Chrono-Nutrition: Understanding the Interplay Between Circadian Rhythms and Personalized Nutrition

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Abstract

Chrono-nutrition, a concept emerging from the integration of chronobiology and nutrition sciences, investigates the timing of food intake in alignment with the body's circadian rhythms. This interplay between dietary patterns and biological rhythms has garnered significant attention in recent years due to its potential implications for health and disease. In this comprehensive review, we explore the key findings from studies in the last decade on chrono-nutrition, focusing on its role in cardiovascular health, diabetes management, glucose metabolism, and the influence of sex, socioeconomic factors, and cultural diversity. The intricate dance between the molecular circadian clock and the gut microbiome is a fascinating area of study in modern biology. Both systems are integral to the regulation of metabolic processes, responding to

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dietary inputs and environmental cues to optimize the host's adaptability and survival. This review delves into the dynamic interplay between circadian rhythms and the gut microbiome, exploring their mutual influence and the implications for human health.

Keywords: Chronobiology, nutrition, microbiome, circadian rhythm.

1 Background

The link between disrupted circadian rhythms and cardiovascular diseases is well-established, with late chronotypes exhibiting a higher susceptibility to adverse cardiovascular events [1–3]. Studies suggest that aligning eating patterns with circadian rhythms, known as chrono-nutrition, may help manage weight, hypertension, dyslipidemia, and diabetes, thereby reducing the risk of cardiovascular diseases [4, 5]. Synchronizing circadian rhythms with daily habits such as eating and sleeping is critical for cardiovascular health, as both protective and adverse effects can result from these alignments [6, 7]. Conversely, circadian rhythm dysfunction has become prevalent in our modern society and can adversely affect human health. This disruption of the natural sleep-wake cycle, commonly caused by factors such as shift work, stress, jetlag, and sleep disruption, also referred to as chronodisruptors, has been linked to an increased risk of metabolic diseases [8–10]. The effective functioning and coordination of our bodies' physiological processes is highly dependent on the synchronization of peripheral clocks, and our bodies clock mechanisms to external and internal cues and is significantly influenced by our diet [5].

There is a direct relationship between the gut microbiome and the circadian rhythm. Research by Rana et al. (2020), Frazier et al. (2020), and Gutierrez Lopez et al. (2021) indicates that disruptions in these rhythms, often exacerbated by an unbalanced gut microbiome, can lead to metabolic dysregulation, a significant risk factor for cardiovascular diseases. Energy consumption at inappropriate circadian times has been linked to adverse health outcomes during the disruption of circadian rhythms and insufficient sleep caused by shiftwork [11]. In particular, energy intake later in the day by individuals showed higher body composition and risk of cardiometabolic disease. The significance of circadian rhythms and individual behavioral traits on cardiometabolic health and cardiovascular disease risks is highlighted by Almoosawi et al. (2019), who notes that late chronotypes, those who sleep stay up late and wake up later in the morning – individuals with disrupted circadian rhythms – are associated with higher cardiovascular risks, such as elevated cholesterol and blood pressure [12].

Circadian rhythms play a crucial role in diabetes management, particularly through the timing and composition of meals. Consuming meals earlier in the day has been demonstrated to significantly enhance glycemic control, contrasting with poorer outcomes associated with eating later. This is largely attributed to the way natural circadian rhythms regulate metabolism. Aligning mealtimes with individual circadian rhythms could therefore improve overall diabetes outcomes and blood glucose management.

Further research underscores the complex interplay between circadian rhythms, sleep quality, and gut microbiota in influencing metabolic health. Disruptions in these systems, whether through poor sleep habits or misaligned eating times, can impair glucose tolerance and escalate the risk of developing diabetes. In managing conditions like fibromyalgia (FM) and chronic fatigue syndrome (CFS), a multidisciplinary approach that includes nutrition and chronobiology has been shown to improve lifestyle and quality of life.

The gut microbiota is highly responsive to the host's dietary habits and the timing of food intake. This responsiveness leads to diurnal variations in microbial composition and function, impacting the synchronization of circadian rhythms within the host. Microbial metabolites, particularly short-chain fatty acids (SCFAs) and bile acids (BAs), serve as key mediators of communication between the gut microbiome and host circadian clocks.

The relationship between an individual's chronotype (whether they tend to be a morning person or a night owl) and dietary choices is well-documented. In addition to consuming fewer fruits and vegetables and following a less healthy diet, late chronotype individuals also differ significantly in their meal timing. The time of day when individuals eat has been shown to be a crucial factor influencing the diurnal rhythms of the microbiota. This suggests that not only the composition of the diet but also the timing of meals contributes to shaping the microbiota profile.

Emerging evidence suggests that circadian rhythms play a crucial role in PD pathogenesis, influencing neuroinflammation and oxidative stress mechanisms implicated in disease progression [13].

Dysbiosis of the gut microbiota, characterized by changes in the abundance of specific bacterial species, has been associated with alterations in mood and behavior. Understanding the microbial mechanisms underlying these disorders holds promise for developing novel therapeutic interventions.

Variances in chrono-nutritional responses between genders suggest the importance of considering sex-specific recommendations. Tailored nutritional strategies based on sex may enhance the effectiveness of interventions, emphasizing the need for personalized approaches in chrono-nutrition research and practice.

Additionally, cultural and ethnic diversity impact dietary preferences and meal timings, necessitating culturally sensitive chrono-nutritional guidelines that are adaptable to diverse dietary practices.

2 Main Text

Cardiovascular Disease (CVD)/Cardiometabolic Health

The disruption of the natural sleep-wake cycle, commonly caused by factors such as shift work, stress, jetlag, and sleep disruption, also referred to as chronodisruptors, has been linked to an increased risk of metabolic diseases [8–10].

CVD: Diet and Circadian Clocks

Divergences from regular eating patterns can result in a desynchronization between environmental cues and the central pacemaker in the suprachiasmatic nucleus [SCN] leading to adverse health outcomes [6]. Under circadian misalignment, the central and peripheral signals are compromised as a result of the discrepancy between light/dark and feeding/fasting cycles. This disruption promotes the development of risk-associated metabolic patterns and chronic diseases such as obesity [1, 8, 6]. Research on chronotypes suggests that individuals with an evening chronotype tend to have irregular eating patterns. Studies have shown an association between higher energy intake in the evening and irregular eating habits, including skipping meals, especially breakfast was related to mood disorders [14]. Furthermore, individuals with later chronotypes tend to consume less fruits and vegetables [15], and have an increased intake of energy drinks and fat, indicating consequences on cardiometabolic health in the long-term [8].

Human studies indicate that eating earlier in the day in comparison to late food intake is connected with improved loss of weight in obese and overweight patients, with one study in particular showing that obese women who ate regular meals for 2 weeks aligned with their circadian rhythm had favorable effects on cardiometabolic risk factors [1]. Frequency of meals, another aspect of chrono-nutrition, is also important since higher risks associated with being obese or overweight was shown from eating more that 5 meals a day compared to less than 3 meals a day [1].

Night shift work is deemed a crucial negative component associated with circadian disruptions that lead to metabolic abnormalities. A meta-analysis of 28 studies demonstrated that shift work had a negative impact on obesity and weight gain, with an odd ratio [OR] of 1.23 [95% confidence interval: 1.17 – 1.29], which suggests that shift workers have a 23% higher odds of obesity compared to non-shift workers, and another study examined the effects of shift work and jet lag by exposing subjects to a light-dark cycle extended to 28 hours, in which the rhythm of melatonin and body temperature free runs with a 24-hour period [8]. The results displayed an increase in postprandial glucose, insulin, and mean arterial pressure. In addition, there were decreases in sleep efficiency and leptin, as well as an entire reversal of the cortisol cycle over the behavioral cycle [8].

Studies show that sustained short sleep durations and/or poor quality of sleep alongside circadian misalignment are associated with metabolic dysfunctions, including obesity, T2DM, and hypertension [6]. They also revealed reduced levels of leptin, increased appetite, and insulin resistance [8].

The Gut Microbiome and Circadian Rhythm in CVD

Recent studies have shown that due to the bidirectional communication between the gut microbiome and the host, disrupted circadian rhythms caused by eating late at night or at irregular intervals influences the gut microbiome, increasing the predisposition of the host to inflammation and metabolic dysfunction [5, 16–18]. In order to understand this concept further, it helps to explore the significance of the microbiota community and its rhythmic patterns within the gut microbiome. The rhythms of bacteria typically span over 24 hours with bacteria varying during light and dark period and governed by melatonin and temperature. In healthy individuals, the principal bacterial phyla include Bacteroidetes and Firmicutes. During sleeping/fasting phases, there is an increase in certain types of bacteria such as Bacteroidetes, Verrucomicrobia, as well as Enterobacteriaceae, which can be opportunistic pathogens. On the contrary, Firmicutes, which is a type of bacteria influenced by diet, is highest during the waking/eating phase. Various studies show that circadian disruptions in eating patterns, diet and sleep affect the day/night cycle of the gut microbiota structure and activity, leading to increased risk of metabolic syndrome [8].

Strategies based on circadian rhythms, such as chronotheraphy and intake of food during daylight hours only, have been suggested as a way to restore the microbiome communities that reside within the gastrointestinal tract, and therefore foster homeostasis and metabolic health [19, 20]. In addition, probiotic and prebiotic supplements alongside a plant-based diet may favorably modify the circadian rhythms and microbiota community in high-risk populations such as shift workers [8].

Chrono-nutrition, which aligns eating patterns with the body's natural rhythms throughout the day, could stabilize these rhythms and potentially improve cardiometabolic health outcomes. Research by Flanagan et al. (2021) explores how personalized nutrition and timed food intake that align with circadian rhythms can substantially benefit metabolic and cardiovascular health, emphasizing the need for personalized nutritional interventions to counteract the negative impacts of modern lifestyle-induced chronodisruption. Research showed that timing of food significantly influences the body's molecular clocks in organs outside of the SNC [suprachiasmatic nucleus], with meal times acting as a signal [zeitgeber] for setting these clocks in other parts of the body [21]. This coordinates the activities of peripheral tissues with the eating schedule. Additional animal studies have shown that the clock gene rhythms in peripheral tissues of mice fed only during the day, quickly adjust to this new feeding schedule, while the SCN clock gene rhythms continue to follow the natural light/dark cycle [21].

Sleep Behavior and Cardiometabolic Health

Research suggests that mild circadian misalignment (minor shifts between the sleep-awake cycle in non-shift workers) can also harm health [12]. The German MONICA/KORA Myocardial Infarction Registry have shown that specific high-risk population subgroups, particularly men, experience an increased risk of acute myocardial infarction during changes to and from daylight saving time. Short sleep duration in adults, especially those with a late chronotype, is associated with engaging in behaviors linked to cardiovascular risk, such as smoking and unhealthy dietary habits [2].

Blood pressure displays a diurnal circadian rhythm, increasing sharply in the morning, peaking during the waking/active period, and decreasing during the night/inactive period [20]. Disruption of this circadian rhythm, resulting in non-dipping blood pressure during the night, has been associated with hypertension, cardiovascular disease, and chronic kidney disease. A meta-analysis showed that individuals from population-based samples with a non-dipping BP pattern (where blood pressure does not drop significantly during sleep) experienced an adjusted hazard ratio of 1.29 (95% confidence interval) or a 29% higher adjusted risk for cardiovascular disease (CVD) events, elucidating the link between abnormal blood pressure pattern and increased risk of CVD events [20].

Results from a large cross-sectional study involving a representative sample of the Finnish population between 25 and 74 years of age, revealed that individuals with an evening chronotype had a "1.3-fold greater odds of arterial hypertension, a faster resting heart rate, and a lower systolic blood pressure, serum total cholesterol, and LDL cholesterol" compared to morning types [2]. This is significant since hypertension is a distinguishing characteristic type 2 diabetes mellitus (T2DM) and is a prominent cause of cardiovascular (CVD) and chronic kidney diseases (CKD) [12]. Circadian rhythms have garnered attention as a possible therapeutic target for preventing and managing hypertension [20]. Considering the impact of food intake as an establish zeitgeber, chrono-nutrition is developing as a prospective lifestyle intervention for the prevention of chronic disease [12].

These findings together suggest that chronotypes may modify physiological processes connected to cardiovascular health, involving blood pressure, blood lipid concentrations and heart rate. However, understanding these associations on a molecular level necessitates further exploration, as well as the impact of diet and lifestyle factors in mitigating long-term health consequences.

Shift workers and Jet Lag on Cardiometabolic Health

With regards to disrupted eating patterns in humans, shift workers were shown to be more prone to cardiovascular diseases than day workers [11, 12, 22]. In particular, energy intake later in the day by individuals showed higher body composition and risk of cardiomatabolic disease. Consistent with other human studies, Dashti et al. (2021) found an association with that late food timing and several metabolic disturbances, including hyperglycemia, dyslipidemia, insulin sensitivity, and metabolic syndrome. They also found a link between eating late and elevated triglyceride levels regardless of body mass index (BMI) [13]. Additionally, there was no significant difference in total energy intake and various dietary components, except for dairy products and soft drinks, thus reinforcing the notion of food timing as an independent risk factor and a unique consideration for cardiometabolic health [23].

Bermingham et al. (2023) found significant social jet lag correlates with poor dietary choices and increased inflammation, exacerbating cardiometabolic risks. Social jet lag reflects the difference in waking and sleeping hours on work days and free days, such as weekends, and is measured as the difference of mid-sleep time of 1 hour or more between work and free days, reflecting the degree of circadian misalignment [15, 22]. Arab et al. (2023) describe social jet lag as the misalignment between social and biological time, which can be characterized as a type of circadian misalignment emerging from variances between sleep/activity schedules on workdays and free days. For adults, social jet lag is usually affected by work schedules, lifestyle, and social activities. Data shows that 50% of workers experience more than 2 hours of social jet lag, and 70% experience minimum 1 hour of jet lag [24].

Changes in cardiovascular risk factors, both indirectly and directly through diet, may be due to circadian misalignment, and as a consequence - disruption of sleep. A systematic review looking at the link between social jet lag and diet found that individuals with more social jet lag reported to eat more processed food, sugary beverages, alcohol and less fruits and vegetables [15, 24], and lower intake of fiber [22]. Since dietary choices contribute significantly to cardiometabolic health, there is evidence suggesting that changes in the diet may play a role in mediating the relationship between metabolic disruption and circadian misalignment [24].

Yan et al. (2021) suggest that aligning eating patterns with circadian rhythms through time-restricted eating and incorporating phytochemicals can significantly enhance gut microbiota health, further supporting cardiovascular and metabolic health. These studies advocate for the integration of chrono-nutritional strategies into lifestyle modifications to mitigate the onset and progression of cardiometabolic diseases.

Meal Composition and Timing on Cardiometabolic Health

The composition of meals is also involved in cardiometabolic damages, shown by studies using animal models showed that high-fat diets alter the cycling and expression of circadian clock genes and clock-controlled genes involved in metabolism [10]. In one study, which included a total of 27,911 from 2003 to 2016 showed that an excess of low quality carbohydrates and animal protein at dinner was considerably associated with a greater cardiovascular disease risk [10]. Further studies have exhibited that fat-rich meals until 13:30 and carbohydrate-rich meals between 16:30 and 22:00 induces worse metabolic conditions in people with weakened glucose metabolism [10].

Time Restricted Feeding and Metabolic Parameters

Over the past decades, numerous researchers have studied the effects of time-restricted feeding [TRF], also known as time-restricted energy [TRE] in human studies, as therapeutic intervention to re-synchronize and thus, prevent cardiometabolic damage, metabolic dysfunction [25] and improve immune functions [26]. For this daily nutritional strategy, food consumption was restricted to specific hours, with daily fasting periods exceeding 12 hours and without changing the quantity or quality of nutrients [10], or the daily eating period decreased from a 12 to 14 hour "eating window" to less than 10 hours a day [27]. Overall, TRF is a form of intermittent fast which involves limiting the feeding period on a daily basis, however, the understanding of restriction is still inexact in human studies, varying from 8 to 12 hours, depending on research sources [28].

When eating and sleeping schedules shifted by approximately 12 hours from their regular active and inactive phases, there were considerable increases in blood sugar and insulin levels after meals, a reversal of cortisol rhythms daily and raised average arterial pressure [27]. Another study involving overweight men at risk for type 2 diabetes investigating the effects of early TRF [8am to 5pm] and delayed TRF [12pm to 9pm] found that both improved fasting triacylglycerols and glucose tolerance, regardless of time TRF started, with a further study demonstrating TRF improving nocturnal and blood sugar control post meals compared to extended feeding time of 15 hours a day [27].

A meta-analysis showed how TRE has a positive effect on improving metabolic parameters such as blood pressure, fasting glucose concentration, and cholesterol profiles [28]. Clinical trials support cardiometabolic improvement from TRE in men with prediabetes, even if TRE did not change their weight. Evidence from an iso-caloric trial on TRE of a feeding/fasting period of 8/16 exhibited better glucose tolerance and a significant reduction in systolic blood pressure, which could be compared to results collected with an ACE inhibitor as pharmacological treatment [28]. In a randomized crossover trial involving eight individuals with prediabetes, demonstrated that isocaloric TRF earlier in the day, specifically a 6 hour feeding period before 15:00 and with dinner, lowered insulin resistance compared with a 12 hour period of eating [29]. Together, data collected from these human studies exhibit the effect that TRE has on the cardiometabolic state of both obese and healthy patients [10, 25].

TRF also provides many health benefits including protecting against metabolic disease and reducing risk of age-related disease in animal models and humans [22, 24]. However, it is not clear whether TRF can delay aging and what molecular mechanisms underlie the TRF-related health benefits. Autophagy protects cells against metabolic stress and prevents genome instability, cell death and senescence. Through its ability to regulate epigenetic and metabolic programs, autophagy can also influence cell fate and regulate stem cell quiescence, activation, differentiation, and self-renewal. Dysfunctional autophagy has been linked to cancer, infectious diseases, neurodegeneration, muscle and heart diseases, as well as aging [30]. An analysis on gene expression demonstrated that TRE boosts the expression of four genes that are involved in longevity and autophagy, and was also the first study to demonstrate that TRE enhances the secretion of BDNF, which is a crucial protective factor against neurodegenerative disorders [28, 31].

Diabetes Management and Chrono-Nutrition

Chrono-nutrition interventions have been shown to improve glucose metabolism, offering potential benefits for blood sugar regulation [9]. Aligning meal timings with the body's circadian rhythm demonstrates efficacy in regulating blood sugar levels, highlighting the importance of chrono-nutrition in metabolic health [9, 32]. Research by Matenchuk et al. (2020) and Hawley et al. (2020) highlights how structured meal timing can harness the benefits of chrono-nutrition to enhance glycemic control and reduce diabetes risk. Studies conducted in laboratories have shown that individuals who are given meals during the circadian night, when melatonin levels are higher, experience a decreased energetic response and impaired glucose tolerance compared to consuming meals during the day [11].

Contingent on the macronutrient content of the diet, following relative amounts of fats, carbohydrates and protein in meals, circadian cycles are modified following complex metabolic pathways. Employing high-throughput metabolomics, analytical techniques used to measure metabolites in biological samples, researchers found that more than 50% of metabolites measured in mouse tissues and organs, showed rhythmic oscillatory patterns over time. This suggests that the clock governs metabolic pathways that will be somewhat adapted to handles numerous nutritional impacts, depending on the time of day. For this reason, the phase of clocks in peripheral tissues is influenced by the timing of food intake [27].

Various studies in both humans and rodents have shown the involvement of the circadian system in regulating energy balance and glucose metabolism in mitigating diabetes [28, 32, 33]. In humans, studies have reported a decrease in the expression of clock genes in the pancreatic islets of diabetic patients, which regulate insulin secretion and glucose homeostasis [5]. This impact on the mRNA expression of specific clock genes like per2, per3, and cry2 correlate with the insulin content of pancreatic tissue, suggesting their role in regulating insulin production [5]. Additionally, in vitro cultures of islets placed in high glucose concentrations showed a decrease in per3 mRNA expression, which collectively, these findings highlight the interplay between the molecular circadian system and endocrine functions in glucose metabolism regulation, and any disruption in these conditions can potentially lead to the development of pathological conditions, including type 2 diabetes (T2D) [5].

Feeding/fasting cycles set off nutrient-sensing pathways that act at both transcriptional and post-transcriptional levels in order to maintain cellular nutrient homeostasis, ensuring availability of essential nutrients and cellular processes. The circadian clock activates nutrient-sensing pathways at regular and anticipated feeding times, maintaining nutrient homeostasis. Conversely, when feeding happens at irregular times, the same nutrient-responsive pathways offer feedback to the circadian clocks to anticipate a new feeding time on following days referred to as "phase shift." This disruption in circadian rhythm affects blood sugar control through disrupting beta cell function and insulin sensitivity, elevating the risk of developing type 2 diabetes [27].

Multiple studies have demonstrated the existence of circadian oscillations in various physiological and structural mechanisms of the gastrointestinal tract. Circadian patterns in basal gastric acid secretion in humans was observed, with lower levels in the morning that increased gradually during the day and declined at dawn. Intestinal motility also exhibited circadian patterns, with gastric emptying time of solid foods being faster in the afternoon [5].

Chronodisruption, particularly from irregular meal timings, exacerbates glycemic imbalances in type 2 diabetes through modifications in the gut microbiota.

Glucose Metabolism and Chrono-Nutrition

Research underscores the important interaction between circadian rhythms and glucose metabolism, highlighting potential strategies for improving metabolic health through chrono-nutrition. Studies such as Aoyama and Shibata (2020) and Henry, Kaur, and Quek (2020) have demonstrated that the timing and composition of meals can profoundly affect postprandial glucose levels, suggesting that aligning meal times with the body's natural circadian rhythms could improve glucose regulation and potentially lower the risk of diabetes [9, 32]. Furthermore, the synchronization of eating patterns with metabolic peaks, as discussed by Poggiogalle et al. (2018), emphasizes the importance of earlier meal times to optimize metabolic responses and prevent circadian misalignment's adverse effects on metabolism [34].

Several studies have explored the effect of meal timing on postprandial glycemic outcomes and metabolic health. Aoyama and Shibata (2020) noted significantly higher blood triglyceride levels after meals at night compared to daytime, highlighting metabolic responses being time dependent. In the same way, Poggiogalle et al. (2018) and Henry, Kaur, and Quek. (2020) highlight the benefits of early TRF and eating larger proportion of calories earlier in the day in improving insulin sensitivity and enhancing glucose metabolism, Collectively, these findings recommend that timing meals to occur earlier in the day, especially focusing on macronutrient composition, can help improve overall metabolic health and postprandial glycemic results.

Participants who ate a breakfast high in carbohydrates had a higher RER [Respiratory Exchange Ratio], increased fasting insulin and glucose, as well as reduced insulin sensitivity, suggesting that a waking meal that is high in carbohydrates may diminish metabolic flexibility [16]. Further studies have exhibited that fat-rich meals until 13:30 and carbohydrate-rich meals between 16:30 and 22:00 induces worse metabolic conditions in people with weakened glucose metabolism [10]. Calorie intake distribution where high morning energy was considered, has shown to lower BMI over time compared to a high ratio of evening-to-morning ratio and energy intake after 20:00 hours. Specifically, consuming more than 33% of total daily energy between 17:00 and 00:00. Various analyses have demonstrated that consuming calories closer to "dim light melatonin onset" [DLMO] impairs glucose homeostasis [21].

Research indicates that food intake at different times of the day impacts glucose metabolism in humans. Previous studies have shown circadian variations of decreased glucose tolerance and insulin sensitivity in healthy participants in the evening compared to the morning. One study looked at the effects of a late evening meal on blood glucose variations throughout the day using continuous glucose monitoring (CGMS), finding that meals late in the evening may result in postprandial hyperglycemia following this decline in glucose tolerance from morning to night [9]. A cohort study established the relationships between eating dinner late at night and glycemic control in type 2 diabetics, showing that late dinner meals after 20:00 correlated independently with a rise in HbA1c [glycated hemoglobin – marker used to measure average blood glucose levels – over previous 2 to 3 months] [9].

These studies revealed that circadian rhythm disruption can exacerbate the natural decrease in glucose tolerance that happens during the night. For example, research found that type 2 diabetic individuals who consumed three identical meals experienced increased spikes in blood sugar levels in the morning than in the evening. Furthermore, there was an improvement in glucose tolerance following the first and third meals of the day, regardless of glycemic control. There was also a shift in circadian variation of insulin sensitivity in individuals with type 2 diabetes. Unlike healthy individuals, type 2 diabetics demonstrated a distinct daily circadian pattern with greater insulin sensitivity towards the night, and higher blood sugar levels in the morning compared to the evening. This modified circadian pattern highlights differences in how blood glucose and insulin levels are regulated throughout the day compared to healthy individuals [9].

Unlike other diets, practicing time-restricted eating (TRE) offers metabolic benefits irrespective of weight or fat reduction [12]. Evidence from research studies supports this assertion. For instance, in one study, participants who practiced early TRE for two weeks showed enhanced glucose tolerance and reduced triglyceride levels [28]. These findings also suggest that TRE has an independent, intrinsic effect on metabolic health, distinct from its potential impact on weight loss or fat mass, which has been explained by its action on circadian rhythm [28].

The link between TRE on blood pressure [BP] and heart rate was observed in clinical trials where TRE seems to be more effective at lowering BP in patients with hypertension or already elevated blood pressure at baseline compared to healthy individuals, or a lowering of blood pressure from TRE in shift-working, pre-diabetic and obese populations, independent of weight loss, especially when the window of meal timing is earlier and aligned with the natural circadian rhythm [12]. As an important principle in chrono-nutrition, limiting consumption of food appears to realign the intake of food with the circadian clock, and this meal timing has an effect on metabolism [2]. However, the precise action of TRE on circadian systems is still not clear in humans, and further studies are needed to comprehend the mechanisms that are involved [12, 28]

Additional research by Yang et al. (2020), Peng et al. (2022), and Stenvers et al. (2019) connects the regulation of key metabolic pathways, including insulin sensitivity and glucose metabolism, directly to circadian rhythms. These studies highlight how disruptions in circadian rhythms, whether through lifestyle factors like shift work or through physiological processes such as the dawn phenomenon, can lead to metabolic dysregulations such as insulin resistance and exacerbated diabetic conditions [29, 35, 36]. Mason et al. (2020) further explore how circadian disruption directly impacts glucose metabolism, presenting a significant risk for the development of type 2 diabetes, thereby underlining the critical need for maintaining consistent circadian rhythms to manage or mitigate diabetes [33].

The effective functioning and coordination of our bodies' physiological processes is highly dependent on the synchronization of peripheral clocks. Several variables exhibit circadian rhythmicity in response to light-dark cues, resulting in specific functional changes. For instance, (i) glucose tolerance is at its peak during daylight hours and lower at night, (ii) melatonin levels decrease at 7:00 and increase at 20:00, (iii) cortisol levels increase at 8:00, (iv) sleep is deepest around 1:00, and (v) body temperature increases at 3:00 [8]. Studies uphold the hypothesis that when the timing of eating is asynchronous with the body's internal clock entrained by light and that regulate processes like metabolism and digestion, it can have negative effects on host metabolism, which in turn may disrupt how nutrients are absorbed and used up in the body, thus affecting the composition of the gut microbiome throughout the day [16].

An example involving nightshift work found that the disruption in circadian rhythm raised the risk of diabetes and obesity, which maintained a ripple effect of irregular eating patterns and distribution of dietary intake over the course of the day, as well as adjusted frequency of meals [1]. When circadian rhythms of sleep and wakefulness are disrupted, this affects energy homeostasis. A short period of a few weeks of the circadian rhythm being misaligned, as a result of sleeping and eating more than 12 hours, resulted in changes in leptin concentrations, higher insulin and glucose concentrations, as well as an energy imbalance [1].

Glycemic Index [GI] is used to define the blood sugar raising potential of carbohydrate foods. A randomized crossover study compared the glycemic effects of changing the GI and glycemic load [GL] and timeline of meal consumptions in healthy individuals, and found that those who consumed higher GL meals in the evening compared to the same meal in the morning, had an increased glucose and insulin response [9]. In the second observation of the same study, a high GI meal provided in the evening created a more noticeable effect on insulin and glucose [9]. These findings suggest that low GI foods, when consumed in the morning compared to at night, were more effective in controlling blood glucose levels. This may be due to variations in insulin sensitivity, shown to decrease during the day, as well as hormones such as cortisol and glucagon, which are influenced by circadian rhythms and influence glycemic response and secretion of insulin [9].

With regard to meal composition, epidemiological studies have demonstrated that consuming carbohydrate-rich meals at the beginning of the day has a protective advantage against diabetes. Some studies have shown that carbohydrate consumption at night affected glucose levels and led to a higher postprandial glucose profile the next morning [9]. The effect of manipulating carbohydrates and fat in day and night-time meals can influence postprandial glycemic response. A randomized crossover trial involving health male participants showed that consuming a diet high in carbohydrates led to a rapid increase in plasma glucose compared to a high fat diet [9]. The effect of a meal high in protein demonstrated a substantial change of blood sugar response at night, with a much lower incremental area under the curve (iAUC) showing no variations in insulin responses in the morning, underlying that increasing amount of protein in a meal can effectively lower postprandial glucose levels at night, mitigating the risk of developing hyperglycemia [9]. These findings underscore the importance of dietary strategies for effective diabetes management.

Sleep & Glucose Metabolism

Studies by Mason et al. (2020), Carasso et al. (2021), and Moreno-Cortés et al. (2024) emphasize how circadian misalignment – common in shift workers or individuals with irregular sleep patterns – adversely affects glucose metabolism, gut microbiota, and overall metabolic health.

Mason et al. (2020) describes an experimental approach that simulates a rapid 12-hour shift in behavioral and environmental cycles, similar to what shift workers experience. This study was used to examine the circadian system and environmental and behavioral factors on glucose tolerance in the morning versus the evening. In a randomized crossover study, participants were given identical mixed meals in the circadian morning or evening when the environmental or behavioral cycle was aligned or misaligned with their central circadian clock. The findings demonstrated that the circadian system had a greater impact on the difference in glucose tolerance between evening and morning compared to environmental and behavioral factors combined, specifically that the circadian phase, independent of behavioral cycle effects, was associated with 17% higher blood glucose levels after meals in the circadian evening compared to the morning [33]. In the circadian evening, the early insulin response after meals was 27% lower compared to the morning, and therefore shows that the circadian influence on glucose tolerance is, at least partially, due to a more robust pancreatic beta-cell reaction in the circadian morning [33]. In summary, the data indicates the substantial impact and control of the circadian system on glucose metabolism in healthy individuals, specifically through its influence on pancreatic beta cell function.

These studies suggest that maintaining regular sleep patterns and synchronized eating schedules could be key strategies in diabetes care [5, 33, 37] and collectively highlight critical areas for intervention and the potential benefits of integrating chrono-nutritional approaches into diabetes management.

Chronobiology and Nutrition: Fibromyalgia (FM)

Clinical improvements in FM were seen after following diets rich in antioxidants, such as plant-based diets, a low FODMAP diet, a low-calorie diet, and a gluten-free diet. A study involving a three-month nutritional intervention based on an anti-inflammatory diet, which included no sugar, gluten, dairy and processed food, with a low FODMAP diet found that "functionality, pain, sleep quality... and quality of life improved after the intervention" [38]. On the other hand, a lacto-ovo vegetarian nutritional intervention with core stabilization exercises enhanced muscle mass and decreased pain and body fat in women with FM. A Mediterranean diet filled with walnuts had positive effects on anxiety, fatigue, depression and eating disorders in individuals with FM [38].

Even though no definite diet therapy has been determined for FM, a diet high in antioxidants, fiber such as fruits and vegetables, reduced processed foods, higher quality proteins, healthy fats, and nutritional supplementation when needed, are advantageous in relieving FM symptoms, whereas there is limited data on specific diets ith regards to CFS. At the same time, micronutrient deficiencies, particularly low levels of iron (low levels of ferritin), vitamin B12, and vitamin D, may contribute to the etiology of FM, especially since iron plays a significant role in metabolism and production of serotonin and dopamine, amongst other functions such as thyroid hormone production [38].

In addition, FM patients also showed to have lower levels of vitamin A, E, selenium, folate, zinc, calcium and magnesium. Since FM has been linked to raised levels of oxidative stress and reduced antioxidant capacity, an increase in antioxidant minerals and vitamins may help to decrease oxidative stress and ameliorate the sensation of pain [38]. Therefore, for FM patients, dietary guidance is essential to help correct inadequate intake of vital nutrients, since by attaining optimal nutritional levels, pain levels are typically reduced [39],

In FM, as it relates to chronobiology, poor quality of sleep is a fundamental symptom and has a strong correlation with severity of pain, depression, tiredness, symptoms of stress and lower quality of life. Furthermore, disruptions in circadian variances of cytokines, melatonin, and serotonin levels, all regulated by the circadian rhythms, were observed in FM, where patients exhibited lower secretion of melatonin at nighttime than healthy individuals, possibly linked to worse sleep at night, daytime tiredness, and a difference in pain perception [38]. In general, the authors recommend fasting at night, reducing the eating window of daytime intake, as well as consuming two to three meals earlier in the day, including breakfast, all contributing to the synchronization of circadian rhythms, which are vital for health.

This approach integrates dietary practices that are in harmony with the body's natural circadian rhythms, enhancing both metabolic and psychological health outcomes. These findings highlight the importance of chronobiology in clinical practice, where synchronizing dietary intake with circadian clocks can optimize physiological processes and potentially reduce symptoms in FM patients.

Interplay Between Circadian Rhythms and the Gut Microbiome

Dietary Influence on Circadian Rhythms and Microbiome

The timing and composition of meals exert profound effects on the gut microbiota, shaping its metabolic output and influencing host health outcomes. Understanding these dietary influences is crucial for unraveling the complex relationship between circadian rhythms and the gut microbiome. Research by Yan et al. (2021) emphasizes the strong interplay between the gut microbiota's diurnal rhythms and the host's circadian rhythms, influenced significantly by dietary patterns and time-restricted eating. This synchrony is crucial for maintaining or enhancing the host's metabolic and immune system functions.

Research indicates that the timing of meals plays an important role in synchronizing host metabolic responses and circadian rhythms, which directly affect gut microbiota composition and function [37, 40, 41]. Time-restricted eating [TRE], by aligning eating patterns with circadian rhythms, enhances metabolic health and lowers the risk of diseases like diabetes [9]. Furthermore, systematic reviews emphasize the significant health impacts of dietary timing and composition across various populations, linking dietary habits with variations in health metrics influenced by the microbiome and circadian rhythms [24, 28].

The interplay between the gut microbiome and circadian rhythms orchestrates the body's metabolic response to diet, emphasizing the critical role of microbiota-derived metabolites in supporting host metabolism and influencing disease progression [16, 42]. Specifically, in humans, alterations in both the gut microbiome (GM) and circadian rhythms have been linked to various gastrointestinal diseases. One study found that changes in the abundance of specific taxa in the GM over time could predict type 2 diabetes in adults. The time of defecation was identified as a significant factor influencing differences in microbiota structure between individuals. The study used time-stamped stool samples from a large group of people to predict host health status based on disrupted microbial rhythmicity. A machine learning model was trained to identify rhythmic bacterial OTUs associated with type 2 diabetes. This model effectively predicted type 2 diabetes but not obesity, showing different time-dependent and microbial signatures for these conditions. Considering the strong links between GM composition and etiology of disease indicate that the GM could be a diagnostic tool for tracking disease progression in humans [16].

The gut microbiota exhibits its own diurnal rhythmicity, largely driven by the timing and composition of meals. This rhythmicity influences the host's circadian rhythms, forming a symbiotic relationship between microbe and host [40]. Disruptions to this relationship can lead to circadian misalignment, contributing to metabolic disorders and other health complications. Modulating the gut microbiota represents a promising avenue for chronotherapeutic interventions aimed at restoring circadian balance and improving host health outcomes. Future research efforts should focus on elucidating the mechanisms underlying this symbiotic relationship and identifying novel therapeutic targets.

Recent research has shown the profound impact of diet on the gut microbiome and its subsequent effect on the host's circadian rhythms. Timing and quality strongly influence the composition of the gut microbiome and its fluctuations throughout the day. The timing of food intake can influence the levels of certain bacteria in the gut, which in turn, has an effect on how we process food and store energy. For example, studies found that Lactobacillus species, previously linked to metabolic disorders and obesity, showed cyclical patterns in normal-fed [NA] and time-restricted fed [FT] mice, whereas this cyclical pattern was absent in a group with free access to food [FA]. Furthermore, the FA group had a higher percentage of body fat and the Ruminococcaceae species, shown to protect against non-alcoholic fatty liver disease and obesity, were considerably more abundant in the FT group compared to the group that had free access to food [FA] [16]. On the whole, these findings suggest that food intake can influence daily fluctuations of gut microbial composition, that cyclical patterns in microbial composition may be gained or lost in response to feeding behavior – time-restricted or free access, and that changes in microbial composition as a result of different feeding behaviors may influence host gene expression and energy balance, thus possibly playing a significant role in metabolic disorders.

Additionally, dietary factors such as eating habits, additives, prebiotic and probiotic supplements, food processing, and cooking techniques can play a crucial role in shaping gut microbiota composition, with the timing of food intake impacting both gut microbiota and circadian rhythms, potentially offering therapeutic avenues for immune responses and metabolism [8]. For example, a high-fat diet can affect gut microbiome composition, leading to decreased microbial diversity, changes in the Fimicutes/Bacteroidetes ratio, and increase Fimicutes phylum bacteria, and on the other hand, the host's circadian rhythm can impact GM composition. However, nutrients and bioactive compounds present in food can change the composition and function of the GM. Therefore, strategies based on manipulating GM have the potential to partially restore normal circadian rhythms, showing that in particular - fiber and polyphenols from plant-based foods can produce bioactive vitamins, SCFAs, bioamines, in order to help resynchronize circadian rhythms and alleviate metabolic changes associated with modern lifestyles [8].

Microbial Metabolites and Circadian Regulation

The gut microbiome, by metabolizing dietary components into critical microbial metabolites such as SCFAs and bile acids, plays an integral role in modulating the host's circadian rhythms. These metabolites, particularly butyrate, influence the host's molecular circadian clock through mechanisms like histone deacetylation, which directly regulates the expression of circadian genes within host tissues [19]. This interaction has been shown to affect key metabolic processes, including adipogenesis and inflammation, ultimately impacting disease progression and metabolic health [16]. Additionally, these microbial metabolites extend their influence to the central and hepatic circadian clocks, impacting sleep patterns and overall health. For instance, fluctuations in microbial composition and the resultant metabolite production can alter circadian gene expression in the liver, demonstrating a profound effect on the host's sleep quality and metabolic stability [17].

These metabolites influence circadian clock gene expression within the host, orchestrating a finely tuned interplay between microbe and host. For example, Short chain fatty acids [SCFAs] have been identified as powerful regulators of circadian rhythms through their histone deacetylation inhibitor [HDACi] activity. This finding suggests that inhibition of histone deacetylase [HDAC], a group of enzymes that play an important role in regulating gene expression by removing acetyl groups from histones, by SCFAs, may be a significant mechanism by which the host circadian rhythm is entrained by the gut microbiota [19]. Unraveling the mechanisms underlying these microbial metabolite-host interactions is essential for deciphering the intricacies of circadian regulation.

Recognizing these interactions offers potential for therapeutic interventions using diet, prebiotics, and probiotics to enhance circadian regulation and treat related metabolic disorders, promising a novel approach to managing circadian dysregulation and its extensive effects on human health [19, 41].

Gut Microbiota, Sleep and Chronotypes

Sleep deprivation further complicates the relationship between diet and the microbiome, as Yang et al. (2023) demonstrate that it exacerbates systemic inflammation and psychiatric disorders through disruptions in microbiota and circadian rhythms. Studies by Lotti et al. (2023) and Carasso et al. (2021) further enrich our understanding by linking chronotypes with microbial composition – early risers ("larks") show different microbial profiles compared to late risers ("owls"), with implications for metabolic pathways and overall health.

Studies by Yang et al. (2023) found that sleep deprivation (SD) led to increased intestinal permeability and leakage of lipopolysaccharide (LPS) from the gut into the bloodstream. LPS is a component of the cell wall of gram-negative bacteria and is considered a biomarker of intestinal permeability. Their findings implied that sleep deprivation disrupted the integrity of the intestinal barrier, which would then allow bacteria and their components like LPS to seep out of the gut and into the bloodstream, therefore stimulating the immune system to release inflammatory molecules such as TNF–α, causing systemic inflammation and having implications for various health conditions.

Research by Carasso et al. (2021) found that early chronotypes had higher levels of Alistipes putredinis in their gut microbiome compared to later chronotypes, showing a possible link between an individual's circadian rhythm and the composition of their gut microbiota. The abundance of Lachnospira pectinoschiza differed significantly between early and late chronotypes ($pFDR = 0.2$), with a higher abundance in the late chronotype. Additionally, microbial metabolic pathways were analyzed, revealing 14 pathways with significant differences among early, intermediate, and late chronotypes ($pFDR < 0.2$). Out of these, 11 pathways showed differences between intermediate and either early or late chronotypes. The three pathways that varied specifically between the early and late chronotypes were the histidine, purine, and pyrimidine biosynthesis super-pathway, the pyrimidine deoxyribonucleotide de novo biosynthesis super-pathway and the gluconeogenesis pathway. Notably, all four pathways exhibited higher abundance in the early compared to the late chronotype [37].

A correlation was observed between higher consumption of fruits and vegetables and an early chronotype. As a result, the relationship between vegetable and fruit consumption and the microbiome was explored. The reported weekly consumption of vegetables and fruits was totaled, and participants were categorized into two groups: those who consumed less than or equal to 10 vegetables and/or fruits and those who consumed more than 10 vegetables and/or fruits. The results indicated that the Ruminococcaceae family was more prevalent in participants who consumed more than 10 fruits and vegetables per week. This finding aligns with previous research, which demonstrated a positive association between high fruit intake and Ruminococcaceae levels in the microbiome. No significant associations were identified in addition between food consumption and microbiome composition and food consumption. However, an increase in the Negativicutes bacterial class was linked to a higher body mass index (BMI), and as previous studies have reported elevated levels of Negativicutes in obese individuals with type 2 diabetes [37].

On the whole, several consistent differences among chronotypes were identified – notably, lower α-diversity, a marker of dysbiosis, was observed in late chronotypes, which is in line with increasing evidence suggesting an elevated risk of cardio-metabolic morbidity and mortality in this group due to an imbalance in the gut microbiome composition. In addition, previous studies have shown that jet lag is linked to dysbiosis in both humans and mice [22, 43]. Since individuals with late chronotypes are more susceptible to social jet lag (i.e., misalignment between endogenous and social circadian clocks), lower gut microbiome diversity was anticipated considering its associated to circadian disruption [37].

Gut Microbiome, Circadian Rhythm and Meal Timing

Evidence for meal timing comes from a study that analyzed gut microbiota composition according to chronotype, where evening subjects, had higher concentrations of Lachnospira, which has recently been linked to greater consumption of energy after 14:00, typical of evening chronotypes, highlighting the value of meal timing on intestinal flora composition [41].

Furthermore, TRF introduction in high-fat diets showed to positive influence gut microbial community structure in experiments with mice, and found that restriction of access to food was linked to decrease in the abundance of various obesogenic microbes, such as Lactobacillus and Lactococcus species, as well as an increase in documented bacteria that are protective, like Oscillibacter and other Ruminococcaceae species [41]. The effect of TRF in mice studies found that it changed the innate immune response to bacterial endotoxin in mice, and that mice fed during the day had suppressed cytokine responses and capacity to kill bacteria compared to mice fed at night or had free access to food, thus showing the important role of meal timing for immune function [26].

Gut Microbiome, Circadian Rhythm and Immunity

The gut microbiota, a collection of microorganisms residing in the intestines, plays a pivotal role in growth, maturation, and regulation of the host's immune system. This influence becomes evident through studies involving germ-free (GF) animals, illustrating that commensal bacteria are indispensable for the development of various immune cell populations, such as including neutrophils, monocytes and macrophages, within the gut lamin propria, as well as within immune sites, like the spleen, liver and bone marrow [16].

The timing and patterns of dietary intake impact the gut microbiome and subsequently host immunity, with circadian rhythms playing a regulatory role, influenced by the host's diet and light/dark cycles. This suggests that appropriate meal timing could have beneficial effects in modulating immune-related diseases through adjustments in the microbiome [26]. On the other hand, mistimed feeding and irregular sleeping patterns led to modifications in immune pathways in healthy individuals, including elevated levels of pro-inflammatory cytokines (IL-3 and IL-5), and a decrease of antigen presentation, compare to controls [26].

The mucosal microbiome adjacent to the epithelial barrier is the most likely target for sampling by mucosal immune components. A coordinated rhythm between the host and the microbiome is essential for maintaining a balance in gut homeostasis between immune tolerance and activation [44]. Addressing these interactions, Butler and Gibbs (2020) discuss how the gut microbiome and its metabolites like short-chain fatty acids and tryptophan derivatives are involved in maintaining the rhythmicity of the host's immune system, suggesting that enhancing these host-microbiome circadian interactions could bolster immune resilience.

Research findings indicate that tryptophan metabolites produced by the gut microbiota play a crucial role in regulating the immune system. For example, Indole-3-aldehyde (IAId), produced by lactobacilli bacteria, induces the production of interleukin-22 (IL-22) in the host, which helps fight against fungal infections and reduces inflammation in mouse models of colitis [44]. In addition, the production of pro-inflammatory cytokines by macrophages is reduced by indole-3-acetate (I3A) and decreases the movement of macrophages toward a chemical signal in an AhR dependent manner. Lastly, a short-chain fatty acid produced by gut bacteria, butyrate, enhances the production of 5-hydroxyindoleacetic acid (5-HIAA), which acts through AhR to uphold regulatory B cells and is essential for maintaining immune homeostasis.

This study underscores the pivotal role of gut microbiota-derived tryptophan metabolites in immune system regulation. These metabolites influence various aspects of immunity, including antifungal resistance, inflammation, integrity of the intestinal barrier, and the function of diverse immune cells such as macrophages and regulatory B cells.

These collective insights underscore the potential of aligning dietary and lifestyle interventions with circadian biology to optimize gut microbiota health and overall well-being, paving the way for novel chronotherapeutic strategies.

Chronobiology and Aging: The Role of the Microbiome

Vallée et al. (2020) found that circadian dysregulation is linked to aging, cancer, and chronic diseases. Aging is associated with alterations in the circadian system, leading to changes in circadian rhythmicity such as reduced amplitude or less distinct daily patterns, increased intra-daily variability less distinct daily patterns, and decreased inter-daily stability of circadian rhythms, which refers a reduced predictability of circadian from day to day, where the body's internal clock is not adequately synchronized with external cues such as light-dark cycles [17].

Time restricted feeding (TRF), in which food intake is restricted to certain hours of the day (usually within 12 h) without altering calorie consumption, has gained a lot of attention as a potential anti-aging intervention [45, 46].

Circadian Rhythms and Parkinson's Disease

Parkinson's Disease (PD) is characterized by the progressive degeneration of dopaminergic neurons (specific neurons in the brain that synthesize and release the neurotransmitter dopamine, which plays an important role in numerous brain functions) in the brain, and results in motor and non-motor symptoms that impact a person's quality of life. Dysregulation of circadian rhythms exacerbates neuroinflammatory responses and oxidative stress within the brain, contributing to neuronal degeneration and disease progression, however, it is unclear whether the changes in circadian rhythms is a result of dopaminergic treatment or the progression of PD progression itself [26]. Targeting circadian rhythms may offer novel therapeutic strategies for managing PD and improving clinical outcomes.

Research highlights the profound impact of circadian rhythms on Parkinson's Disease (PD), underscoring their role in both the pathogenesis and progression of the disease. Studies like those conducted by Vallée et al. (2020) and Leng et al. (2019) establish a critical link between circadian rhythm disruptions and neurodegenerative processes, also shown through mechanisms involving neuroinflammation and oxidative stress. Studies found a bidirectional relationship between circadian rhythms and PD, where the disruption of circadians rhythms was associated with the progression of PD, altered rest and activity cycles as well as changes in heart rate, blood pressure and autonomic dysfunction being common in PD patients [13]. On the other hand, key circadian clock genes, including BMAL1, CRY1, PER1, and PER2, show altered gene expression patterns in PD, and PD-related changes, such as depletion of dopamine, which plays an important role in not only regulating circadian rhythms, but is also characteristic of PD and can lead to circadian dysfunction by disrupting the central molecular clock [13].

These disruptions not only exacerbate PD symptoms but also precede the onset of motor symptoms, thereby offering a potential window for early intervention [13, 47]. Additional research by De Lazzari et al. (2018) and Mattis et al. (2016) utilizes Drosophila models and studies on aging populations to further explore how genetic mutations affecting circadian rhythms and age-related sleep pattern disruptions contribute to PD pathology, advocating for circadian rhythm modulation as a therapeutic strategy [48]. De Lazzari et al. (2018) found that PD patients repeatedly showed alterations in various physiological factors, which are partly or fully controlled by the circadian rhythm, where changes in their daily rest and activity rhythms were recorded declines in both day activity and nocturnal rest. Furthermore, 65% to 95% of individuals with PD experience sleep disturbances [49], which is now understood as being a significant contributor to reduced quality of life in patients [50].

Further investigations into circadian mechanisms reveal their broader implications across various brain disorders, including other α-synucleinopathies. Studies like those by Hunt et al. (2022), Kunz et al. (2023), and Kou et al. (2022) emphasize the necessity of targeting these mechanisms to alleviate symptoms and slow neurodegeneration, highlighting the role of circadian proteins like Rev-erbα in neuroprotection by modulating microglial activation and neuroinflammation. The comprehensive analysis by Fifel et al. (2021) of circadian system dysfunctions in PD provides crucial insights into how these rhythms affect disease progression, supporting the strategic targeting of circadian disruptions as a promising therapeutic avenue [51, 52].

Gut Microbiota Composition and Mental Health

The gut microbiota plays a pivotal role in modulating brain function and behavior through the gut-brain axis. Alterations in gut microbiota composition have been linked to various mental health disorders, including anxiety and depression [53].

Research has increasingly highlighted the intricate link between circadian rhythms, diet, and the gut microbiota in influencing mental health. Disruptions in circadian rhythms, often caused by modern lifestyle factors, are closely associated with severe psychiatric symptoms and metabolic comorbidities. Shift workers, shown to experience irregular timing of meals have a 25% to 40% greater risk of anxiety and depression, as well as increased rates of other mental problems [40]. Strategies that resynchronize these rhythms, known as chronotherapeutics, can improve mental health by modulating the gut microbiota, which adheres to a diurnal pattern influenced by meal timing [40].

Nutrients and bioactive compounds of food can modify gut microbial composition and functions, thus several recent strategies based on the manipulation of GM may at least partially consolidate host circadian rhythms. In particular, plant-food-derived fiber and polyphenols can generate bioactive SCFAs, vitamins, and bioamines, which in turn might help resynchronize circadian rhythms, mitigating some of the modern-lifestyle-associated metabolic alterations.

The timing of food intake is controlled centrally by the host's circadian system and is influenced by food availability, hunger, food availability, as well as social and cultural norms. In mice studies, those with disturbances in circadian light entrainment exhibited a reduction in fecal microbiome diversity oscillations, in addition to more weight gain and weakened glucose tolerance. Similarly, in a mouse model of jet lag where, for 4 weeks, the light-dark cycle shifted by 8 hours every 3 days, showed reduced diurnal oscillations in microbiome abundance, likely due to the disruption of the normal diurnal pattern of food consumption [44].

Systematic reviews also indicate that individuals with anxiety or depression typically exhibit an imbalance in gut microbiota, characterized by a higher abundance of proinflammatory species and a lower presence of beneficial short-chain fatty acid-producing bacteria, suggesting a pathway through which gut health affects mental well-being [53].

A distinctive bacterial pattern associated with depression has been recently identified. This pattern was characterized by an increased presence of pro-inflammatory species, including Enterobacteriaceae and Desulfovibrio, and a decreased abundance of short-chain fatty acid (SCFA)-producing bacteria, such as Faecalibacterium [41]. SCFAs, which are metabolites produced by these bacteria, have been found to play a role in regulating circadian rhythms by modulating the expression of circadian clock genes.

Furthermore, irregular eating patterns disrupting circadian rhythms can lead to gut microbiota changes, linked to mood disorders and altered host behavior [14]. The interplay between sleep and gut microbiota is also critical; acute sleep deprivation can exacerbate systemic inflammation and psychiatric disorders by disturbing both gut microbiota and circadian rhythms, highlighting the importance of maintaining sleep quality for mental and gut health [54]. Sex differences in molecular rhythms within the human cortex further underscore the complexity of these interactions, potentially explaining observed variations in mood and cognitive functions between genders [55].

Chrono-Nutrition and Sex Differences

Recent studies have highlighted significant sex differences in circadian rhythms and their implications for chrono-nutrition and disease susceptibility, emphasizing the need for sex-specific research and interventions. These differences not only affect how nutrients are processed at different times of the day (chrono-nutrition) but also impact how susceptible each sex is to various diseases. Walton et al. (2022) stress the importance of considering both time-of-day and biological sex in studies due to their combined effects on physiological and behavioral processes [56]. Similarly, Joye and Evans (2022) examine how sex and gonadal hormones influence circadian functions, particularly within the suprachiasmatic nucleus (SCN), which is crucial for developing tailored chrono-nutritional strategies [57].

Further research by Logan et al. (2019) shows that there are nearly twice as many rhythmic transcripts in the dorsolateral prefrontal cortex in males compared to females, suggesting that molecular rhythms can affect how nutritional strategies impact different sexes [58]. Additionally, studies by Škrlec et al. (2021) on circadian genes like ARNTL, CLOCK, CRY2, and PER2 indicate these genes' roles in myocardial infarction susceptibility differ between sexes, supporting the critical role of circadian biology in gender-specific health outcomes [59]. The study by Škrlec et al. (2021) explores the link between single nucleotide polymorphisms (SNPs) in circadian rhythm genes – specifically ARNTL, CLOCK, CRY2, and PER2 – and the risk of myocardial infarction, with a focus on gender differences. It reveals that the SNP rs11932595 in the CLOCK gene presents notable sex-specific variations, significantly affecting women more than men, with an odds ratio of 2.66, indicating a substantially higher risk of myocardial infarction in women possessing this polymorphism. This finding emphasizes the potential of sex-specific genetic screenings and targeted interventions to improve therapeutic outcomes based on genetic predispositions related to circadian rhythm genes.

Socioeconomic and Cultural Influences

Socioeconomic factors, such as income and access to nutritious foods, significantly influence adherence to chrono-nutritional recommendations. Integrating socio-economic considerations is crucial for designing inclusive and effective personalized nutrition plans.

Franzago et al. (2023) and Flanagan et al. (2021) offer valuable insights into the socio-economic and cultural factors that significantly influence the effectiveness of chrono-nutritional interventions. Franzago et al. (2023) emphasize the challenges faced by individuals from lower socioeconomic backgrounds in adhering to chrono-nutritional recommendations, primarily due to restricted access to healthy foods. This highlights the critical need for creating personalized nutrition plans that are not only scientifically sound but also economically and culturally viable across different populations. On the other hand, Flanagan et al. (2021) discuss the impact of cultural practices and societal norms on meal timing and dietary habits, underscoring the importance of integrating cultural diversity into chrono-nutritional guidelines to ensure they are meaningful and practical for diverse groups. Both studies stress that overlooking these socio-economic and cultural dimensions may result in suboptimal health outcomes and low adherence to prescribed dietary plans.

Building on this, Gentry et al. (2021) detail how genetic and environmental factors, including cultural habits, contribute to variations in human circadian rhythms, which can significantly affect how dietary interventions are received and adhered to across different populations. Their research supports the notion that chrono-nutritional guidelines must be flexible and adaptable to accommodate the broad spectrum of dietary habits and cultural nuances present globally. This approach ensures that chrono-nutritional advice is not only applicable but also tailored to meet the specific needs and circumstances of various cultural groups, thereby enhancing the overall effectiveness and acceptance of such interventions in diverse settings. Together, these studies provide a compelling case for the inclusion of socio-economic and cultural considerations in the development and implementation of chrono-nutritional strategies, aiming to bridge the gap between broad dietary guidelines and individualized patient care.

Future Directions in Microbiota Research

Future studies should aim to rigorously assess potential confounders that can impact the gut microbiota, such as diet and medication use. Additionally, there is a need to explore the functional role of microorganisms beyond their abundance, shedding light on their contribution to host physiology and health outcomes. By unraveling the complex interplay between circadian rhythms, the gut microbiome, and host health, researchers can identify novel therapeutic targets and develop personalized interventions for a range of metabolic and neurological disorders.

3 Conclusion

Chrono-nutrition represents a promising approach to improve health outcomes by aligning dietary patterns with circadian rhythms. Evidence suggests that chrono-nutrition interventions may have positive effects on cardiovascular health, diabetes management, glucose metabolism, and other metabolic processes. However, further research is needed to fully understand the mechanisms underlying chrono-nutrition and its long-term effects on health. Integrating individual differences in chronotypes, sex, socioeconomic status, and cultural backgrounds is essential for developing personalized chrono-nutritional recommendations that can effectively promote health and prevent chronic diseases. Overall, chrono-nutrition holds great potential as a holistic approach to optimize nutrition and improve overall well-being.

The interplay between circadian rhythms and the gut microbiome is a fascinating area of research with profound implications for human health. By elucidating the mechanisms underlying this interplay, researchers can uncover novel therapeutic targets and develop personalized interventions for a range of metabolic and neurological disorders. Future research efforts should focus on unraveling the molecular pathways linking circadian rhythms, microbial metabolites, and host physiology, paving the way for innovative chronotherapeutic strategies in healthcare.

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