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REVIEW

Circadian rhythms, gut microbiota, and diet: Possible implications for health

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Abstract *Aims:* Over the past years, interest in chrono-nutrition has grown enormously as the fundamental role of circadian rhythms in regulating most physiological and metabolic processes has become clearer. Recently, the influence of circadian rhythms on the gut microbiota (GM) composition has also emerged, as more than half of the total microbial composition fluctuates rhythmically throughout the day. At the same time, other studies have observed that the GM itself synchronises the host's circadian biological clock through signals of a different nature. Therefore, it has been hypothesised that there is a two-way communication between the circadian rhythms of the host and the GM, but researchers have only just begun to identify some of its action mechanisms. The manuscript aim is, therefore, to gather and combine the latest evidence in the field of chrono-nutrition with the more recent research on the GM, in order to investigate their relationship and their potential impact on human health.
Data synthesis: Considering current evidence, a desynchronization of circadian rhythms is closely associated with an alteration in the abundance and functionality of the gut microbiota with consequent deleterious effects on health, such as increased risk of numerous pathologies, including cardiovascular disease, cancer, irritable bowel disease, and depression. A key role in maintaining the balance between circadian rhythms and GM seems to be attributed to meal-timing and diet quality, as well as to certain microbial metabolites, in particular short-chain fatty acids.
Conclusions: Future studies are needed to decipher the link between the circadian rhythms and specific microbial patterns in relation to different disease frameworks.

1. Introduction

Chrono-nutrition, a science that combines components of nutritional research with elements of chronobiology, has gained increasing interest as the scientific community has emphasised the impacting effect of biological rhythms on nutritional response [1]. Indeed, 'when we eat' is linked to our internal 24-h biological timing system and plays a key role in regulating a multiplicity of physiological and metabolic processes in human [2]. Interestingly, the latest

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research has also highlighted the influence of circadian rhythms on the gut microbiota (GM) composition and function.

The gut microbiota is widely considered the largest endocrine organ playing a crucial role in maintaining host homeostasis. This colony of trillions of microorganisms achieves many essential and beneficial physiological processes, like the digestion of macronutrients, synthesis of some vitamins and especially the immunity modulation [3,4]. To date, some studies have demonstrated that GM composition and function fluctuate throughout the day under the regulation of circadian rhythms [5,6]. At the same time, Flower et al. have recently observed that the GM itself synchronises the host's circadian biological clock by releasing signals of a different nature [7].

Thus, there seems to be a two-way communication between the circadian rhythms of the host and the gut microbiota. A focal point of this communication network is occupied by food consumption. Indeed, diet is one of the environmental factors that most influences the peripheral clocks [8]; similarly, diet quality and mealtimes have an impact on both composition and function of gut microbes [9].

So far, researchers hypothesize that a disruption of circadian rhythms can lead to a functional and structural dysbiosis, favouring the onset of pathological mechanisms. Considering that currently we live in a society that encourages the disruption of circadian rhythms through continuous work shifts, unregulated eating and light pollution [10], it is increasingly crucial to understand the relationship between biological rhythms, gut microbiota, and diet. The aim of our review is, therefore, to gather and combine the latest evidence in the field of chrono-nutrition with the more recent research on the gut microbiota, in order to investigate this relationship and their potential impact on human health.

2. Circadian rhythms

Human nature is characterised by temporal components marked by circadian rhythms. These rhythms are a series of endogenous oscillators generated by the circadian clock system that coordinates nearly all the physiological processes with the external environment. This endogenous clock system works over a period of about 24 h and is called "circadian" from the Latin word *circa* and *diem*, which can translate as "about a day" [11].

2.1. Circadian clock system

In mammals, the circadian system consists of a hierarchical network of clocks where the master circadian clock,

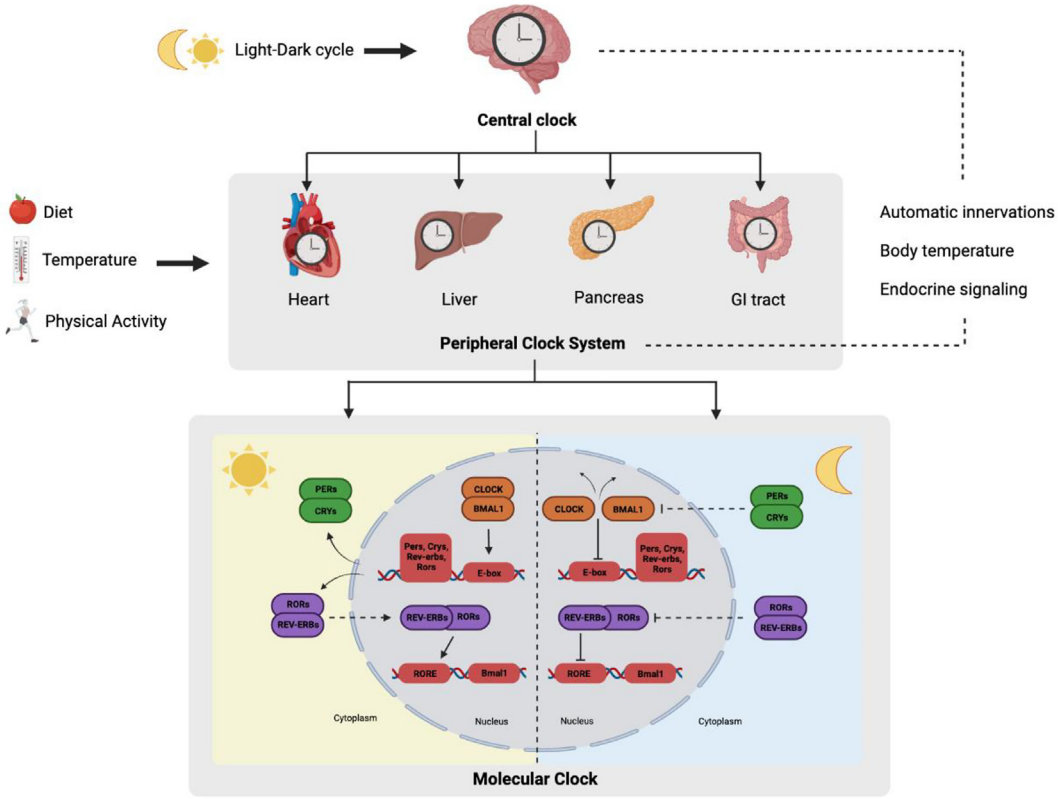

Figure 1 The human circadian clock system. The retinal cells of the eye perceive light stimuli from the external environment and convey them to the hypothalamic superchiasmatic nucleus. The central biological clock located in the hypothalamus sends different type of signals to peripheral clocks located in various organs, such as the heart, liver, pancreas and gastro-intestinal tract (GI). In addition to being synchronised by the central clock, these peripheral clocks are synchronised by other environmental stimuli such as nutrition, temperature, and physical activity. At the cellular level, circadian oscillations are controlled by a molecular clock that consists of cell-autonomous transcriptional/translational feedback loops.

located in the suprachiasmatic nucleus (SCN) of the hypothalamus, synchronises clocks in peripheral tissues to drive behavioural and humoral rhythms (Fig. 1). The location of the SCN, which is adjacent to the optic chiasm, makes it ideal for receiving light input that is detected by retinal ganglion cells, that contain photopigment melanopsin, and sent to the master clock via the retinohypothalamic tract [12]. Although the light is the main driving agent for the master clock in the SCN, other external cues, also called "synchronizers" or "zeitgebers", can influence the circadian rhythm synchronization [8]. These include body temperature, mealtimes, social interactions, and physical exercise, and are particularly important for the circadian clock system in peripheral tissues that cannot perceive daylight signals [13]. The master circadian clock processes a neurohumoral output after receiving external timing cues to control physiological activity in numerous tissues and organs [11].

The linking between the master circadian clock and peripheral tissues involves numerous mediators, including circulating hormones, cytokines, metabolites, and sympathetic activation [8]. At the cellular level, the circadian oscillations are controlled by cell-autonomous transcriptional/translational feedback loops (TTFLs). At the cycle beginning, two transcription activators included in the core clock genes, CLOCK and BMAL1, produce a heterodimer, bind to the *cis*-acting promoter element E-box (5′-CACGTG-3′), and activate the transcription of the PER and CRY genes [8]. After translation, PER and CRY proteins accumulate, dimerise, and produce complexes that translocate back to the nucleus and inhibit the transcriptional activity of the CLOCK/BMAL1 heterodimer [11]. Another loop is coupled to the core TTFLs to complete the oscillation. This loop comprises RORs and REV-ERB, two proteins that are positive and negative regulators of BMAL1 transcription, respectively. Together, these two interlocking transcriptional feedback loops make an oscillatory expression pattern over a period of approximately 24 h, regulating numerous physiological processes including immune responses, hormone secretion and digestion [14,15].

The presence of a circadian transcriptional clock in almost every cell of the body suggests that the rhythmicity of metabolic functions is a key health component. When behaviours such as sleep or eating are not synchronised with the surrounding environment (e.g., dark/light cycles), an alteration of circadian rhythms occurs. This condition is defined as chrono-disruption, i.e. a major disturbance in the circadian organization of physiology, endocrinology, metabolism and behaviour, with consequent negative effects on the body's homeostasis [10]. In particular, numerous studies have shown that an alteration in circadian rhythms leads to an inflammatory state and impaired immune system function [16,17], promoting the onset of several cardiometabolic diseases and cancer [18,19]. More recently, a chrono-disruption has also been associated with the development of age-related neurodegenerative diseases such as Alzheimer's and Parkinson's disease [20]. However, further investigations are needed to better prove this link.

2.2. Chronotype

Individual expression of circadian rhythmicity is defined as 'chronotype', a complex phenotype that reflects individual differences in sleep timing and activity preferences [21]. There are three chronotypes expressed as a continuum between two extremes, from morningness to eveningness [22]. People with a morning chronotype tend to wake up early and perform activities better in the early hours of the day. In contrast, the evening chronotype is characterised by a propensity to perform activities better in the afternoon or evening and by a later bedtime and wake-up time [23]. Finally, intermediate subjects report intermediate habits between the two chronotypes.

2.2.1. Chronotype assessment

Chronotype can be measured by a variety of methods, ranging from questionnaires based on self-reported information to biological measures such as the Dim Light Melatonin Onset (DLMO). Currently, the administration of questionnaires remains the most widely used measure to define the chronotype. In particular, the most used in literature seems the Morningness-Eveningness Questionnaire (MEQ), which specifically measures psychological preference for behaviour [22]. The MEQ also exists in a reduced form (rMEQ), in which the 19 questions of the original format are reduced to only five questions [24]. Other diffuse questionnaires are the Composite Scale of Morningness (CSM), the Preferences Scale, and the Munich Chronotype Questionnaire (MCTQ). The latter offers the advantage of collecting detailed information on sleep-wake behaviour that allows the evaluation of the "social jet lag", quantified by the difference between the median sleep points on work days and free days in hours [25,26].

In spite of the ease and inexpensiveness of questionnaires, the greatest reliable measure of the circadian phase of the human master clock is the DMLO [27]. It consists of measuring melatonin secretion in blood or saliva samples collected under low-light conditions in the hours before the onset of usual sleep. Other potential innovative approaches range from metabolomic and transcriptomic approaches to non-invasive techniques that combine data of motor activity, body position and body temperature [28,29]. More interesting is the actigraphy that is to say the study of sleep through the use of an actigraph, a three-dimensional movement sensor placed on the wrist like a watch and that allows the movements made by the patient's body to be recorded for a duration of one or more days [30]. Recent evidence has found that acrophasic activity in evening subjects occurs almost 2:20 h later than in morning subjects [31]. In fact, evening subjects reach peak activity in the late afternoon versus morning subjects who reach it in the early afternoon [31]. However, to date there is still no optimal method to objectively measure the chronotype and future research is certainly needed to establish the validity of more innovative approaches.

2.2.2. Factors influencing chronotype

The distribution of chronotypes in a given population is defined by numerous factors, both genetic and environmental. In general, the 60% of the population shows an intermediate chronotype, with the remaining 40% shifted between the morning and evening chronotypes [21]. In recent years, several genome-wide association studies have characterised important polymorphisms in clock genes that might underlie some of the inter-individual and inter-ethnic differences in chronotype [32,33]. In addition, demographic characteristics, such as gender and age, also appear to moderate the morningness-eveningness trait. Regarding the gender, although not all studies agree, a higher prevalence of morningness has been found in women than in men, who reported higher eveningness [34]. Interestingly, having children has been found to be a strong determinant of morningness in women [34]. Age is another factor that influences the time preferences, which vary throughout human life. Children predominantly show a morning chronotype that changes to eveningness during adolescence [35], and then returns to morningness again around the 50 age [36]. These variations are probably due to changes in gonadal hormone secretion and societal and lifestyle demands [37,38]. For example, while artificial light prolongs daylight and allows humans to work at night, favouring a change in subjects' chronotype towards the eveningness, school and certain work schedules that begin early in the morning may favour a shift of the evening chronotype towards the morningness [39].

3. Gut microbiota

The gut microbiota is an ecosystem composed of trillions of microbes, including bacteria, viruses, fungi, archaea and some parasites. It functions as a host 'organ', fully interconnected with the other vital systems of body, with which it interacts to regulate various physiological systems, including the immune, metabolic, and nervous systems [40]. It is therefore clear that an alteration in the balance of intestinal flora can favour the onset of various chronic diseases, such as obesity, diabetes and other metabolic syndromes, cancer and autoimmune diseases [41–43].

3.1. Gut microbiota and circadian rhythms

Although disruption in both circadian rhythmicity and GM eubiosis is known to underlie many pathological processes, Thaiss and colleagues were among the first to demonstrate a link between the two [5]. They found that an abundance of 60% of the microbiota composition oscillates over a 24 h-period, as the 20% of the microbial functional pathways [5]. Further studies in mice confirmed these findings, showing that although gut microbes are not exposed to light, diurnal host signals induce oscillations in both abundance and GM function [6,44]. Interestingly, functions involved in energy metabolism, DNA repair, and cell growth appear to be optimally performed during the dark phase (active phase of mice), while the light phase is characterised by functions involved in detoxification, motility, and environmental sensing [5]. Moreover, mice with genetic mutations in clock genes, such as BMAL1 and PER1/2, exhibit significantly altered microbial community profiles and loss of rhythms in specific microbial taxa [5,44]. In addition to mutations in canonical clock genes, other alterations in the host's organism influence fluctuations in the gut microbiome, such as feeding times, mucus and metabolite production [45]. It is hypothesised that these factors influence microbial concentration throughout the day by acting on the adhesion of bacteria to the intestinal mucosa [46]. A key role is played by REG3γ, an antimicrobial peptide secreted by enterocytes that binds to the peptidoglycan layer on the surface of Gram-positive pathogens by reducing the adhesion of mucosal bacteria to intestinal epithelial cells [47]. Predictably, the diurnal rhythmicity of mucosa-associated bacteria was not observed in Reg3γ-deficient mice [46]. Further investigations in mice have shown that the adhesion of bacteria to the intestinal mucosa is also influenced by the thickness of the intestinal mucus, which follows diurnal dynamics [46].

At the same time, the GM itself synchronises the host's circadian biological clock by releasing different natural signals [7]. Studies evaluating the synchronizing GM function towards the circadian system have shown that mice lacking gut microbes exhibit completely different transcriptional patterns of the liver and SCN, particularly regarding circadian and major metabolic pathways [6]. A similar effect was observed in intestinal epithelial cells of antibiotic-treated or germ-free mice, in which the expression of clock and metabolism genes was reduced [48,49]. The synchronizing action of gut microbiota on the host's circadian clock system is mediated by hundreds of bacterial metabolites. Among the few identified so far are short-chain fatty acids (SCFA) that show diurnal oscillations in their abundance and, as reported by several studies, promote a significant shift in the expression pattern of circadian clock genes [45]. For instance, a study in mice observed that butyrate and acetate produced by the microbiota regulate hepatic circadian gene expression [6]. In particular, an alteration in the circadian production of these SCFAs was associated with an alteration in both the rhythmicity and amplitude of circadian clock genes such as PER2, PER230 and ARNTL (encoding BMAL1). Interestingly, SCFA production is highly dependent on host diet, as the study authors observed that mice fed a high-fat diet had a reduced oscillation of certain SCFA-producing microbial families, such as *Lachnospiraceae*, compared to mice fed a low-fat diet [6]. These results suggest that diet influences the production and fluctuation of SCFAs with a subsequent impact on the expression of some circadian clock genes. Further research has suggested that unconjugated bile acids are another mediator through which the gut microbiota regulates the host's peripheral circadian clocks. Bile acids are largely secreted as conjugated compounds by the liver and are then deconjugated by gut microorganisms [50]. One study observed that in the Caco-2 intestinal epithelial cell line model, in which cells were synchronised to have the same circadian rhythms, treatment with unconjugated bile acids significantly altered the amplitude and cyclic behaviour of circadian clock genes including CLOCK,

Figure 2 The central role of diet in the communication between circadian rhythms and gut microbiota.

ARNTL, PER, CRY, RORA, NRID1 (encoding REV-ERBα) [51]. Recently, other bacterial metabolites involved in GM-circadian clock communication, such as polyamines, amino acids, biotin, vitamin K, and lipopolysaccharide have been identified [52]. Of particular interest are polyamines, a group of metabolites produced by both the mammalian host and the gut microbiota. Polyamines are known to regulate circadian oscillations by influencing interactions between clock proteins, PER2 and CRY1 in mice [53]. Indeed, it has been observed that a diet low in polyamines alters the hepatic circadian transcriptome, with changes comparable to those observed in antibiotic-treated mice [46]. On the other hand, the polyamine oscillation in serum is affected by the gut microbiota, as its absence has been associated with a reduction in the production of polyamines [46].

4. Diet as a link between circadian rhythms and gut microbiota

As shown in Fig. 2, diet plays a central role in the microbial-circadian communication network, as eating habits directly influence both circadian rhythms and gut microbiota. Although most research in the field of chrono-nutrition focuses on the temporal aspects of diet, particularly timing, frequency, and regularity of food intake, some studies have also reported an association with diet quality [54 Mazri].

4.1. Meal timing

Since food is the main synchronizer of the peripheral clocks located in the liver, pancreas, and gastrointestinal tract, which cannot perceive light as a synchronization stimulus, eating late can lead to a misalignment of circadian clocks and altered hormone secretion [8]. The daily physiology of the human being consists of an active phase, which begins at 10 a.m., and a resting phase, which starts at 10 p.m. The alternation of these two phases regulates the oscillations of several hormones involved in metabolic regulation, many of which peak during the active phase [54]. For this reason, the early hours of the day seem to be better for food intake than the evening hours, when food intake is at odds with the rhythm of the internal clock and may cause chrono-disruption [55].

A recent review comprising 36 studies showed that evening subjects had later meal timing and distributed a greater amount of energy and nutrient intake to the later day part [56]. The delay in meal consumption between the morning and evening subjects was quantified at approximately 1–1.5 h. As observed by Wirth et al. in the NHANES dataset, each 1-h increase in the time of the last meal of the day is associated with an increase in C-reactive protein, insulin, glucose, glycated haemoglobin (HbA1c) and a reduction in HDL levels [57]. A significant association was also found between the meal time and energy utilisation, with different effects on weight loss. In the study by Garaulet et al., subjects who ate lunch late lost significantly less weight than those who ate lunch early [58].

In this scenario, it is more interesting the "time restricted feeding" (TRF), defined as the consumption of the desired amount of food by a person or animal during a specific window of time. The TRF introduction in high-fat diet experiments has been shown to reverse many detrimental metabolic consequences and to positively affect gut microbial community structure in mice [59,60]. In particular, the restriction of food access time was associated with a decrease in the relative abundance of several presumed obesogenic microbes, such as *Lactobacillus* and *Lactococcus* species, and abundance increase of documented protective bacteria, such as *Oscillibacter* and other *Ruminococcaceae* species [61]. A common hypothesis for the observed benefits of TRF is that it mimics natural eating patterns based on circadian rhythms [9].

Further proof of the importance of meal timing on the composition of the intestinal flora was provided by the results of the first study that analyzed the GM composition according to chronotype. Carasso and colleagues observed that evening subjects reported a higher concentration of *Lachnospira* [62]. This higher concentration has recently been associated with the consumption of higher amounts of energy after 2 p.m., a typical characteristic of evening subjects [9].

4.2. Meal frequency and regularity

The concepts of meal frequency and regularity are closely associated, as meal frequency indicates the number of times macronutrients are introduced during the day, while meal regularity indicates the constancy with which meals are introduced throughout the day, thus reflecting circadian rhythms [63]. Previous studies have shown that skipping a meal or eating it irregularly throughout the day can cause an exacerbation of circadian misalignment [10]. This is due to the fact that the central hypothalamic biological clock uses light as its main synchronizer, while peripheral clocks use food intake. When food is taken outside the usual time, peripheral clocks are activated while the central clock remains synchronised according to the light/dark cycle.

To date, evening subjects have been associated with irregular eating habits and the tendency to skip some meals more than other chronotypes [56]. This is particularly true for breakfast, as highlighted in a recent scoping review by Phoi and colleagues, in which 5 out of 6 studies showed a greater tendency to skip breakfast in evening subjects [64]. This association has also been observed in

some younger peoples, such as university students [65,66] and school-age children [67]. Furthermore, evening subjects tend to skip lunch and/or dinner more frequently than the other chronotypes, although this relationship has been examined by fewer studies [68–70]. In a recent study of 1267 Italian adults, it was observed, for the first time, that evening subjects had a significantly higher frequency of skipping even the mid-morning snack [71].

The meal skipping observed in evening people may be related to their sleeping habits, especially about breakfast. Since evening types are more frequently associated with social jet lag, which forces them to adapt their biological rhythms to the schedules imposed by society, they tend to accumulate a sleep debt during the week, which is then recovered at the weekend [26,72]. Thus, evening subjects sleep less than required and they may prefer to sleep a little longer in the morning instead of having breakfast [65]. A further hypothesis is that meal skipping observed in evening subjects is linked to a genetic predisposition, as shown in a study of 53 pairs of female twins which found that the time and consumption of breakfast and lunch are significantly influenced by genetic factors [73].

To our knowledge, only one study, which was conducted on horses, has investigated the effect of meal frequency on the GM composition. According to the results, a higher feeding frequency has been associated with a decreased relative abundance of *Prevotella, Lactobacillus, Streptococcus, Coprococcus*, and *Phascolarctobaterium* [74]. Additional research in humans is needed to determine whether meal frequency and regularity affect the microbial taxa.

4.3. Diet quality

Based on the available literature, it is not clear whether chronotype is a determinant of dietary patterns or simply a reflection of a complex set of behaviours that also influence diet. The few available studies suggest a potential influence of chronotype on the quality of the diet. Regarding the intake of micro- and macronutrients, most studies have not reported significant differences between chronotypes in the daily consumption of carbohydrates, proteins and fats [56]. Even more limited evidence is available for fibre and micronutrients [54. The greatest concordance of results is for sucrose consumption, which is significantly higher in evening subjects [75,76].

Analysing the consumption of specific food groups, a higher intake of sweet food and beverages was observed in evening subjects [75,76]. The latter usually joint with other unhealthy eating practices, such as lower consumption of vegetables and higher intake of caffeine and alcohol. Interestingly, some studies have revealed that alcohol and caffeine consumption may increase the predisposition to the evening chronotype [77,78], probably because subjects who go to bed later are more likely to engage in “evening habits”, including drinking [79]. Some studies also revealed that evening chronotypes consume significantly more alcoholic beverages after 8 p.m. than morning and intermediate chronotypes [76].

During the past two years, research has also begun to assess whether there is a chronotype influence on adherence to specific dietary patterns such as the Mediterranean diet (MD). MD is characterised by high consumption of plant foods, moderate consumption of fish, dairy products, and eggs, and low consumption of meat and meat products [80]. Thanks to its composition, it is globally recognized as one of the best diets to prevent cardiometabolic diseases and reduce morbidity and mortality from all causes [81]. Most of the studies that have recently evaluated the relationship between chronotype and MD have been conducted in Spain and Italy [66,71,82–84]. All of these studies associated morning subjects with a higher adherence to MD, mainly due to a high consumption of fruit, legumes, olive oil and a reduced consumption of meat and meat products. Of particular interest are the results of De Amicis et al., who associated morning people with significantly higher adherence to MD and lower waist circumference and visceral fat values than evening subjects [83]. There are several potential mechanisms that may predispose evening persons to be less adherent to a healthy diet, including social jet lag [26,79], and different personality traits among chronotypes. In fact, it was observed that evening subjects tend to be less conscientious and have less self-control than the other chronotypes [76].

Regarding the link between diet quality, microbiota and circadian rhythm, Leone et al. were among the first to suggest that “what we eat” can disrupt the circadian oscillations [6]. In fact, they observed that a high-fat diet alters the chronobiology of intestinal microbes. These altered GM oscillations led to an altered production of microbial metabolites, affecting both circadian rhythms and metabolism of the host [6]. In another study, experimental mice exposed to a high-fat diet experienced a more significant decrease in richness and abundance of some GM microbes following weekly light-dark phase reversals than mice given a normal meal [85]. More specifically, mice that consumed the high-fat diet showed a higher ratio of *Firmicutes* and *Bacteroidetes*, a typical imbalance associated with obesity in both rodents and humans [86]. It was also found that consumption of ad libitum high-fat diet in mice determine a shift in food intake, with a higher percentage of total calories consumed during the normal resting period [87]. The summary of animal studies that analyzed the effect of diet quality on circadian rhythms and GM is reported in Table 1.

5. Impact on health status

The multiple mechanisms linking diet to circadian rhythm and GM structure and function provide a novel framework to understand the development of numerous chronic diseases associated with diet-related chrono-disruption and dysbiosis, as showed in Fig. 3.

5.1. Cardiovascular risk

Cardiovascular disease (CVD) is a globally leading cause of high morbidity and mortality. It is a complex disease with a multifactorial aetiology, and the potential role of

Table 1 Summary of animal studies that analyzed the effect of diet quality on circadian rhythms and gut microbiota.

Study	Animal model information	Type of diet	Circadian manipulation	Outcomes
Leone et al., 2015 [6]	9 Male mice C57BL/6J Germ free, conventionalized, conventionally raised SPF 8–10 week old	High fat diet	No circadian manipulation	Induction of Bmal1 and Clock gene expression during the dark phase Reduction of microbial oscillation Reduction of SCFAs prosecution and increase of hydrogen sulphide
Kohsaka et al., 2007 [87]	10 Male mice C57BL/6J 6 week old	High fat diet	12 h light/12 h dark	Higher percentage of daily food intake during the rest period Expression of Bmal1 and Per2 was reduced, in both fat and liver
Tahara et al., 2018 [88]	167 Male mice C57BL/6J	SCFAs and high fibre	12 h light/12 h dark	SCFAs caused phase advance in the peripheral clock High fibre diet speeds the clock entrainment induced by feeding
Voigt et al., 2014 [85]	33 Male mice C57BL/6J Wild type 6–8 week old	High fat and high sugar diet	12 h shift of the light-dark cycle	Reduction of microbial diversity Alteration of microbial composition: ↑ Firmicutes and Ruminococcacea ↓ Bacteroidetes and Lactobacillus
Zarrinpar et al., 2014 [61]	24 Male mice C57BL/6 Wild type 12 week old	High fat diet	Time restricted feeding (TRF)	Higher percentage of daily food intake during the rest period Reduction of microbial oscillation Alteration of microbial composition:Ruminococcacea Lactobacillus and Lactocossus

SCFAs = short fatty acids; SPF = specific-pathogen-free
↑ Increase ↓ Decrease

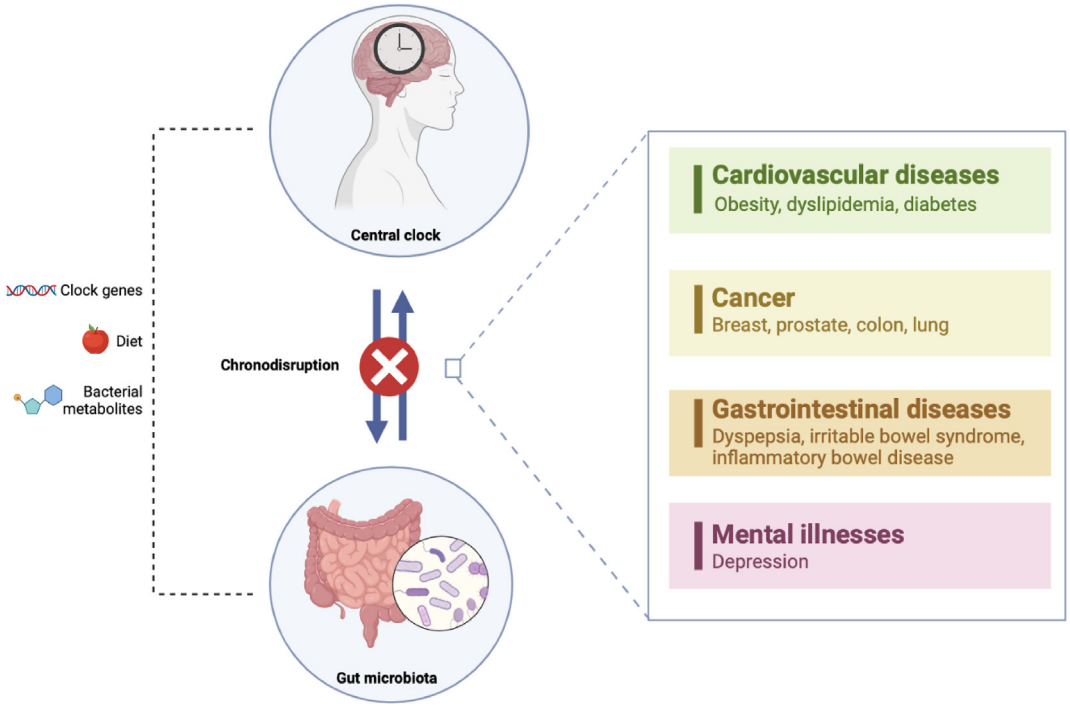

Figure 3 Chronic diseases associated with an alteration of circadian rhythms and gut dysbiosis.

circadian rhythms and microbial composition in its pathogenesis has only recently been hypothesised.

The latest evidence in chrono-nutrition associated evening subjects with a worse cardiometabolic profile compared to other chronotypes. Recent meta-analysis results associated subjects with an evening chronotype with higher concentrations of LDL-cholesterol, triglycerides, fasting blood glucose and glycated haemoglobin compared to morning people [89]. As previously reported, evening subjects tend to eat later than morning subjects and this has a significant impact on the lipid profile, particularly on triglyceride concentrations [90]. In addition to eating meals late, evening persons have been associated with skipping some meals, especially breakfast, which may result in poorer glycaemic control and an increased risk of type 2 diabetes [91].

Another more recent hypothesis suggests that in a condition of disruption of circadian rhythms due to irregularity and late consumption of meals, the rhythmicity of the gut microbiota is altered. As Reitmer et al. showed in a study of a large German cohort, this loss of intestinal microbial rhythmicity is strongly associated with type 2 diabetes [92].

5.2. Cancer risk

A growing body of evidence has associated evening subjects with an increased risk of different cancer types, such as breast, prostate and colon [19,93,94]. The most accredited theory is that i) the direct functions' disruption of circadian clock genes that control cell proliferation, or ii) the disruptions of clock-controlled settings such as sleep disturbances, may increase the cancer risk [93,95]. Furthermore, the circadian disruption may promote the survival of cancer cells by making them more adept at utilising available energy sources [96]. A dysbiosis condition, often associated with the chrono-circadian alteration as seen above, can also have a significant impact on carcinogenesis [97]. As noted recently by Gui and colleagues, patients with lung cancer show low levels of butyrate-producing bacteria, such as *Clostridium leptum*, *Faecalibacterium prausnitzii*, *Ruminococcus* and *Clostridial* cluster [98]. In fact, the anti-tumor function performed by short-chain fatty acids is well documented and it has recently been defined that even bile acids can reduce tumor cells' proliferation by 10−20% and inhibit the epithelial-mesenchymal cell transition [98].

5.3. Irritable bowel syndrome (IBS)

Reduced production of SCFAs by gut microbes and an alteration of circadian rhythms may also favour the onset of several gastrointestinal diseases, including gastric dyspepsia, IBS and inflammatory bowel disease (IBD). As suggested by the study conducted by Swanson and colleagues on 57 patients with IBD, a misalignment of the circadian clock may be associated with aggressive IBD phenotype and altered GM composition. In particular, a significant decrease in butyrate-producing commensal taxa and an increase in pro-inflammatory bacteria emerged in subjects with a chronically altered and aggressive IBD profile [99].

5.4. Mental disorders

Some mental illnesses, especially depression, are associated with an imbalance between GM and circadian rhythms. A meta-analysis of 36 studies identified a significant positive correlation between evening subjects and depression [100]. This was confirmed by our meta-analysis that reported a significantly higher depression risk of 14% in evening people, compared to morning ones [89]. The probable reason is the altered rhythmic activity of neurotransmitter systems involved in mood regulation, including dopamine and serotonin secretion [101]. More recently, a depression-specific bacterial pattern was identified. It was characterised by a higher abundance of pro-inflammatory species, such as *Enterobacteriaceae* and *Desulfovibrio*, and lower SCFA producing-bacteria, such as *Faecalibacterium,* that may have an impact on the regulation of circadian rhythms, as these metabolites regulate the expression of circadian clock genes [102].

6. Conclusions

In conclusion, there are numerous communication pathways between the circadian host rhythms and the gut microbiota that contribute to this complex two-way system, but researchers have only just begun to identify some of its action mechanisms. Diet appears to play a fundamental role in this interplay, especially the timing of meal consumption and the quality of the dietary regimen. Of course, future studies are needed to better investigate the effect of meal frequency and regularity on the gut microbiota, a field that has been little explored to date.

Considering the current evidence, an alteration of circadian rhythms is closely associated with an alteration of microbial rhythmicity with consequent deleterious effects on host health. In particular, cardiometabolic diseases, certain cancers, irritable bowel disease and depression seem to be strongly influenced by the balance between circadian rhythms and gut microorganisms. A key role in maintaining this balance seems to be attributed to certain microbial metabolites, especially the short-chain fatty acids.

The research that has so far focused on studying the relationship between circadian rhythms and the GM has some limitations, first and foremost the fact that most studies have been conducted on animal models. Therefore, to obtain more conclusive evidence, future studies should be conducted on humans. Moreover, being an emerging field of research, the number of works is rather limited and some studies tend to evaluate the circadian rhythms and the GM separately. However, the results obtained so far are promising and make this area of research interesting to explore to obtain evidence associating chronotype with specific microbial patterns in relation to different pathological frameworks.

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References

[1] St-Onge MP, Ard J, Baskin ML, Chiuve SE, Johnson HM, Kris-Etherton P, Varady K. American heart association obesity committee of the council on lifestyle and cardiometabolic health; council on cardiovascular disease in the young; council on clinical cardiology; and stroke council. Meal timing and frequency: implications for cardiovascular disease prevention: a scientific statement from the American heart association. Circulation 2017;135:e96–121.
[2] Flanagan A, Bechtold DA, Pot GK, Johnston JD. Chrono-nutrition: from molecular and neuronal mechanisms to human epidemiology and timed feeding patterns. J Neurochem 2021;157:53–72.
[3] Butler TD, Gibbs JE. Circadian host-microbiome interactions in immunity. Front Immunol 2020;11:1783.
[4] Witkowski M, Weeks TL, Hazen SL. Gut microbiota and cardiovascular disease. Circ Res 2020;127:553–70.
[5] Thaiss CA, Zeevi D, Levy M, Zilberman-Schapira G, Suez J, Tengeler AC, Abramson L, Katz MN, Korem T, Zmora N, Kuperman Y, Biton I, Gilad S, Harmelin A, Shapiro H, Halpern Z, Segal E, Elinav E. Transkingdom control of microbiota diurnal oscillations promotes metabolic homeostasis. Cell 2014;159:514–29.
[6] Leone V, Gibbons SM, Martinez K, Hutchison AL, Huang EY, Cham CM, Pierre JF, Heneghan AF, Nadimpalli A, Hubert N, Zale E, Wang Y, Huang Y, Theriault B, Dinner AR, Musch MW, Kudsk KA, Prendergast BJ, Gilbert JA, Chang EB. Effects of diurnal variation of gut microbes and high-fat feeding on host circadian clock function and metabolism. Cell Host Microbe 2015;17:681–9.
[7] Fowler S, Hoedt EC, Talley NJ, Keely S, Burns GL. Circadian rhythms and melatonin metabolism in patients with disorders of gut-brain interactions. Front Neurosci 2022;16:825246.
[8] Xie Y, Tang Q, Chen G, Xie M, Yu S, Zhao J, Chen L. New insights into the Circadian Rhythm and its related diseases. Front Physiol 2019;10:682.
[9] Kaczmarek JL, Thompson SV, Holscher HD. Complex interactions of circadian rhythms, eating behaviors, and the gastrointestinal microbiota and their potential impact on health. Nutr Rev 2017;75:673–82.
[10] Erren TC, Reiter RJ. Definition of chronodisruption. J Pineal Res 2009;46:245–7.
[11] Cagampang FR, Bruce KD. The role of the circadian clock system in nutrition and metabolism. Br J Nutr 2012;108:381–92.
[12] Lananna BV, Musiek ES. The wrinkling of time: aging, inflammation, oxidative stress, and the circadian clock in neurodegeneration. Neurobiol Dis 2020;139:104832.
[13] Hirota T, Fukada Y. Resetting mechanism of central and peripheral circadian clocks in mammals. Zool Sci 2004;21:359–68.
[14] Takahashi JS. Transcriptional architecture of the mammalian circadian clock. Nat Rev Genet 2017;18:164–79.
[15] Vallée A, Lecarpentier Y, Guillevin R, Vallée JN. Circadian rhythms, neuroinflammation and oxidative stress in the story of Parkinson's disease. Cells 2020;9:314.
[16] Zheng D, Ratiner K, Elinav E. Circadian influences of diet on the microbiome and immunity. Trends Immunol 2020;41:512–30.
[17] Colombini B, Dinu M, Murgo E, et al. Ageing and low-level chronic inflammation: the role of the biological clock. Antioxidants 2022;11:2228.
[18] Patterson RE, Sears DD. Metabolic effects of intermittent fasting. Annu Rev Nutr 2017;37:371–93.
[19] Hurley S, Goldberg D, Von Behren J, Clague DeHart J, Wang S, Reynolds P. Chronotype and postmenopausal breast cancer risk among women in the California Teachers Study. Chronobiol Int 2019;36:1504–14.
[20] Verma AK, Singh S, Rizvi SI. Aging, circadian disruption and neurodegeneration: interesting interplay. Exp Gerontol 2023;172:112076.
[21] Adan A, Archer SN, Hidalgo MP, Di Milia L, Natale V, Randler C. Circadian typology: a comprehensive review. Chronobiol Int 2012;29:1153–75.
[22] Horne JA, Ostberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol 1976;4:97–110.
[23] Bakotic M, Radosevic-Vidacek B, Koscec Bjelajac A. Morningness-eveningness and daytime functioning in university students: the mediating role of sleep characteristics. J Sleep Res 2017;26:210–8.
[24] Adan A, Almirall H. Horne & Östberg morningness-eveningness questionnaire: a reduced scale. Pers Indiv Differ 1991;12:241–53.
[25] Zavada A, Gordijn MC, Beersma DG, Daan S, Roenneberg T. Comparison of the Munich chronotype questionnaire with the Horne-Östberg's morningness-eveningness score. Chronobiol Int 2005;22:267–78.
[26] Wittmann M, Dinich J, Merrow M, Roenneberg T. Social jetlag: misalignment of biological and social time. Chronobiol Int 2006;23:497–509.
[27] Randler C, Díaz-Morales JF, Rahafar A, Vollmer C. Morningness-eveningness and amplitude - development and validation of an improved composite scale to measure circadian preference and stability (MESSi). Chronobiol Int 2016;33:832–48.
[28] Ortiz-Tudela E, Martinez-Nicolas A, Campos M, RolMA, Madrid JA. A new integrated variable based on thermometry, actimetry and body position (TAP) to evaluate circadian system status in humans. PLoS Comput Biol 2010;6:e1000996.
[29] Laing EE, Moller-Levet CS, Poh N, Santhi N, Archer SN, Dijk DJ. Blood transcriptome based biomarkers for human circadian phase. Elife 2017;6:e20214.
[30] Santisteban JA, Brown TG, Gruber R. Association between the Munich chronotype questionnaire and wrist actigraphy. Sleep Disord 2018;2018:5646848.
[31] Montaruli A, Castelli L, Mulè A, Scurati R, Esposito F, Galasso L, Roveda E. Biological rhythm and chronotype: new perspectives in health. Biomolecules 2021;11:487.
[32] Smith MR, Burgess HJ, Fogg LF, Eastman CI. Racial differences in in the human endogenous circadian period. PLoS One 2009;4:e6014.
[33] Goel N, Basner M, Rao H, Dinges DF. Circadian rhythms, sleep deprivation, and human performance. Prog Mol Biol Transl Sci 2013;119:155–90.
[34] Almoosawi S, Vingeliene S, Gachon F, Voortman T, Palla L, Johnston JD, Van Dam RM, Darimont C, Karagounis LG. Chronotype: implications for epidemiologic studies on chrono-nutrition and cardiometabolic health. Adv Nutr 2019;10:30–42.
[35] Jankowski KS. Composite Scale of Morningness: psychometric properties, validity with Munich ChronoType Questionnaire and age/sex differences in Poland. Eur Psychiatr 2015;30:166–71.
[36] Carrier J, Monk TH, Buysse DJ, Kupfer DJ. Sleep and morningness-seveningness in the 'middle' years of life (20-59 y). J Sleep Res 1997;6:230–7.
[37] Broms U, Pitkäniemi J, Bäckmand H, Heikkilä K, Koskenvuo M, Peltonen M, Sarna S, Vartiainen E, Kaprio J, Partonen T. Long-term consistency of diurnal-type preferences among men. Chronobiol Int 2014;31:182–8.
[38] Lee JH, Kim SJ, Lee SY, Jang KH, Kim IS, Duffy JF. Reliability and validity of the Korean version of morningness–eveningness questionnaire in adults aged 20–39 years. Chronobiol Int 2014;31:479–86.
[39] Fabbian F, Zucchi B, De Giorgi A, Tiseo R, Boari B, Salmi R, Cappadona R, Gianesini G, Bassi E, Signani F, Raparelli V, Basili S, Manfredini R. Chronotype, gender and general health. Chronobiol Int 2016;33:863–82.
[40] Frazier K, Chang EB. Intersection of the gut microbiome and circadian rhythms in metabolism. Trends Endocrinol Metabol 2020;31:25–36.
[41] Niccolai E, Boem F, Russo E, Amedei A. The Gut–Brain Axis in the neuropsychological disease model of obesity: a classical movie revised by the emerging director "microbiome". Nutrients 2019;11:156.
[42] Niccolai E, Boem F, Emmi G, Amedei A. The link "Cancer and autoimmune diseases" in the light of microbiota: evidence of a potential culprit. Immunol Lett 2020;222:12–28.
[43] Parolini C, Amedei A. Editorial: gut microbiota and inflammation: relevance in cancer and cardiovascular disease. Front Pharmacol 2020;11:613511.
[44] Liang X, Bushman FD, FitzGerald GA. Rhythmicity of the intestinal microbiota is regulated by gender and the host circadian clock. Proc Natl Acad Sci U S A 2015;112:10479–84.

[45] Choi H, Rao MC, Chang EB. Gut microbiota as a transducer of dietary cues to regulate host circadian rhythms and metabolism. Nat Rev Gastroenterol Hepatol 2021;18:679–89.
[46] Thaiss CA, Levy M, Korem T, et al. Microbiota diurnal rhythmicity programs host transcriptome oscillations. Cell 2016;167:1495–1510.e12.
[47] Ratiner K, Fachler-Sharp T, Elinav E. Small intestinal microbiota oscillations, host effects and regulation-a zoom into three key effector molecules. Biology 2023;12:142.
[48] Mukherji A, Kobiita A, Ye T, Chambon P. Homeostasis in intestinal epithelium is orchestrated by the circadian clock and microbiota cues transduced by TLRs. Cell 2013;153(4):812–27.
[49] Kuang Z, Wang Y, Li Y, et al. The intestinal microbiota programs diurnal rhythms in host metabolism through histone deacetylase 3. Science 2019;365:1428–34.
[50] Martinez KB, Pierre JF, Chang EB. The gut microbiota: the gateway to improved metabolism. Gastroenterol Clin N Am 2016;45:601–14.
[51] Govindarajan K, MacSharry J, Casey PG, Shanahan F, Joyce SA, Gahan CG. Unconjugated bile acids influence expression of circadian genes: a potential mechanism for microbe-host crosstalk. PLoS One 2016;11:e0167319.
[52] Gutierrez Lopez DE, Lashinger LM, Weinstock GM, Bray MS. Circadian rhythms and the gut microbiome synchronize the host's metabolic response to diet. Cell Metabol 2021;33:873–87.
[53] Zwighaft Z, Aviram R, Shalev M, et al. Circadian clock control by polyamine levels through a mechanism that declines with age. Cell Metabol 2015;22:874–85.
[54] Gamble KL, Berry R, Frank SJ, Young ME. Circadian clock control of endocrine factors. Nat Rev Endocrinol 2014;10:466–75.
[55] Charlot A, Hutt F, Sabatier E, Zoll J. Beneficial effects of early time-restricted feeding on metabolic diseases: importance of aligning food habits with the circadian clock. Nutrients 2021;13:1405.
[56] Mazri FH, Manaf ZA, Shahar S, Mat Ludin AF. The association between chronotype and dietary pattern among adults: a scoping review. Int J Environ Res Publ Health 2019;17:68.
[57] Wirth MD, Zhao L, Turner-McGrievy GM, Ortaglia A. Associations between fasting duration, timing of first and last meal, and cardiometabolic endpoints in the national health and nutrition examination survey. Nutrients 2021;13:2686.
[58] Garaulet M, Gómez-Abellán P, Alburquerque-Béjar JJ, Lee YC, Ordovás JM, Scheer FA. Timing of food intake predicts weight loss effectiveness. Int J Obes 2013;37:604–11.
[59] Hatori M, Vollmers C, Zarrinpar A, et al. Time-restricted feeding without reducing caloric intake prevents metabolic diseases in mice fed a high-fat diet. Cell Metabol 2012;15:848–60.
[60] Ye Y, Xu H, Xie Z, et al. Time-restricted feeding reduces the detrimental effects of a high-fat diet, possibly by modulating the circadian rhythm of hepatic lipid metabolism and gut microbiota. Front Nutr 2020;7:596285.
[61] Zarrinpar A, Chaix A, Yooseph S, Panda S. Diet and feeding pattern affect the diurnal dynamics of the gut microbiome. Cell Metabol 2014;20:1006–17.
[62] Carasso S, Fishman B, Lask LS, Shochat T, Geva-Zatorsky N, Tauber E. Metagenomic analysis reveals the signature of gut microbiota associated with human chronotypes. FASEB J 2021;35:e22011.
[63] Pot GK, Almoosawi S, Stephen AM. Meal irregularity and cardiometabolic consequences: results from observational and intervention studies. Proc Nutr Soc 2016;75:475–86.
[64] Phoi YY, Rogers M, Bonham MP, Dorrian J, Coates AM. A scoping review of chronotype and temporal patterns of eating of adults: tools used, findings, and future directions. Nutr Res Rev 2022;35:112–35.
[65] Teixeira GP, Mota MC, Crispim CA. Eveningness is associated with skipping breakfast and poor nutritional intake in Brazilian undergraduate students. Chronobiol Int 2018;35:358–67.
[66] Rodríguez-Muñoz PM, Carmona-Torres JM, Rivera-Picón C, Fabbian F, Manfredini R, Rodríguez-Borrego MA, López-Soto PJ. Associations between chronotype, adherence to the mediterranean diet and sexual opinion among university students. Nutrients 2020;12:1900.
[67] Yu BY, Yeung WF, Ho YS, Ho FYY, Chung KF, Lee RLT, Lam MY, Chen S. Associations between the chronotypes and eating habits of Hong Kong school-aged children. Int J Environ Res Publ Health 2020;17:2583.
[68] Sato-Mito N, Sasaki S, Murakami K, Okubo H, Takahashi Y, Shibata S, Yamada K, Sato K. Freshmen in Dietetic Courses Study II group. The midpoint of sleep is associated with dietary intake and dietary behavior among young Japanese women. Sleep Med 2011;12:289–94.
[69] Friborg O, Rosenvinge JH, Wynn R, Gradisar M. Sleep timing, chronotype, mood, and behavior at an Arctic latitude (69° N). Sleep Med 2014;15:798–807.
[70] Takeuchi H, Yamazaki Y, Oki K, Wada K, Noji T, Kawada T, Nakade M, Krejci M, Harada T. Effects of chronotype and environmental factors upon sleep and mental health in Japanese students aged 18–40 yrs. Biol Rhythm Res 2015;46(6):771–84.
[71] Lotti S, Pagliai G, Asensi MT, Giangrandi I, Colombini B, Sofi F, Dinu M. Morning chronotype is associated with higher adherence to the Mediterranean diet in a sample of Italian adults. Nutr Metabol Cardiovasc Dis 2022. S0939-4753(22)249-6.
[72] Silva CM, Mota MC, Miranda MT, Paim SL, Waterhouse J, Crispim CA. Chronotype, social jetlag and sleep debt are associated with dietary intake among Brazilian undergraduate students. Chronobiol Int 2016;33:740e8.
[73] Lopez-Minguez J, Dashti HS, Madrid-Valero JJ, Madrid JA, Saxena R, Scheer FAJL, Ordoñana JR, Garaulet M. Heritability of the timing of food intake. Clin Nutr 2019;38:767–73.
[74] Venable EB, Fenton KA, Braner VM, et al. Effects of feeding management on the equine cecal microbiota. J Equine Vet Sci 2017;49:113–21.
[75] Kanerva N, Kronholm E, Partonen T, Ovaskainen ML, Kaartinen NE, Konttinen H, Broms U, Männistö S. Tendency toward eveningness is associated with unhealthy dietary habits. Chronobiol Int 2012;29:920–7.
[76] Maukonen M, Kanerva N, Partonen T, Kronholm E, Tapanainen H, Kontto J, Männistö S. Chronotype differences in timing of energy and macronutrient intakes: a population-based study in adults. Obesity 2017;25:608–15.
[77] Rupp TL, Acebo C, Carskadon MA. Evening alcohol suppresses salivary melatonin in young adults. Chronobiol Int 2007;24:463–70.
[78] Robinson D, Gelaye B, Tadesse MG, Williams MA, Lemma S, Berhane Y. Daytime Sleepiness, Circadian Preference, Ca eine Consumption and Khat Use among College Students in Ethiopia. J. Sleep Disord. Treat. Care 2013;3.
[79] Wittmann M, Paulus M, Roenneberg T. Decreased psychological well-being in late "chronotypes" is mediated by smoking and alcohol consumption. Subst Use Misuse 2010;45:15–30.
[80] Dinu M, Lotti S, Pagliai G, Pisciotta L, Zavatarelli M, Borriello M, Solinas R, Galuffo R, Clavarino A, Acerra E, Sofi F. On behalf of the working group of the facciamoComunicAzione project. Mediterranean diet adherence in a sample of Italian adolescents attending secondary school-the "#facciamoComunicAzione" project. Nutrients 2021;13:2806.
[81] Dinu M, Pagliai G, Casini A, Sofi F. Mediterranean diet and multiple health outcomes: an umbrella review of meta-analyses of observational studies and randomised trials. Eur J Clin Nutr 2018;72:30–43.
[82] Zerón-Rugerio MF, Cambras T, Izquierdo-Pulido M. Social jet lag associates negatively with the adherence to the mediterranean diet and body mass index among young adults. Nutrients 2019;11:1756.
[83] De Amicis R, Galasso L, Leone A, Vignati L, De Carlo G, Foppiani A, Montaruli A, Roveda E, Cè E, Esposito F, Vanzulli A, Battezzati A, Bertoli S. Is abdominal fat distribution associated with chronotype in adults independently of lifestyle factors? Nutrients 2020;12:592.
[84] Muscogiuri G, Barrea L, Aprano S, Framondi L, Di Matteo R, Laudisio D, Pugliese G, Savastano S, Colao A. On behalf of the opera prevention project. Chronotype and adherence to the mediterranean diet in obesity: results from the opera prevention project. Nutrients 2020;12:1354.
[85] Voigt RM, Forsyth CB, Green SJ, Mutlu E, Engen P, Vitaterna MH, Turek FW, Keshavarzian A. Circadian disorganization alters intestinal microbiota. PLoS One 2014;9:e97500.
[86] Turnbaugh PJ, Hamady M, Yatsunenko T, et al. A core gut microbiome in obese and lean twins. Nature 2009;457:480–4.
[87] Kohsaka A, Laposky AD, Ramsey KM, et al. High-fat diet disrupts behavioral and molecular circadian rhythms in mice. Cell Metabol 2007;6:414–21.
[88] Tahara Y, Yamazaki M, Sukigara H, et al. Gut microbiota-derived short chain fatty acids induce circadian clock entrainment in mouse peripheral tissue. Sci Rep 2018;8:1395.

[89] Lotti S, Pagliai G, Colombini B, Sofi F, Dinu M. Chronotype differences in energy intake, cardiometabolic risk parameters, cancer, and depression: a systematic review with meta-analysis of observational studies. Adv Nutr 2022;13:269–81.
[90] Morgan L, Hampton S, Gibbs M, Arendt J. Circadian aspects of postprandial metabolism. Chronobiol Int 2003;20:795–808.
[91] Merikanto I, Lahti T, Puolijoki H, Vanhala M, Peltonen M, Laatikainen T, Vartiainen E, Salomaa V, Kronholm E, Partonen T. Associations of chronotype and sleep with cardiovascular diseases and type 2 diabetes. Chronobiol Int 2013;30:470–7.
[92] Reitmeier S, Kiessling S, Clavel T, et al. Arrhythmic gut microbiome signatures predict risk of type 2 diabetes. Cell Host Microbe 2020; 28:258–272.e6.
[93] Kolstad HA. Nightshift work and risk of breast cancer and other cancers–a critical review of the epidemiologic evidence. Scand J Work Environ Health 2008;34:5–22.
[94] Lozano-Lorca M, Olmedo-Requena R, Vega-Galindo MV, Vázquez-Alonso F, Jiménez-Pacheco A, Salcedo-Bellido I, Sánchez MJ, Jiménez-Moleón JJ. Night shift work, chronotype, sleep duration, and prostate cancer risk: CAPLIFE study. Int J Environ Res Publ Health 2020;17:6300.
[95] Fritschi L, Glass DC, Heyworth JS, Aronson K, Girschik J, Boyle T, Grundy A, Erren TC. Hypotheses for mechanisms linking shiftwork and cancer. Med Hypotheses 2011;77:430–6.
[96] Bishehsari F, Voigt RM, Keshavarzian A. Circadian rhythms and the gut microbiota: from the metabolic syndrome to cancer. Nat Rev Endocrinol 2020;16:731–9.
[97] Zhao Y, Liu Y, Li S, Peng Z, Liu X, Chen J, Zheng X. Role of lung and gut microbiota on lung cancer pathogenesis. J Cancer Res Clin Oncol 2021;147:2177–86.
[98] Gui Q, Li H, Wang A, Zhao X, Tan Z, Chen L, Xu K, Xiao C. The association between gut butyrate-producing bacteria and non-small-cell lung cancer. J Clin Lab Anal 2020;34:e23318.
[99] Swanson GR, Kochman N, Amin J, Chouhan V, Yim W, Engen PA, Shaikh M, Naqib A, Tran L, Voigt RM, Forsyth CB, Green SJ, Keshavarzian A. Disrupted circadian rest-activity cycles in inflammatory bowel disease are associated with aggressive disease phenotype, subclinical inflammation, and dysbiosis. Front Med 2022;8:770491.
[100] Au J, Reece J. The relationship between chronotype and depressive symptoms: a meta-analysis. J Affect Disord 2017;218: 93–104.
[101] Taillard J, Sagaspe P, Philip P, Bioulac S. Sleep timing, chronotype and social jetlag: impact on cognitive abilities and psychiatric disorders. Biochem Pharmacol 2021;191:114438.
[102] Simpson CA, Diaz-Arteche C, Eliby D, Schwartz OS, Simmons JG, Cowan CSM. The gut microbiota in anxiety and depression - a systematic review. Clin Psychol Rev 2021;83:101943.