononutrition

It is well documented that US adults tend to have erratic eating patterns and long eating windows.[140,144,145] However, there is limited understanding of specific social, cultural, and behavioral contexts and other influences that shape chrononutrition practices in free-living settings. Cultural and environmental factors, behavioral and personal preference, and physiological factors may influence the time when people consume foods and beverages.[157] Gaining a more comprehensive understanding of the determinants of eating timing may facilitate the design of appropriate and acceptable interventions. Highlighted below are some specific research directions and unanswered questions within this topic.

1. What are the most important determinants of eating timing? Are there socioeconomic disparities in the ability to choose one's own eating times? At a minimum, these factors should be considered as potential confounders in research on chrononutrition and health outcomes. They also raise important questions about the feasibility of modifying temporal patterns of eating across different populations. There are currently limited data on chrononutrition in minoritized populations underscoring the need for investigation into the interplay between social drivers of health and chrononutrition.
2. Uncovering the multidimensionality of chrononutrition: How does the timing of eating correlate with other circadian-related behaviors and exposures, including light, physical activity, and sleep? For example, in the presence of an overall healthy diet, does the timing of eating have an appreciable effect on cardiometabolic health? Alternatively, do sleep duration and exercise timing influence timing of eating and nutritional choices? Can optimal dietary timing attenuate adverse health effects of short sleep, shift work, or sedentariness? Multimodal studies are needed to investigate these behaviors together to inform future interventions, which will likely need to encompass multiple domains.
3. What are the structural barriers to implementing chrononutrition interventions in clinical and community settings? For example, barriers in hospital operations or scheduling may preclude optimizing the timing of nutritional feeds for hospitalized patients.

CONCLUSIONS

The goals of the National Heart, Lung, and Blood Institute chrononutrition workshop were to examine discoveries linking circadian and nutrition science and identify important future directions for research to expand this knowledge and help to translate it to enhance treatment and prevention of cardiometabolic diseases. Panelists shared lessons learned from lab-based and observational research, identified key gaps in knowledge, and defined short- and long-term opportunities for chrononutrition research, such as balancing mechanistic and clinical research priorities. Critical themes that permeated this discussion were the importance of developing sustainable interventions that are tailored and appropriate for individuals along with the need for building collaborations between basic, clinical, and implementation scientists to bring chrononutrition interventions into real-world settings. Moreover, advancing this research field will require (1) standardization of terminology, metrics, and definitions; (2) tools and assessments for real-world settings; (3) consideration of individual differences that act as effect modifiers; and (4) deeper understanding of social, behavioral, and cultural influences in chrononutrition research. While chrononutrition as a research field is still at its early stages, the data support

enormous potential to improve cardiometabolic health through circadian-based, therapeutic dietary intervention strategies.

ARTICLE INFORMATION

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