

Chronotype: Implications for Epidemiologic Studies on Chrono-Nutrition and Cardiometabolic Health

Suzana Almoosawi,^{1,2} Snieguole Vingeliene ,³ Frederic Gachon ,^{4,5} Trudy Voortman ,⁶ Luigi Palla ,⁷ Jonathan D Johnston,⁸ Rob Martinus Van Dam ,⁹ Christian Darimont,² and Leonidas G Karagounis ^{2,10,11}

¹Brain, Performance, and Nutrition Research Center, Northumbria University, Newcastle-upon-Tyne, United Kingdom; ²Nestlé Research Center, Institute of Nutritional Sciences, Lausanne, Switzerland; ³Clinical Epidemiology and Biostatistics, School of Medical Sciences, Örebro University, Örebro, Sweden; ⁴School of Life Sciences, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland; ⁵Department of Diabetes and Circadian Rhythms, Nestlé Institute of Health Sciences, Lausanne, Switzerland; ⁶Department of Epidemiology, Erasmus MC, University Medical Center, Rotterdam, Netherlands; ⁷Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom; ⁸Faculty of Health and Medical Sciences, University of Surrey, Guildford, United Kingdom; ⁹Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore; ¹⁰Nestlé Health Science, Vevey, Switzerland; and ¹¹Experimental Myology and Integrative Physiology Cluster, Plymouth Marjon University, Plymouth, United Kingdom

ABSTRACT

Chrono-nutrition is an emerging research field in nutritional epidemiology that encompasses 3 dimensions of eating behavior: timing, frequency, and regularity. To date, few studies have investigated how an individual's circadian typology, i.e., one's chronotype, affects the association between chrono-nutrition and cardiometabolic health. This review sets the directions for future research by providing a narrative overview of recent epidemiologic research on chronotype, its determinants, and its association with dietary intake and cardiometabolic health. Limited research was found on the association between chronotype and dietary intake in infants, children, and older adults. Moreover, most of the evidence in adolescents and adults was restricted to cross-sectional surveys with few longitudinal cohorts simultaneously collecting data on chronotype and dietary intake. There was a gap in the research concerning the association between chronotype and the 3 dimensions of chrono-nutrition. Whether chronotype modifies the association between diet and cardiometabolic health outcomes remains to be elucidated. In conclusion, further research is required to understand the interplay between chronotype, chrono-nutrition, and cardiometabolic health outcomes. *Adv Nutr* 2018;0:1–13.

Keywords: chrono-nutrition, chronotype, nutrition, circadian rhythm, cardiometabolic health, epidemiology

Introduction

In modern societies, individuals often engage in activities that are misaligned with their circadian clock system and the natural rhythm of the light-dark cycle. Increasingly, we find ourselves consuming food at different time points during the day, away from home and therefore at what may be considered, from an evolutionary perspective, physiologically inappropriate times of the day (1). This irregularity in eating

patterns is often enforced by external pressures to conform to social schedules. The resulting misalignment between the sleep-awake, fasting-feeding cycles, and the light-dark cycle subsequently disrupts the natural oscillations of physiologic processes such as glucose, lipid metabolism, and blood pressure, eventually manifesting itself as heightened risk of developing type 2 diabetes and cardiovascular disease (1–4).

One key factor influencing behavioral patterns is chronotype, defined as the circadian typology of an individual. It is a behavioral manifestation of an individual's internal circadian clock system, which can be assessed with the use of multiple methodologies that classify individuals as having, e.g., a morning or an evening chronotype (5–9). Generally, in the absence of environmental stimuli such as light, endogenous circadian clocks oscillate in a manner

The authors reported no funding received for this study.
 Author disclosures: SV, TV, LP, JDJ, and RMVD, no conflicts of interest. SA, FG, CD, and LGK were or are employed by Nestlé.
 Address correspondence to LGK (e-mail: leonidas.karagounis@nestle.com).
 Abbreviations used: DLMO, dim-light melatonin onset; HbA1c, glycated hemoglobin; MCTQ, Munich Chronotype Questionnaire; MEQ, Horne-Östberg Morningness-Eveningness Questionnaire.

approximating a 24-h cycle, hence the term originating from Latin “circa” and “diem” meaning “per day” (5). In an individual presenting with an extreme evening chronotype, the circadian phase of biological rhythms could be shifted by as much as 2–3 h compared with that of an extreme morning chronotype (10). This shift can result in a desynchronization between the period of biological night, as regulated by the intrinsic circadian clock system, and the environmental night governed by the light-dark cycle (11). Accordingly, mounting evidence suggests a potential association between an evening chronotype and increased risk of cardiovascular disease (12, 13) and metabolic disorders including type 2 diabetes (11, 13).

Food is often referred to as a *zeitgeber* (14) because of its ability to regulate various peripheral body clocks and metabolic rhythms (2, 15, 16). Food intake and eating patterns likewise exhibit diurnal rhythms (14, 17), and there is emerging evidence suggesting that the timing of dietary intake, so-called chrono-nutrition, may be influenced by an individual’s chronotype (18–21). In particular, research indicates that individuals presenting with an evening chronotype have a tendency towards consuming fewer and larger meals and delaying food intake due to later awakening time (19, 22). This, in turn, may result in a redistribution of energy and macronutrient intake towards later in the day. The implication of such chronotype-driven differences in timing of energy and macronutrient intake on health is yet to be fully elucidated. In epidemiology, such research is currently hindered by the fact that few cross-sectional surveys or longitudinal cohorts assess chronotype or use dietary assessment methods that permit assessment of the timing of dietary intake. Thus, the relevance and applicability of differing methodologies for determining chronotype in large-scale nutrition surveys and cohorts need to be evaluated. Moreover, considering the potential impact of chronotype on timing of energy and nutrient intake, identifying the most appropriate dietary assessment methods for capturing timing, frequency, and regularity of dietary intake needs to be assessed or developed. To this end, factors such as cost, participant burden, and misreporting continue to affect the scalability of the few epidemiologic studies that deploy traditional paper-based 24-h recalls or food records to capture the 3 time dimensions of eating (23). Observational studies incorporating assessments of timing, frequency, and regularity of food intake could contribute to our understanding of how individual differences in chronotype might affect the association between diet and cardiometabolic health, thereby guiding us towards the development of effective health-promotion strategies. Such research would be timely in shaping our understanding of the implications of chrono-nutrition for public health.

The present review aims to provide an overview of recent epidemiologic research on chronotype, how it is measured, some of its nonmodifiable and modifiable determinants, as well as its association with dietary intake, eating behavior, and cardiometabolic health. The objective of the present

work is to propose future directions of research on chronotype, chrono-nutrition, and cardiometabolic health.

Current Status of Knowledge

Chronotype is a construct that captures an individual’s circadian phenotype, be it a behavioral preference for morningness or eveningness, or a subjective measurement based on the timing of reported behaviors related to the sleep-awake cycle (8, 9, 24). This circadian phenotype is orchestrated by the evolutionarily acquired circadian clock system (25). This circadian clock system is organized in a hierarchic manner with a master pacemaker located in the suprachiasmatic nucleus of the hypothalamus which synchronizes peripheral oscillators present in nearly all body cells (25). Chronotype is believed to be influenced by an individual’s master circadian clock (24), and there is evidence to suggest that the underlying distribution of chronotypes follows a normal bell shape, with tail ends reflecting extreme morning and evening chronotypes (6).

Multiple measures exist enabling the assessment of chronotype, ranging from biological measures such as dim-light melatonin onset (DLMO) to questionnaires based on self-reported information. Currently, the most reliable measure of circadian phase in the human master clock is DLMO (26). It involves the measurement of melatonin secretion in blood or saliva samples collected under dim-light conditions in the hours before usual sleep onset. Such sampling procedures may be burdensome in the context of large-scale studies, because they require a large set of resources and participant supervision (26). In contrast, the use of urine samples to measure melatonin metabolites is widely reported in epidemiologic studies (27) but is limited because of the poorer urine sample resolution which affects the accuracy of measurement (28). Other potential novel approaches range from the metabolomics and transcriptomics approaches that permit assessment of an individual’s circadian phase with the use of ≥ 1 blood samples under free-living conditions (29, 30), to noninvasive techniques combining activity monitors and body temperature sensors to estimate chronotype based on the combined data on motor activity, body position, and body temperature (31).

Considering the inherent issues with sample collection for DLMO and the need for further research to establish the validity of more novel techniques, the use of validated questionnaires that categorize individuals into differing chronotypes might still be most appropriate for large epidemiologic studies (32). To this end, several questionnaires have been described and their strengths and weaknesses have been reviewed (8, 9, 33). These questionnaires include the Munich Chronotype Questionnaire (MCTQ), the Horne-Östberg Morningness-Eveningness Questionnaire (MEQ), the reduced Morningness-Eveningness Questionnaire, the Composite Scale of Morningness, and the Preferences Scale (8, 9). The MEQ specifically measures the psychological preference for behavior but has been shown to correlate less with DLMO than measures of sleep timing obtained with the MCTQ in one study (34) but not in another (26).

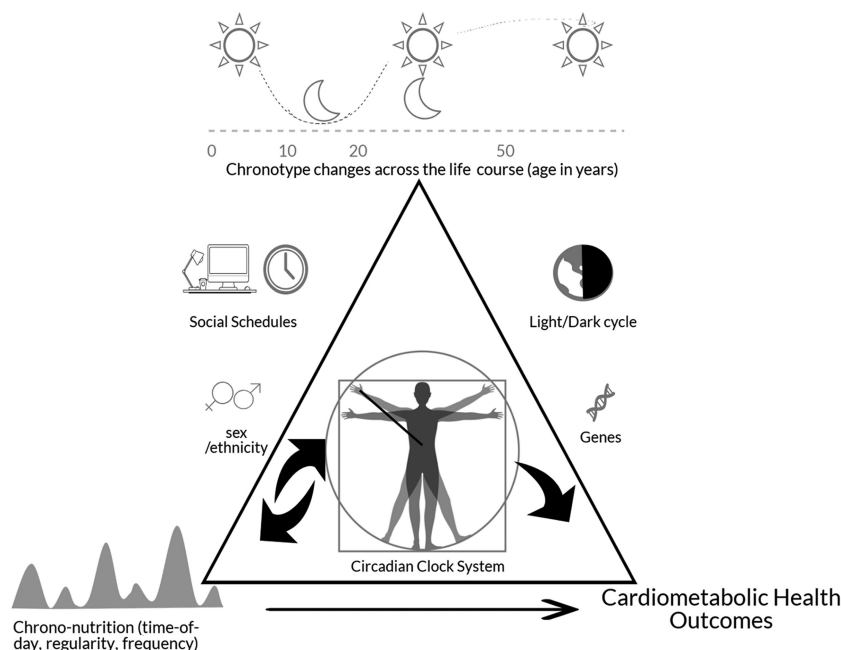


FIGURE 1 Summary of the determinants of chronotype and research framework for examining the association between chronotype, chrono-nutrition, and cardiometabolic health outcomes.

To our knowledge, such correlations have as yet not been investigated in larger samples of the population (26). Overall, the MCTQ provides the advantage of collecting detailed information on sleep-wake behavior that allows for the assessment of phenomena such as social jet lag (difference in mid-sleep timing between school and work days and school-and work-free days) (24, 33). Moreover, the MCTQ has been developed in response to methodological weaknesses that were observed with the use of the MEQ in epidemiologic studies (9) and has been subsequently widely used in genetic and epidemiologic studies (9). Recently, Randler et al. (32) advocated the use of a newly developed questionnaire: the Morningness-Eveningness-Stability Scale Improved. This questionnaire includes 3 dimensions: morningness, eveningness, and measurement of circadian amplitude and stability (32). Other variations of the MEQ have been proposed but remain to be validated in large-scale studies (35).

Determinants of chronotype

Both genetic variations and environmental factors influence the distribution of chronotypes in a given population (24) (Figure 1). Understanding these nonmodifiable and modifiable factors is essential for planning cross-sectional surveys and longitudinal cohorts and identifying covariates of interest when studying how chronotype affects the association between chrono-nutrition and cardiometabolic health.

Concerning the influence of nonmodifiable determinants, rare cases of familial extreme chronotype disorders, such as advanced sleep-phase syndrome, have been described (36, 37). Herein, specific mutations in circadian clock regulators that affect human circadian behavior and the period of the

underlying clock have been identified (38, 39). More recently, genome-wide association studies that used questionnaire-based evaluations of individual chronotypes have characterized important polymorphisms in regions containing known clock genes as well as other loci (40–43). Such genetic variants may underlie some of the interindividual (44) and interethnic differences (45) in the period (or τ) of the endogenous circadian cycle that manifest themselves as differences in chronotype. In relation to ethnicity, data from the UK Biobank Study have demonstrated that individuals with a British black ethnicity are 1.4 times more likely to have a morning chronotype compared with white British (46). This was argued to be due to the shorter τ reported previously in individuals with black ethnicity (45) and may carry important public health implications because individuals with a black ethnicity are more likely to undertake shift work according to some studies (46, 47).

Sex is another example of a nonmodifiable determinant of chronotype. Some studies (48, 49) but not others (9, 24) found a greater prevalence of eveningness in men compared with women, who exhibit greater morningness. The lack of consistency in findings could be due to the absence of information on relevant confounders that could affect a potential association between sex and chronotype. For instance, in women, but not in men, having children was found to be the strongest determinant of morningness. This may imply that having children is a more important social factor influencing a woman's chronotype compared with their partner (49), and potentially an effect modifier that needs to be considered in the analysis of nutritional surveys or cohorts.

The lack of sex differences in some studies could also be attributed to sex differences in sleep duration changing with age and age being an important determinant of chronotype (50) (Figure 1). In children, the morning chronotype is more prevalent, with a shift towards eveningness being observed during puberty (51). By contrast, a shift towards morningness is seen at ~50 y of age (52), indicating that aging influences chronotype (51). In adolescents, various physiologic and environmental factors have been hypothesized to predict a higher prevalence of evening chronotype. For instance, boys whose parents did not enforce a bedtime routine during childhood were more likely to have an evening chronotype during adolescence (53). In relation to older adults, disruptions in circadian biology arising from the aging process are believed to underlie the change in chronotype (54), indicating a potential opportunity for developing personalized nutritional approaches to counteract the physiologic consequences of changes in normal rhythmicity, particularly those related to glucose and lipid metabolism.

Environmental cues such as light, social interactions, and study/work schedules are each thought to entrain the circadian system (Figure 1). Light is believed to be the strongest synchronizer of the master clock, and variations in the light-dark cycle across different latitudes and time zones are thought to influence the circadian system, leading to differences in chronotype across the globe (55). Accordingly, country-specific differences in chronotype have been reported by several studies (46, 56–58). In a cross-country comparison, Germans were found to have a greater prevalence of evening chronotype than were Indians and Slovaks (57). In a comparable study, Turkish adolescents were more likely to have a morning chronotype than were German adolescents (58).

In addition to country-specific differences, variations in chronotype between urban and rural areas within the same country have been observed in Japanese adolescents (53, 59, 60) and in adults in Brazil, India, and elsewhere (61–63). One particular study found that the distribution of chronotype in urban Sao Paulo in Brazil was similar to that in London, despite differences in latitude (61). This led the authors to conclude that the photoperiod might not be the major driver behind determining the distribution of chronotype within a population, but rather social conditions imposed by different cultures or lifestyles (rural or urban) may more likely determine the prevalence of one chronotype over another within a specific population (61).

Indeed, the role of social factors as key modifiable determinants of an individual's chronotype is increasingly recognized (64, 65). For instance, it could be argued that social conditions may influence timing and duration of exposure to artificial or dim light compared with outdoor daylight, which would then entrain the circadian clock system. Consistent with the latter, Roenneberg et al. (66) observed that the timing of exposure to strong outdoor daylight determines the phase of sleep and that every additional hour spent outdoors is associated with 30 min of advance sleep. Hale and Do (67) similarly reported that factors such as noise, ambient light,

and crowding within an urban environment may underlie some of the ethnic differences in sleep duration. Social schedules may also directly interfere with individual sleep preferences, subsequently affecting health (24). Accordingly, in a sample of the general population in Switzerland and Germany, it was observed that individuals with an evening chronotype accumulate sleep debt during the work week, which they compensate for by sleeping longer on weekends (66). By contrast, extreme morning types show a smaller shift in sleep times between work and free days, although they do accumulate sleep debt during weekends in an attempt to keep up with social norms (66). These findings have been replicated in other populations and countries (68, 69). For instance, in a representative sample in Italy of 6631 adolescents aged 14–18 y, eveningness was associated with later bedtime and wake-up time (especially on weekends), shorter time in bed during the week, longer time in bed at the weekend, irregular sleep-wake schedule, and more frequent napping during school days (70). In another study involving 5000 adults aged 30–49 y from New Zealand, chronotype was assessed via the MEQ (71). The sample was balanced in relation to the proportions of the population with a morning or evening chronotype (71). After controlling for ethnicity, sex, and socioeconomic status, work schedules were found to predict chronotype, with night workers being more likely to be “definitely evening-type” and the unemployed less likely to be “moderately morning-type” compared with other workers (71). Such studies suggest that factors including study or work schedules should be considered in epidemiologic studies investigating the relation between chronotype, diet, and health and trying to elucidate the causal pathways linking them.

Chronotype: associations with food and nutrient intake across the life course

It is not clear based on the currently available literature whether or not chronotype is a determinant (causal factor) of eating patterns or food intake or merely a reflection of a complex set of behaviors that also affect diet (associated to diet owing to confounding factors). Furthermore, it may be that chronotype is a consequence of (caused by) the entraining effect of food constituents (16) or eating patterns on the peripheral clocks (15) (Figure 1). The literature on this topic is currently emerging and we are far from understanding the link between chronotype and diet. **Tables 1 and 2** provide a summary of the characteristics and main findings of observational studies that have investigated the association between chronotype and dietary intake or eating behavior.

Studies in infants and young children. To date, there are limited studies that have investigated the association between chronotype and diet in infants and young children. When considered in light of the detrimental influence of evening chronotype on various dimensions of dietary intake and eating behavior in adolescents and adults (20, 24, 74, 75, 80), understanding how variations in chronotype in young

TABLE 1 Summary of characteristics of cross-sectional studies investigating the relation between chronotype and diet¹

Study (reference)	Country	Sample size, population (age)	Chronotype assessment
Maukonen 2016 (72)	Finland	1854 adults (25–74 y)	Horne and Östberg's MEQ
Maukonen et al. (73)	Finland	4421 adults (25–74 y)	Horne and Östberg's MEQ
Mota et al. (74)	Brazil	72 physicians	Horne and Östberg's MEQ
Patterson et al. (75)	United Kingdom	439,933 adults (40–69 y)	Self-Morningness-Eveningness
Silva et al. (76)	Brazil	204 undergraduate students (18–39 y)	Mid-sleep time on free days at the weekend
Suh et al. (77)	Korea	2976 adults (49–79 y)	MEQ
Tran et al. (78)	Thailand	3000 undergraduate students (mean ± SD: 20.3 ± 1.3 y)	Horne and Östberg's MEQ
Whittier et al. (79)	Peru	2581 undergraduate students (mean ± SD: 21.1 ± 2.7 y)	MEQ
Kanerva et al. (80)	Finland	4493 adults (25–74 y)	Horne and Östberg's MEQ
Meule et al. (19)	Germany	471 students (mean ± SD: 23.08 ± 2.68 y)	MEQ
Sato-Mito et al. (81)	Japan	3304 dietetics students (18–20 y)	The midpoint of sleep was calculated with the use of self-reported bedtimes and rise times
Sato-Mito et al. (82)	Japan	112 women (19–36 y)	MEQ
Fleig and Randler (83)	Germany	152 adolescents (11–17 y)	Midpoint of sleep
Nakade et al. (84)	Japan	800 female students (18–29 y)	MEQ
Wittmann et al. (24)	Germany	501 adolescents and adults (14–94 y)	Munich Chronotype Questionnaire
Monk et al. (85)	United States	100 adults (20–59 y)	Composite Scale for Morningness
Adan (86)	Spain	537 students and professionals	MEQ

¹MEQ, Morningness-Eveningness Questionnaire.

children influence the development of dietary habits and eating patterns appears to be imperative.

A recent review concluded that, as early as during fetal development, disruption of circadian rhythms in the mother may adversely affect fetal development and growth (87). One feature of circadian misalignment is the altered timing of nutrient supply to the fetus, which may potentially play a role that is yet to be fully elucidated (87). Most of the evidence on the impact of chronodisruption on gestational development is currently based on animal models, and few studies have investigated how variations in chronotype among mothers influence long-term offspring health in humans (87). The association between maternal disruptions of chronotype such as those induced by modifiable factors and long-term child health also remains to be explored.

After birth, the development of the 24-h circadian rest-activity rhythm is observed in infants as young as 3 wk old and is potentially influenced by a mother's rest-activity cycle (88) and maternal melatonin rhythm (89). Breast milk is also believed to play an important role in determining the circadian phase in infants, which is evident by the circadian variation in nutrient composition of breast milk (90–93) and cytokine concentrations (93).

The few studies that have investigated chronotype in young children, through the use of the Children's Chronotype Questionnaire or DLMO, all have repeatedly observed a greater prevalence of morning chronotype in young children (5, 94, 95). Wickersham (96), in particular, found that >90% of 2-y-old children exhibit a morning chronotype, a proportion that declines to 58% by the time children reach 6 y of age. The implications of the differing chronotype trajectories on dietary behavior and diet quality remain unknown. The factors that determine the shift from morning to evening chronotype also remain to be clarified. It could

be hypothesized that after a certain age, children begin to shift their rhythms to follow parental social schedules and eventually daycare or school schedules, which may interfere with their circadian phase preference and sleep time (97), leading to greater prevalence of the evening chronotype. In this respect, the role of diet in synchronizing the biological rhythms remains to be clarified. An observational study in Japan found that consumption of a breakfast high in tryptophan is associated with greater morningness, as assessed through the use of a morningness-eveningness questionnaire, in infants and elementary school children (0–8 y old) but not in adolescents (>8 y old) (98). In the latter study, the foods with the highest tryptophan content included meat, bread or rice, fish, natto, and milk. A further small-scale study in Japan ($n = 111$) investigated the effect of drinking bovine milk at breakfast on the chronotype of children aged 1–6 y. The dietary intervention involved asking children to drink milk at breakfast and to get up early and to eat breakfast. Children who drank milk at breakfast more than once a week and who ate breakfast 4 times/wk were more likely to shift from an evening to a morning chronotype (99). However, in the latter study, the circadian typology was only assessed via a subjective questionnaire with no objective biological measures such as DLMO. As a result, it is not clear if the intervention induced any changes in the circadian clock mechanism or physiology as opposed to simply changing behavior.

Studies in adolescents and young adults. Several cross-sectional studies indicate that chronotype might be an important determinant of dietary intake in adolescents. Later bed- and rise times have been found to be associated with increased likelihood of caffeinated drink and fast-food consumption and a lower likelihood of dairy product

TABLE 2 Summary of main findings of cross-sectional studies investigating the relation between chronotype and diet¹

Study (reference)	Dietary assessment	Main findings
Maukonen 2016 (72)	24-h food recall	↑ Eveningness ↓ energy and macronutrient intakes in morning, ↑ energy and macronutrient intakes in the evening, ↑ eating occasion frequency and irregularity
Maukonen et al. (73)	Validated FFQ	↑ Eveningness ↓ Baltic Sea dietary pattern score
Mota et al. (74)	3-nonconsecutive-day food diary	↑ Eveningness ↓ sweet and vegetable intakes
Patterson et al. (75)	24-h food recall	Early chronotypes ↑ servings of fruit and vegetables per day relative to later chronotypes
Silva et al. (76)	3-nonconsecutive-day food diary	Chronotype correlated with breakfast and lunch time. Social jetlag ↓ intake of beans, cereals, and pasta and ↑ intake of dairy
Suh et al. (77)	Validated semiquantitative FFQ	Evening types ↑ caffeinated beverages at night, ↑ heavy meals before bedtime
Tran et al. (78)	Nonvalidated FFQ	Evening types ↑ energy drinks
Whittier et al. (79)	Self-administered FFQ	Evening chronotype ↑ alcohol consumption
Kanerva et al. (80)	Validated FFQ	↓ Morningness ↑ intake of alcohol, fat, vitamin D, and sucrose, ↓ intake of carbohydrates, protein, fiber, folic acid, and sodium
Meule et al. (19)	Food Cravings Questionnaire	More morning types than evening types have breakfast. Morning types ↓ feelings of intense desire to eat in the evening compared with the morning. Food deprivation was longer in evening types, particularly in the evening.
Sato-Mito et al. (81)	Validated, self-administered diet history questionnaire	Late midpoint of sleep associated with ↓ percentage energy from protein, carbohydrates, potassium, calcium, magnesium, iron, zinc, vitamin A, vitamin D, thiamin, folate, riboflavin, vitamin B-6, rice, vegetables, pulses, eggs, milk, and milk products. Late midpoint of sleep associated with ↑ percentage energy from alcohol and fat and energy-adjusted intake of noodles, confections, fat and oil, and meat. Subjects with a later midpoint of sleep ate meals later and skipped meals more frequently
Sato-Mito et al. (82)	Validated, self-administered diet history questionnaire	Evening type ↓ energy-adjusted intake of protein, calcium, magnesium, zinc, vitamins (D, riboflavin, and B-6), and vegetables and ↑ intake of noodles. Later midpoint of sleep ↓ energy-adjusted intake of protein, potassium, calcium, magnesium, zinc, vitamins (D, riboflavin, B-6, and B-12), soy, fish, shellfish, and eggs, ↑ intake of noodles, bread, and confections.
Fleig and Randler (83)	Self-administered diet history questionnaire	Later bed- and rise times associated with ↑ caffeinated drinks and fast food, ↓ dairy intake. Mean breakfast time at the weekend was later in late chronotypes because of their later rise times.
Nakade et al. (84)	7-d food logs	Morning types ↓ alcohol and ate breakfast more regularly and earlier than evening types
Wittmann et al. (24)	Nonvalidated questionnaire	↑ Evening chronotype ↑ stimulant consumption
Monk et al. (85)	Consumption of stimulants questionnaire	Morning types were more regular in their lifestyle with respect to event timing
Adan (86)	2-wk 5-item Social Rhythm Metric Diary Interview	Evening types consumed more alcohol, coffee, and cola, whereas morning types consumed more tea

¹ ↑, increased/increase in; ↓, decreased/decrease in.

consumption in a small-scale cross-sectional survey of adolescents (83). Several other studies have reported cross-sectional associations between an evening chronotype and higher consumption of stimulants such as caffeine, energy drinks, sugar-sweetened beverages, and alcohol in adolescents (24) and in college or university students (49, 78, 79, 84). In another study involving students and professionals, individuals with an evening chronotype were found to consume more alcohol, coffee, and cola, whereas morning types consumed more tea (86).

In addition to stimulant consumption, several studies have reported an association between an individual's chronotype and dietary intake of selected food groups, energy, macronutrients, and micronutrients. In a large-scale cross-sectional study involving 3304 female dietetics students from 53 institutions in Japan, the midpoint of sleep was assessed by calculating the midpoint between self-reported bedtimes and rise times (81). A late midpoint of sleep was associated with

a lower percentage of energy from protein and carbohydrates and a lower intake of rice, vegetables, pulses, eggs, and milk products (81). It was, however, associated with a higher percentage of energy from alcohol and fat and higher intake of noodles, confectionery, fats and oils, and meat. In another study, individuals with an evening chronotype likewise had inadequate intakes of several minerals and vitamins including calcium, magnesium, zinc, and vitamin D, riboflavin, and vitamin B-6 (82). More recently, Diederichs et al. (100) defined the term "eveningness in energy intake" and found that it was associated with greater total energy intake over the day in the Dortmund Nutritional and Anthropometric Longitudinally Designed (DONALD) study and may be potentially linked to the shift in chronotype between childhood and adolescence.

Besides dietary intake, studies suggest that individuals with a morning chronotype exhibit more regular eating behavior than individuals with an evening chronotype

(83, 85). Adolescents with an evening chronotype experience greater shifts in timing of breakfast consumption between weekdays and weekends, with later awakening times during weekends corresponding to later breakfast consumption (20). This irregularity in timing of eating based on an individual's chronotype has also been reported in relation to timing of lunch (76, 81). Considering that dietary habits persist from adolescence into adulthood (101), and that cardiometabolic disease risk factors are often formed in childhood and adolescence (102), understanding how chronotype influences diet quality and eating patterns in childhood and adolescence is essential in guiding the development of dietary strategies to prevent chronic disease development. This is particularly true considering that irregularity of meal patterns has been identified as a novel risk factor for cardiometabolic disorders (103).

One key limitation of the previously described studies is the cross-sectional design where associations are reported but causality is not investigated. It remains unclear whether changing an individual's behavioral chronotype might alter their physiologic chronotype or dietary intake. In a randomized crossover design study, 67 adolescents were asked to change bedtimes to create 5-night periods of sleep restriction (6.5 h in bed) compared with healthy sleep (10 h in bed induced by earlier sleep) (104). Caloric intake was measured via the 24-h recall USDA Multiple Pass Method. During the intervention involving healthy sleep, adolescents with a morning chronotype were found to reduce their evening energy intake, whereas no changes in evening energy intake were seen in adolescents with an evening chronotype. The authors concluded that subsequent studies should investigate if, in adolescents with an evening type, extending sleep time by waking up later, rather than advancing bedtime, might have a greater effect on their dietary energy intake (104).

Studies in adults. Comparable with findings in adolescents and young adults, data from the UK Biobank project demonstrate that adults with a morning chronotype consume a mean of 0.25 more servings of fruit and 0.13 more servings of vegetables/d, as assessed through the use of 24-h recalls, than do adults with an evening chronotype (75). Similarly, in a random sample of the Finnish population, chronotype was assessed via a shortened version of the MEQ (80). Dietary data were collected with the use of a validated FFQ. Greater eveningness, as demonstrated by lower morning-to-evening score, was associated with a lower intake of whole grains, rye, potatoes, and vegetables and roots, whereas intake of wine and chocolate was higher. Intakes of alcohol (as a percentage of total energy intake) and sucrose were also higher, whereas intakes of carbohydrates, protein, fiber, folic acid, and sodium were lower with lower morning-to-evening scores (80). In the FINRISK 2007 study, the association between chronotype as assessed via the MEQ and adherence to the Baltic Sea dietary pattern was examined (73). Evening types were found to have a lower adherence to the Baltic Sea dietary pattern and were more likely to be smokers, physically inactive, and have lower perceived health than other chronotypes (73). In

addition to studies on individual foods and dietary patterns, a recent study in Finland investigating the relation between chronotype and chrono-nutrition found that evening types reported lower energy and macronutrient intakes in the morning compared with morning types according to data collected through the use of 48-h food recalls (72). By contrast, in the evening, evening types reported higher intakes of energy, sucrose, fat, and saturated fatty acids than did morning types. These differences were more pronounced in the weekends and evening types reported eating more frequently and irregularly than morning types (72). Consistent with the Finnish study, one study in Japan found that adults with an evening chronotype are more likely to skip meals more frequently and to have a higher probability of watching television at breakfast, lunch, and dinner (81). A further study involving 72 physicians reported that greater morningness was associated with lower consumption of sweets and vegetables as assessed via a 3-d food record and greater leisure-time physical activity (74). Inverse associations between later bedtime, wake time, or midpoint of sleep and time spent in moderate-to-vigorous physical activity or sedentary behavior have been noted in other studies (73, 105). Considering that adults with an evening chronotype skip breakfast more often than do individuals with a morning chronotype (19), and that breakfast skipping has been related to lower physical activity in some studies (106), it remains to be determined whether the observed differences in physical activity between the 2 chronotypes may also be explained by breakfast-consumption habits. Alternatively, it could be argued that modifiable factors such as physical activity and eating behavior might form part of a broader phenotype that may interact cumulatively to affect physiology.

Studies in older adults. Consistent with the findings in adolescents, young adults, and adults, older adults with an evening chronotype have been found to consume more caffeinated beverages at night, eat heavier meals before bedtime, have irregular sleep-wake schedules, and nap more frequently (77). Interestingly, Suh et al. (77) reported specific sociodemographic factors that were associated with the evening chronotype. In particular, elderly individuals with an evening chronotype were more likely to be current smokers, have more sleep disturbances, engage in more sleep-interfering behaviors (i.e., evening caffeine or alcohol consumption, heavy meals before bedtime), and to have lower physical activity (77), emphasizing once more the need to understand the clustering of different lifestyle behaviors. To our knowledge, this is the only study that has investigated the impact of chronotype on diet in the elderly. The association between sleep disturbances and chronotype warrants investigation given that a recent analysis of the Newcastle 85+ study found that abnormal sleep-wake patterns are related to cognitive impairment, disability, depression, and arthritis (107), and given that a further randomized controlled trial study demonstrated that consumption of a tryptophan-rich breakfast could improve sleep in the elderly (18).

Chronotype and cardiovascular diseases

Severe circadian misalignment has long been recognized to be a risk factor for the development of cardiovascular diseases (108). Most of this evidence is derived from studies on different models of shift work, which found that shift workers working during their circadian night are more likely to develop metabolic disturbances (109). This evidence has been replicated in animal models of shift work, recently reviewed (110), as well as in human interventions involving experimentally induced circadian misalignment (111, 112). More recent research findings suggest that mild circadian misalignment, experienced as minor shifts between the sleep-awake cycle in non-shift workers, is also detrimental to health (50, 113). For instance, data from the German MONICA/KORA Myocardial Infarction Registry indicated that specific high-risk subgroups of the population, particularly men, experience a higher risk of acute myocardial infarction during transitions to and from daylight saving time (114). Although chronotype was not assessed in that study, the authors argued that men are more likely to have an evening chronotype and accumulate sleep debt during the time transition, which may lead to acute myocardial infarction. More recent data from the UK Biobank Project have demonstrated that short sleep duration in adults, particularly in those with a late chronotype, is associated with a greater tendency to engage in behaviors related to cardiovascular risk, including smoking, low intake of fruit and vegetables, and sedentary behavior (75). An adverse impact of time transitions on sleep has also been reported in adolescents with an evening chronotype (115).

It is known that cerebrovascular and cardiovascular events exhibit a bimodal pattern (116). Strokes, for instance, follow a circadian rhythm with a major morning peak and a secondary early evening peak. This circadian rhythm is believed to reflect the circadian rhythms of vascular tone, coagulative balance, and blood pressure and may be affected by the temporal patterns of exogenous factors such as eating behavior and physical activity (116). Because chronotype is a determinant of the bimodality of sleep-awake and fasting-feeding cycles, researchers hypothesized that chronotype may correlate with cerebrovascular and cardiovascular disease risk (12, 13). In relation to cerebrovascular events, only 1 small-scale study ($n = 56$) has been conducted so far on stroke, wherein no association between chronotype and stroke incidence was observed, although alterations in chronotype were reported after stroke (12). In relation to cardiovascular risk factors, the evidence appears to be more consistent. In a larger cross-sectional analysis of the national FINRISK 2007 study, which included a representative sample of the Finnish population aged 25–74 y ($n = 6258$), individuals with an evening type had 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 than morning types (13). These associations occurred independently of sleep duration and sufficiency (13). These findings are partially consistent with findings from another small-scale German study ($n = 55$), wherein

individuals with an evening chronotype had lower heart rate variability but higher systolic blood pressure than did morning types (117). Evening chronotype has also been related to lower HDL-cholesterol concentrations (118). Taken together, this evidence implies that chronotype may modulate physiologic processes linked to cardiovascular health, including heart rate, blood pressure, and blood lipid concentrations. The molecular basis of such associations warrants further investigation and may potentially be mediated by lifestyle factors including diet. Moreover, given the limited research in this area, it remains to be determined if variations in chronotype during childhood or adolescence could influence trajectories of cardiovascular disease risk factors later in life, and whether this effect could be modulated by timing of eating among other components of chrono-nutrition.

Chronotype, glucose metabolism, and type 2 diabetes

Glucose metabolism is another example of a physiologic process that follows a circadian rhythm. In humans, glucose tolerance generally declines over the course of the day, reaching a nadir in the evening. This circadian rhythmicity of glucose metabolism arises as a consequence of changes in glucose utilization, insulin sensitivity, and insulin secretion based on the time of day (119). Different forms of shift work are reported to induce multiple forms of circadian misalignment, which are believed to underlie the observed raised postprandial glucose (120) and insulin concentrations in shift workers (121), as well as the increased risk of impaired glucose tolerance (122) and type 2 diabetes observed in epidemiologic studies (81). A recent meta-analysis of 12 observational studies found that among different types of shift work, rotating shift work is associated with increased risk of type 2 diabetes (123). In experimental studies, a combination of circadian misalignment and sleep restriction has been shown to reduce insulin sensitivity (124), increase inflammation (112), and impair glucose tolerance (125). In one particular study, circadian misalignment led some subjects to exhibit postprandial glucose responses akin to the range observed in prediabetes (111). Together, such findings imply that circadian misalignment may predispose individuals to the development of type 2 diabetes.

Indeed, in the FINRISK 2007 study, individuals with an evening chronotype had 2.5-fold greater odds of type 2 diabetes than individuals with a morning chronotype (13). Likewise, in the Korean Genome and Epidemiology Study, evening chronotype, compared with morning chronotype, was associated with a higher prevalence of diabetes and metabolic syndrome after adjustment for age, sex, smoking, alcohol, exercise, occupation, sleep duration, and medications for hypertension, diabetes, and dyslipidemia, and in addition, after adjustment for BMI in the analysis on diabetes (11). Interestingly, in the latter study, sex differences in the association were evident, wherein evening chronotype was related to diabetes in men and to metabolic syndrome in women (11).

Besides possible associations with type 2 diabetes development, chronotype has been related to glycemic control in

individuals with diabetes. In a study in 210 patients with type 2 diabetes who were non-shift workers, patients completed an interview and questionnaires on diabetes history, habitual sleep duration, and sleep timing (126). Chronotype was assessed with the use of the Composite Score of Morningness and with the use of mid-sleep time on free days. Later bedtime on weekends was related to both shorter sleep duration and poorer glycemic control (126).

The mechanisms underlying the association between chronotype and disturbances in glucose metabolism need to be elucidated, but are likely to be multifactorial. For instance, experimental sleep loss, such as induced by circadian misalignment and social jet lag, reduces insulin sensitivity and induces inflammation (127), which may, in turn, modulate insulin sensitivity (128) and is a risk factor for cardiometabolic disturbance (129). Chronotype may also affect dietary intake and eating patterns, which could in the short term influence glucose metabolism and potentially in the long term lead to type 2 diabetes and the metabolic syndrome (130, 131). More recently, variants of circadian clock genes associated with chronotype and sleep homeostasis have been linked to glucose metabolism (132), potentially pointing towards the existence of an underlying network between circadian clocks, chronotype, and glucose homeostasis.

Differences in dietary habits between type 2 diabetes patients with a morning as opposed to an evening chronotype have been observed. Accordingly, in a study involving 194 non-shift-working type 2 diabetes patients attending outpatient clinics, data on sleep timing were collected and midpoint of sleep on free days was selected as an indicator of chronotype (21). Data on breakfast skipping and diet were collected with the use of 24-h dietary recall, whereas glycated hemoglobin (HbA1c) values were obtained from medical records. Overall, 22 (11.3%) type 2 diabetes patients reported skipping breakfast. Those individuals were found to have significantly higher HbA1c concentrations, higher BMI, and later midpoint of sleep than breakfast eaters. Breakfast skipping was related to higher HbA1c values, even after adjusting for age, sex, race, BMI, number of diabetes complications, insulin use, depressive symptoms, perceived sleep debt, and percentage of daily caloric intake at dinner. The authors concluded that breakfast skipping is related to having a later chronotype and that the relation between breakfast skipping and HbA1c is mediated by chronotype (21). In an earlier study, later chronotype and having a large dinner were associated with poorer glycemic control independently of sleep disturbances (133). Whether similar findings could be observed in prediabetes remains to be clarified.

Recommendations

In this review, the applicability of various methodologies to assess chronotype in the context of epidemiology was evaluated, alongside the current epidemiologic evidence of the relation between chronotype, dietary intake, and cardiometabolic health.

In relation to chronotype assessment, the applicability of the different methodologies used to assess chronotype remains to be established. It was evident that the use of subjective questionnaires is a common practice in epidemiologic studies. To this end, the MCTQ is known to provide data on social jet lag and has been reported to correlate better than the MEQ with biological measures such as DLMO in one study (34) but not in another (26). Subsequently, further work is required to assess the correlation between the MCTQ or MEQ and DLMO in large-scale studies. An objective measure of the internal circadian phase might still be necessary to test hypotheses concerning how chronotype influences dietary intake and modifies, confounds, or mediates the relation between timing of energy or nutrient intake and health. In this respect, existing research on metabolomics and transcriptomics or the use of noninvasive methods of measuring circadian phase warrants further investigation (29–31).

As for determinants, a number of nonmodifiable and modifiable factors influencing chronotype were identified. These determinants include genetic factors and environmental factors such as cultural influences, urban lifestyle, environmental factors, family, and social schedules. These factors were selected based on their impact on dietary behavior and should, as such, be considered as potential confounders when examining the association between chronotype and diet. What remains to be clarified are the relative contribution of each of these determinants to chronotype and how the interaction between these different factors affects chronotype over various stages of the life course. Given the cross-sectional nature of most studies, the direction of the causal pathway also remains to be determined. For instance, whether individuals with an evening type generally prefer working night shifts or whether working schedules impose and dictate the circadian typology of an individual. These factors are summarized within Figure 1, which provides a framework for epidemiologic studies investigating the relation between chronotype, chrono-nutrition, and cardiometabolic health outcomes.

A similar point emerges in epidemiologic evidence, wherein most of the evidence of the association between chronotype and diet, or chronotype and cardiometabolic health, is based on cross-sectional studies that do not permit identification of cause and effect or temporality of associations. Studies were also limited by the unrepresentativeness of the samples, mainly due to the small sample size, by selection bias, and by other inherent biases of observational studies. This is not to mention the limited evidence in specific population subgroups such as infants, older adults, and those at risk of developing cardiovascular diseases or type 2 diabetes. Dietary assessment methods varied, with most studies using either FFQs or 24-h food recalls, which either do not capture the timing of consumption or do not permit assessment of the variability in intake between different days. The latter are key issues considering that timing of macronutrient intake has been shown to affect the circadian clock in rodent models, with little data from

human studies (16, 134). Thus, in addition to studying relations with overall diet, it is imperative that surveys and cohort studies adopt dietary assessment methods that permit capturing the temporal aspects of energy and nutrient intake. In this respect, novel advances in the use of technology-based dietary assessment may provide opportunities to better capture the various dimensions of chrono-nutrition (135).

A further limitation is that none of the studies cited herein assessed the context within which foods are consumed at different time points, to identify if there are associations between the socioenvironmental factors and consumption of specific nutrients at a given eating occasion. The implication is that further studies are needed involving population-based samples, more appropriate dietary assessment methods, and more advanced statistical analyses that permit capturing of temporal trends of energy and nutrient intake. The latter is important considering that chronotype may not only influence specific aspects of overall food, energy, and macronutrient intake but might also be related to different dimensions of eating patterns including the timing, frequency, and regularity of meals. Understanding how chronotype influences or is influenced by diet and eating patterns is essential in guiding the development of appropriate dietary strategies to prevent chronic disease development. This is particularly true considering that no study has examined whether chronotype could affect the association between diet and cardiometabolic health across various stages of the life course.

Conclusions

In conclusion, scientific evidence is providing increasing insight into the relation between chronotype, diet, and cardiometabolic health. Overall, cross-sectional studies suggest that evening chronotype is associated with lower intake of fruits and vegetables and higher intake of energy drinks, alcoholic, sugary, and caffeinated beverages, as well as higher energy intake from fat. A limited number of observational studies also demonstrate that evening chronotype is potentially related to changes in timing of food intake, irregular eating, and meal skipping, particularly breakfast skipping. However, further research on the best methods to assess chronotype is required to consolidate the research fields of chronobiology and chrono-nutrition and to examine how chronotype may affect the association between chrono-nutrition and long-term cardiometabolic health. The latter will potentially guide the development of health-promotion strategies aimed at preventing and treating chronic diseases based on an individual's chronotype.

Acknowledgments

The authors' responsibilities were as follows—SA: conceptualized the review, conducted the literature search, and wrote the manuscript; SV: developed the search strategies and critically reviewed the manuscript; SV, FG, LGK, RMVD, CD, and TV: supported the review process; FG: provided critical interpretation of in vitro studies and assisted in writing the manuscript; LGK: contributed to the writing of the manuscript; LGK and JDJ: provided critical interpretation

of the data and reviewed the manuscript; LP: assisted in the review and write-up of the epidemiologic components of the review and development of recommendations for future research; JDJ: assisted in the development of concepts; RMVD and CD: provided critical input into the interpretation of data and revision of the manuscript; TV: provided critical interpretation of dietary data; and all authors: read and approved the final manuscript.

References

1. Almoosawi S, Vingeliene S, Karagounis LG, Pot GK. Chrono-nutrition: a review of current evidence from observational studies on global trends in time-of-day of energy intake and its association with obesity. *Proc Nutr Soc* 2016;75(4):487–500.
2. Johnston JD, Ordovas JM, Scheer FA, Turek FW. Circadian rhythms, metabolism, and chrononutrition in rodents and humans. *Adv Nutr* 2016;7(2):399–406.
3. Bedrosian TA, Fonken LK, Nelson RJ. Endocrine effects of circadian disruption. *Annu Rev Physiol* 2016;78:109–31.
4. St-Onge M-P, Ard J, Baskin ML, Chiuev SE, Johnson HM, Kris-Etherton P, Varady K. Meal timing and frequency: implications for cardiovascular disease prevention: a scientific statement from the American Heart Association. *Circulation* 2017;135(9):e96–121.
5. Roenneberg T, Kuehne T, Pramstaller PP, Ricken J, Havel M, Guth A, Meroow M. A marker for the end of adolescence. *Curr Biol* 2004;14(24):R1038–9.
6. Allebrandt KV, Roenneberg T. The search for circadian clock components in humans: new perspectives for association studies. *Braz J Med Biol Res* 2008;41(8):716–21.
7. Gottlieb DJ, Hek K, Chen TH, Watson NF, Eiriksdottir G, Byrne EM, Cornelis M, Warby SC, Bandinelli S, Cherkas L, et al. Novel loci associated with usual sleep duration: the CHARGE Consortium genome-wide association study. *Mol Psychiatry* 2015;20(10):1232–9.
8. Di Milia L, Adan A, Natale V, Randler C. Reviewing the psychometric properties of contemporary circadian typology measures. *Chronobiol Int* 2013;30(10):1261–71.
9. Levandovski R, Sasso E, Hidalgo MP. Chronotype: a review of the advances, limits and applicability of the main instruments used in the literature to assess human phenotype. *Trends Psychiatry Psychother* 2013;35:3–11.
10. Lack LC, Bailey ME, Lovato N, Wright HR. Chronotype differences in circadian rhythms of temperature, melatonin, and sleepiness as measured in a modified constant routine protocol. *Nat Sci Sleep* 2009;1:1–8.
11. Yu JH, Yun C-H, Ahn JH, Suh S, Cho HJ, Lee SK, Yoo HJ, Seo JA, Kim SG, Choi KM, et al. Evening chronotype is associated with metabolic disorders and body composition in middle-aged adults. *J Clin Endocrinol Metab* 2015;100(4):1494–502.
12. Kantermann T, Meisel A, Fitzthum K, Penzel T, Fietze I, Ulm L. Changes in chronotype after stroke: a pilot study. *Front Neurol* 2014;5:287.
13. 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(4):470–7.
14. Stephan FK. The “other” circadian system: food as a Zeitgeber. *J Biol Rhythms* 2002;17(4):284–92.
15. Wehrens SMT, Christou S, Isherwood C, Middleton B, Gibbs MA, Archer SN, Skene DJ, Johnston JD. Meal timing regulates the human circadian system. *Curr Biol* 2017;27(12):1768–75. e3.
16. Oike H. Modulation of circadian clocks by nutrients and food factors. *Biosci Biotechnol Biochem* 2017;81(5):863–70.
17. Mendoza J. Circadian clocks: setting time by food. *J Neuroendocrinol* 2007;19(2):127–37.
18. Bravo R, Matito S, Cubero J, Paredes S, Franco L, Rivero M, Rodríguez A, Barriga C. Tryptophan-enriched cereal intake improves nocturnal

- sleep, melatonin, serotonin, and total antioxidant capacity levels and mood in elderly humans. *Age* 2013;35(4):1277–85.
19. Meule A, Roeser K, Randler C, Kübler A. Skipping breakfast: morningness-eveningness preference is differentially related to state and trait food cravings. *Eat Weight Disord* 2012;17(4):e304–8.
 20. Randler C, Schaal S. Morningness-eveningness, habitual sleep-wake variables and cortisol level. *Biol Psychol* 2010;85(1):14–18.
 21. Reutrakul S, Hood MM, Crowley SJ, Morgan MK, Teodori M, Knutson KL. The relationship between breakfast skipping, chronotype, and glycemic control in type 2 diabetes. *Chronobiol Int* 2014;31(1):64–71.
 22. Dashti HS, Scheer FAJL, Jacques PF, Lamon-Fava S, Ordovas JM. Short sleep duration and dietary intake: epidemiological evidence, mechanisms, and health implications. *Adv Nutr* 2015;6(6):648–59.
 23. Amoutzopoulos B, Steer T, Roberts C, Cade J, Boushey C, Collins C, Trolle E, De Boer E, Ziauddeen N, van Rossum C. Traditional methods v. new technologies – dilemmas for dietary assessment in large-scale nutrition surveys and studies: a report following an international panel discussion at the 9th International Conference on Diet and Activity Methods (ICDAM9), Brisbane, 3 September 2015. *J Nutr Sci* 2018;7:e11.
 24. Wittmann M, Dinich J, Meroow M, Roenneberg T. Social jetlag: misalignment of biological and social time. *Chronobiol Int* 2006;23(1–2):497–509.
 25. Mohawk JA, Green CB, Takahashi JS. Central and peripheral circadian clocks in mammals. *Annu Rev Neurosci* 2012;35:445–62.
 26. Kantermann T, Sung H, Burgess HJ. Comparing the Morningness-Eveningness Questionnaire and Munich ChronoType Questionnaire to the Dim Light Melatonin Onset. *J Biol Rhythms* 2015;30(5):449–53.
 27. Mirick DK, Davis S. Melatonin as a biomarker of circadian dysregulation. *Cancer Epidemiol Biomarkers Prev* 2008;17(12):3306–13.
 28. Benloucif S, Burgess HJ, Klerman EB, Lewy AJ, Middleton B, Murphy PJ, Parry BL, Revell VL. Measuring melatonin in humans. *J Clin Sleep Med* 2008;4(1):66–9.
 29. Kasukawa T, Sugimoto M, Hida A, Minami Y, Mori M, Honma S, Honma K, Mishima K, Soga T, Ueda HR. Human blood metabolite timetable indicates internal body time. *Proc Natl Acad Sci USA* 2012;109(37):15036–41.
 30. 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.
 31. Ortiz-Tudela E, Martinez-Nicolas A, Campos M, Rol MA, 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(11):e1000996.
 32. Randler C, Diaz-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(7):832–48.
 33. 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(2):267–78.
 34. Kitamura S, Hida A, Aritake S, Higuchi S, Enomoto M, Kato M, Vetter C, Roenneberg T, Mishima K. Validity of the Japanese version of the Munich ChronoType Questionnaire. *Chronobiol Int* 2014;31(7):845–50.
 35. Turco M, Corrias M, Chiaromanni F, Bano M, Salamanca M, Caccin L, Merkel C, Amodio P, Romualdi C, De Pitta C, et al. The self-morningness/eveningness (Self-ME): an extremely concise and totally subjective assessment of diurnal preference. *Chronobiol Int* 2015;32(9):1192–200.
 36. von Schantz M. Phenotypic effects of genetic variability in human clock genes on circadian and sleep parameters. *J Genet* 2008;87(5):513–19.
 37. Jones CR, Campbell SS, Zone SE, Cooper F, DeSano A, Murphy PJ, Jones B, Czajkowski L, Ptacek LJ. Familial advanced sleep-phase syndrome: a short-period circadian rhythm variant in humans. *Nat Med* 1999;5(9):1062–5.
 38. Toh KL, Jones CR, He Y, Eide EJ, Hinz WA, Virshup DM, Ptacek LJ, Fu YH. An hPer2 phosphorylation site mutation in familial advanced sleep phase syndrome. *Science* 2001;291(5506):1040–3.
 39. Xu Y, Padiath QS, Shapiro RE, Jones CR, Wu SC, Saigoh N, Saigoh K, Ptacek LJ, Fu YH. Functional consequences of a CK1delta mutation causing familial advanced sleep phase syndrome. *Nature* 2005;434(7033):640–4.
 40. Hu Y, Shmygelska A, Tran D, Eriksson N, Tung JY, Hinds DA. GWAS of 89,283 individuals identifies genetic variants associated with self-reporting of being a morning person. *Nat Commun* 2016;7:10448.
 41. Allebrandt KV, Teder-Laving M, Akyol M, Pichler I, Muller-Myhsok B, Pramstaller P, Merrow M, Meitinger T, Metspalu A, Roenneberg T. CLOCK gene variants associate with sleep duration in two independent populations. *Biol Psychiatry* 2010;67(11):1040–7.
 42. Jones SE, Tyrrell J, Wood AR, Beaumont RN, Ruth KS, Tuke MA, Yaghootkar H, Hu Y, Teder-Laving M, Hayward C, et al. Genome-wide association analyses in 128,266 individuals identifies new morningness and sleep duration loci. *PLoS Genet* 2016;12(8):e1006125.
 43. Lane JM, Vlasac I, Anderson SG, Kyle SD, Dixon WG, Bechtold DA, Gill S, Little MA, Luik A, Loudon A, et al. Genome-wide association analysis identifies novel loci for chronotype in 100,420 individuals from the UK Biobank. *Nat Commun* 2016;7:10889.
 44. Goel N, Basner M, Rao H, Dinges DF. Circadian rhythms, sleep deprivation, and human performance. *Prog Mol Biol Transl Sci* 2013;119:155–90.
 45. Smith MR, Burgess HJ, Fogg LF, Eastman CI. Racial differences in the human endogenous circadian period. *PLoS One* 2009;4(6):e6014.
 46. Malone SK, Patterson F, Lu Y, Lozano A, Hanlon A. Ethnic differences in sleep duration and morning-evening type in a population sample. *Chronobiol Int* 2016;33(1):10–21.
 47. Jackson CL, Hu FB, Redline S, Williams DR, Mattei J, Kawachi I. Racial/ethnic disparities in short sleep duration by occupation: the contribution of immigrant status. *Soc Sci Med* 2014;118:71–9.
 48. Lehnkering H, Siegmund R. Influence of chronotype, season, and sex of subject on sleep behavior of young adults. *Chronobiol Int* 2007;24(5):875–88.
 49. Leonhard C, Randler C. In sync with the family: children and partners influence the sleep-wake circadian rhythm and social habits of women. *Chronobiol Int* 2009;26(3):510–25.
 50. Roenneberg T, Allebrandt KV, Merrow M, Vetter C. Social jetlag and obesity. *Curr Biol* 2012;22(10):939–43.
 51. Jankowski KS. Composite Scale of Morningness: psychometric properties, validity with Munich ChronoType Questionnaire and age/sex differences in Poland. *Eur Psychiatry* 2015;30(1):166–71.
 52. Carrier J, Monk TH, Buysse DJ, Kupfer DJ. Sleep and morningness-eveningness in the 'middle' years of life (20–59 y). *J Sleep Res* 1997;6(4):230–7.
 53. Takeuchi H, Inoue M, Watanabe N, Yamashita Y, Hamada M, Kadota G, Harada T. Parental enforcement of bedtime during childhood modulates preference of Japanese junior high school students for eveningness chronotype. *Chronobiol Int* 2001;18(5):823–9.
 54. Chen C-Y, Logan RW, Ma T, Lewis DA, Tseng GC, Sibille E, McClung CA. Effects of aging on circadian patterns of gene expression in the human prefrontal cortex. *Proc Natl Acad Sci USA* 2016;113(1):206–11.
 55. Miguel M, Oliveira VC, Pereira D, Pedrazzoli M. Detecting chronotype differences associated to latitude: a comparison between Horne-Östberg and Munich Chronotype questionnaires. *Ann Hum Biol* 2014;41(2):105–8.
 56. Randler C. Morningness-eveningness comparison in adolescents from different countries around the world. *Chronobiol Int* 2008;25(6):1017–28.
 57. Randler C, Prokop P, Sahu S, Haldar P. Cross-cultural comparison of seven morningness and sleep-wake measures from Germany, India and Slovakia. *Int J Psychol* 2015;50(4):279–87.
 58. Horzum MB, Randler C, Masal E, Besuluk S, Onder I, Vollmer C. Morningness–eveningness and the environment hypothesis – a

- cross-cultural comparison of Turkish and German adolescents. *Chronobiol Int* 2015;32(6):814–21.
59. Louzada PR, Sebollela A, Scaramello ME, Ferreira ST. Predissociated dimers and molten globule monomers in the equilibrium unfolding of yeast glutathione reductase. *Biophys J* 2003;85(5):3255–61.
 60. Louzada F, Inacio AM, Souza FH, Moreno CR. Exposure to light versus way of life: effects on sleep patterns of a teenager—case report. *Chronobiol Int* 2004;21(3):497–9.
 61. von Schantz M, Taporoski TP, Horimoto AR, Duarte NE, Vallada H, Krieger JE, Pedrazzoli M, Negrão AB, Pereira AC. Distribution and heritability of diurnal preference (chronotype) in a rural Brazilian family-based cohort, the Baependi study. *Sci Rep* 2015;5:9214.
 62. Nag C, Pradhan RK. Impact of lifestyle on circadian orientation and sleep behaviour. *Sleep Biol Rhythms* 2012;10(2):94–9.
 63. Evans DS, Snitker S, Wu SH, Mody A, Njajou OT, Perlis ML, Gehrman PR, Shuldiner AR, Hsueh WC. Habitual sleep/wake patterns in the Old Order Amish: heritability and association with non-genetic factors. *Sleep* 2011;34(5):661–9.
 64. Levandovski R, Dantas G, Fernandes LC, Caumo W, Torres I, Roenneberg T, Hidalgo MP, Allebrandt KV. Depression scores associate with chronotype and social jetlag in a rural population. *Chronobiol Int* 2011;28(9):771–8.
 65. Carvalho FG, Hidalgo MP, Levandovski R. Differences in circadian patterns between rural and urban populations: an epidemiological study in countryside. *Chronobiol Int* 2014;31(3):442–9.
 66. Roenneberg T, Wirz-Justice A, Mrosovsky M. Life between clocks: daily temporal patterns of human chronotypes. *J Biol Rhythms* 2003;18(1):80–90.
 67. Hale L, Do DP. Racial differences in self-reports of sleep duration in a population-based study. *Sleep* 2007;30(9):1096–103.
 68. Yadav A, Singh S. Relationship of chronotype to sleep pattern in a cohort of college students during work days and vacation days. *Indian J Exp Biol* 2014;52(5):569–74.
 69. Kabrita CS, Hajjar-Muca TA, Duffy JF. Predictors of poor sleep quality among Lebanese university students: association between evening typology, lifestyle behaviors, and sleep habits. *Nat Sci Sleep* 2014;6: 11–18.
 70. Giannotti F, Cortesi F, Sebastiani T, Ottaviano S. Circadian preference, sleep and daytime behaviour in adolescence. *J Sleep Res* 2002;11(3):191–9.
 71. Paine S-J, Gander PH, Travier N. The epidemiology of morningness/eveningness: influence of age, gender, ethnicity, and socioeconomic factors in adults (30–49 years). *J Biol Rhythms* 2006;21(1):68–76.
 72. Mirkka M, Noora K, Timo P, Erkki K, Heli T, Jukka K, Satu M. Chronotype differences in timing of energy and macronutrient intakes: a population-based study in adults. *Obesity* 2017;25(3):608–15.
 73. Maukonen M, Kanerva N, Partonen T, Kronholm E, Konttinen H, Wennman H, Mannisto S. The associations between chronotype, a healthy diet and obesity. *Chronobiol Int* 2016;33(8):972–81.
 74. Mota MC, Waterhouse J, De-Souza DA, Rossato LT, Silva CM, Araujo MB, Tufik S, de Mello MT, Crispim CA. Association between chronotype, food intake and physical activity in medical residents. *Chronobiol Int* 2016;33(6):730–9.
 75. Patterson F, Malone SK, Lozano A, Grandner MA, Hanlon AL. Smoking, screen-based sedentary behavior, and diet associated with habitual sleep duration and chronotype: data from the UK Biobank. *Ann Behav Med* 2016;50(5):715–26.
 76. 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(6):740–8.
 77. Suh S, Yang HC, Kim N, Yu JH, Choi S, Yun CH, Shin C. Chronotype differences in health behaviors and health-related quality of life: a population-based study among aged and older adults. *Behav Sleep Med* 2016;15(5):1–16.
 78. Tran J, Lertmaharit S, Lohsoonthorn V, Pensuksan WC, Rattananupong T, Tadesse MG, Gelaye B, Williams MA. Daytime sleepiness, circadian preference, caffeine consumption and use of other stimulants among Thai college students. *J Public Health Epidemiol* 2014;8(6):202–10.
 79. Whittier A, Sanchez S, Castaneda B, Sanchez E, Gelaye B, Yanez D, Williams MA. Eveningness chronotype, daytime sleepiness, caffeine consumption, and use of other stimulants among Peruvian university students. *J Caffeine Res* 2014;4(1):21–7.
 80. Kanerva N, Kronholm E, Partonen T, Ovaskainen M-L, Kaartinen NE, Konttinen H, Broms U, Männistö S. Tendency toward eveningness is associated with unhealthy dietary habits. *Chronobiol Int* 2012;29(7):920–7.
 81. 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(3): 289–94.
 82. Sato-Mito N, Shibata S, Sasaki S, Sato K. Dietary intake is associated with human chronotype as assessed by both morningness-eveningness score and preferred midpoint of sleep in young Japanese women. *Int J Food Sci Nutr* 2011;62(5):525–32.
 83. Fleig D, Randler C. Association between chronotype and diet in adolescents based on food logs. *Eat Behav* 2009;10(2):115–18.
 84. Nakade M, Takeuchi H, Kurotani M, Harada T. Effects of meal habits and alcohol/cigarette consumption on morningness-eveningness preference and sleep habits by Japanese female students aged 18–29. *J Physiol Anthropol* 2009;28(2):83–90.
 85. Monk TH, Buysse DJ, Potts JM, DeGrazia JM, Kupfer DJ. Morningness-eveningness and lifestyle regularity. *Chronobiol Int* 2004;21(3):435–43.
 86. Adan A. Chronotype and personality factors in the daily consumption of alcohol and psychostimulants. *Addiction* 1994;89(4):455–62.
 87. Serón-Ferré M, Richter HG, Valenzuela GJ, Torres-Farfan C. Circadian rhythms in the fetus and newborn: significance of interactions with maternal physiology and the environment. In: DW Walker, editor. *Prenatal and postnatal determinants of development. Neuromethods*, vol. 109. Berlin: Springer; 2016. p. 147–65.
 88. Nishihara K, Horiuchi S, Eto H, Uchida S. The development of infants' circadian rest-activity rhythm and mothers' rhythm. *Physiol Behav* 2002;77(1):91–8.
 89. Davis FC. Melatonin: role in development. *J Biol Rhythms* 1997;12(6):498–508.
 90. Sánchez CL, Cubero J, Sánchez J, Franco L, Rodríguez AB, Rivero M, Barriga C. Evolution of the circadian profile of human milk amino acids during breastfeeding. *J Appl Biomed* 2013;11(2):59–70.
 91. Lubetzky R, Littner Y, Mimouni FB, Dollberg S, Mandel D. Circadian variations in fat content of expressed breast milk from mothers of preterm infants. *J Am Coll Nutr* 2006;25(2):151–4.
 92. Schneider N, Mutungi G, Cubero J. Diet and nutrients in the modulation of infant sleep: a review of the literature. *Nutr Neurosci* 2018;21(3):151–61.
 93. Morais TC, Honorio-França AC, Silva RR, Fujimori M, Fagundes DLG, França EL. Temporal fluctuations of cytokine concentrations in human milk. *Biol Rhythm Res* 2015;46(6):811–21.
 94. Simpkin CT, Jenni OG, Carskadon MA, Wright KP, Akacem LD, Garlo KG, LeBourgeois MK. Chronotype is associated with the timing of the circadian clock and sleep in toddlers. *J Sleep Res* 2014;23(4):397–405.
 95. Werner H, LeBourgeois MK, Geiger A, Jenni OG. Assessment of chronotype in four- to eleven-year-old children: reliability and validity of the Children's Chronotype Questionnaire (CCTQ). *Chronobiol Int* 2009;26(5):992–1014.
 96. Wickersham L. Time-of-day preference for preschool-aged children. *Chrestomathy* 2006;5:259–68.
 97. Randler C, Fontius I, Vollmer C. Delayed weekend sleep pattern in German infants and children aged 0–6 years. *Biol Rhythm Res* 2012;43(3):225–34.
 98. Harada T, Hirotsu M, Maeda M, Nomura H, Takeuchi H. Correlation between breakfast tryptophan content and morningness-eveningness in Japanese infants and students aged 0–15 yrs. *J Physiol Anthropol* 2007;26(2):201–7.

99. Kawada T, Takeuchi H, Nakade M, Tsuji F, Krejci M, Noji T, Taniwaki N, Harada T. Questionnaire and intervention study on effects of drinking cows' milk at breakfast on the circadian typology and mental health of Japanese infants aged 1 - 6 years. *Nat Sci* 2016;8(9):381.
100. Diederichs T, Perrar I, Roßbach S, Alexy U, Buyken AE. In adolescence a higher 'eveningness in energy intake' is associated with higher total daily energy intake. *Appetite* 2018;128:159–66.
101. Leech RM, McNaughton SA, Timperio A. The clustering of diet, physical activity and sedentary behavior in children and adolescents: a review. *Int J Behav Nutr Phys Act* 2014;11(1):1–9.
102. Matthews KA, Pantesco EJM. Sleep characteristics and cardiovascular risk in children and adolescents: an enumerative review. *Sleep Med* 2016;18:36–49.
103. Pot GK, Almoosawi S, Stephen AM. Meal irregularity and cardiometabolic consequences: results from observational and intervention studies. *Proc Nutr Soc* 2016;75(4):475–86.
104. Beebe DW, Zhou A, Rausch J, Noe O, Simon SL. The impact of early bedtimes on adolescent caloric intake varies by chronotype. *J Adolesc Health* 2015;57(1):120–2.
105. Shechter A, St-Onge MP. Delayed sleep timing is associated with low levels of free-living physical activity in normal sleeping adults. *Sleep Med* 2014;15(12):1586–9.
106. Corder K, van Sluijs E, Steele R, Stephen A, Dunn V, Bamber D, Goodyer I, Griffin S, Ekelund U. Breakfast consumption and physical activity in British adolescents. *Br J Nutr* 2011;105(2):316–21.
107. Anderson KN, Catt M, Collerton J, Davies K, von Zglinicki T, Kirkwood TB, Jagger C. Assessment of sleep and circadian rhythm disorders in the very old: the Newcastle 85+ cohort study. *Age Ageing* 2014;43(1):57–63.
108. Baron KG, Reid KJ. Circadian misalignment and health. *Int Rev Psychiatry* 2014;26(2):139–54.
109. Canuto R, Garcez AS, Olinto MT. Metabolic syndrome and shift work: a systematic review. *Sleep Med Rev* 2013;17(6):425–31.
110. Moran-Ramos S, Baez-Ruiz A, Buijs RM, Escobar C. When to eat? The influence of circadian rhythms on metabolic health: are animal studies providing the evidence? *Nutr Res Rev* 2016;1(2):1–14.
111. Scheer FA, Hilton MF, Mantzoros CS, Shea SA. Adverse metabolic and cardiovascular consequences of circadian misalignment. *Proc Natl Acad Sci USA* 2009;106(11):4453–8.
112. Leproult R, Holmbäck U, Van Cauter E. Circadian misalignment augments markers of insulin resistance and inflammation, independently of sleep loss. *Diabetes* 2014;63(6):1860–9.
113. Roenneberg T, Kantermann T, Juda M, Vetter C, Allebrandt KV. Light and the human circadian clock. In: A Kramer, M Mellow, editors. *Handbook of experimental pharmacology*, vol. 217. Berlin: Springer; 2013. p. 311–31.
114. Kirchberger I, Wolf K, Heier M, Kuch B, von Scheidt W, Peters A, Meisinger C. Are daylight saving time transitions associated with changes in myocardial infarction incidence? Results from the German MONICA/KORA Myocardial Infarction Registry. *BMC Public Health* 2015;15:778.
115. Schneider A-M, Randler C. Daytime sleepiness during transition into daylight saving time in adolescents: are owls higher at risk? *Sleep Med* 2009;10(9):1047–50.
116. Manfredini R, Boari B, Smolensky MH, Salmi R, la Cecilia O, Maria Malagoni A, Haus E, Manfredini F. Circadian variation in stroke onset: identical temporal pattern in ischemic and hemorrhagic events. *Chronobiol Int* 2005;22(3):417–53.
117. Roeser K, Obergefell F, Meule A, Vogele C, Schlarb AA, Kubler A. Of larks and hearts—morningness/eveningness, heart rate variability and cardiovascular stress response at different times of day. *Physiol Behav* 2012;106(2):151–7.
118. Wong PM, Hasler BP, Kamarck TW, Muldoon MF, Manuck SB. Social jetlag, chronotype, and cardiometabolic risk. *J Clin Endocrinol Metab* 2015;100(12):4612–20.
119. Van Cauter E, Polonsky KS, Scheen AJ. Roles of circadian rhythmicity and sleep in human glucose regulation 1. *Endocr Rev* 1997;18(5):716–38.
120. Hampton SM, Morgan LM, Lawrence N, Anastasiadou T, Norris F, Deacon S, Ribeiro D, Arendt J. Postprandial hormone and metabolic responses in simulated shift work. *J Endocrinol* 1996;151(2):259–67.
121. Lund J, Arendt J, Hampton SM, English J, Morgan LM. Postprandial hormone and metabolic responses amongst shift workers in Antarctica. *J Endocrinol* 2001;171(3):557–64.
122. Suwazono Y, Dochi M, Oishi M, Tanaka K, Kobayashi E, Sakata K. Shiftwork and impaired glucose metabolism: a 14-year cohort study on 7104 male workers. *Chronobiol Int* 2009;26(5):926–41.
123. Gan Y, Yang C, Tong X, Sun H, Cong Y, Yin X, Li L, Cao S, Dong X, Gong Y, et al. Shift work and diabetes mellitus: a meta-analysis of observational studies. *Occup Environ Med* 2015;72(1):72–8.
124. Morris CJ, Yang JN, Garcia JJ, Myers S, Bozzi I, Wang W, Buxton OM, Shea SA, Scheer FA. Endogenous circadian system and circadian misalignment impact glucose tolerance via separate mechanisms in humans. *Proc Natl Acad Sci USA* 2015;112(17):E2225–34.
125. Nedeltcheva AV, Scheer FA. Metabolic effects of sleep disruption, links to obesity and diabetes. *Curr Opin Endocrinol Diabetes Obes* 2014;21(4):293–8.
126. Reutrakul S, Siwasaranond N, Nimitphong H, Saetung S, Chirakalwasan N, Ongphiphadhanakul B, Thakkinstian A, Hood MM, Crowley SJ. Relationships among sleep timing, sleep duration and glycemic control in type 2 diabetes in Thailand. *Chronobiol Int* 2015;32(10):1469–76.
127. Rangaraj VR, Knutson KL. Association between sleep deficiency and cardiometabolic disease: implications for health disparities. *Sleep Med* 2016;18:19–35.
128. Esser N, Paquot N, Scheen AJ. Anti-inflammatory agents to treat or prevent type 2 diabetes, metabolic syndrome and cardiovascular disease. *Expert Opin Investig Drugs* 2015;24(3):283–307.
129. Maiorino MI, Bellastella G, Giugliano D, Esposito K. Cooling down inflammation in type 2 diabetes: how strong is the evidence for cardiometabolic benefit? *Endocrine* 2017;55(2):360–5.
130. Almoosawi S, Prynne CJ, Hardy R, Stephen AM. Time-of-day and nutrient composition of eating occasions: prospective association with the metabolic syndrome in the 1946 British birth cohort. *Int J Obes (Lond)* 2013;37(5):725–31.
131. Almoosawi S, Prynne CJ, Hardy R, Stephen AM. Diurnal eating rhythms: association with long-term development of diabetes in the 1946 British birth cohort. *Nutr Metab Cardiovasc Dis* 2013;23(10):1025–30.
132. Kalsbeek A, la Fleur S, Fliers E. Circadian control of glucose metabolism. *Mol Metab* 2014;3(4):372–83.
133. Reutrakul S, Hood MM, Crowley SJ, Morgan MK, Teodori M, Knutson KL, Van Cauter E. Chronotype is independently associated with glycemic control in type 2 diabetes. *Diabetes Care* 2013;36(9):2523–9.
134. Oosterman JE, Kalsbeek A, la Fleur SE, Belsham DD. Impact of nutrients on circadian rhythmicity. *Am J Physiol Regul Integr Comp Physiol* 2015;308(5):R337–50.
135. Boushey CJ, Spoden M, Zhu FM, Delp EJ, Kerr DA. New mobile methods for dietary assessment: review of image-assisted and image-based dietary assessment methods. *Proc Nutr Soc* 2017;76(3):283–94.