THE RELEVANCE OF CHRONOTYPE FOR MEAL TIMING, GLYCEMIC RESPONSE AND HUNGER SENSATIONS

THE CHRONOTYPE AND NUTRITION STUDY

DISSERTATION

zur Erlangung des Grades

Doktor der Naturwissenschaften (Dr. rer. nat.)

an der Fakultät für Naturwissenschaften

am Institut für Ernährung, Konsum und Gesundheit

Universität Paderborn

vorgelegt im April 2024

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DANKSAGUNG

Obwohl ich bereits einen beeindruckenden Einblick in die Forschungsarbeit in Helsinki bekam, kam Forschung als Berufsfeld für mich zunächst nicht infrage. Allerdings hat mich das ausgeschriebene Projekt zum Thema Chronotyp sofort begeistert und zu meiner großen Freude bekam ich die Zusage für eine Doktorandenstelle. Rückblickend bin ich erstaunt, was für eine vielfältige und intensive Reise ich während meiner Zeit als Doktorandin erlebt habe und möchte mich bei allen Mitreisenden ausdrücklich bedanken. Meinen Dank möchte ich für folgende Personen hervorheben:

Der größte Dank geht an Anette Buyken, die zu jeder Zeit ein offenes Ohr für mich hatte und mich mit großen Vertrauen in meine Arbeit hat wachsen lassen. Mich haben Anettes Begeisterung für das Projekt und Pragmatismus bestärkt, nicht nur am Ball zu bleiben, sondern auch in ganz andere Richtungen zu denken. Es war eine besondere Zusammenarbeit, die erste Interventionsstudie am Institut EKG aufzubauen. Außerdem möchte ich mich bei Claus Reinsberger bedanken, der nicht nur als Gutachter fungiert, sondern uns bei der Ernährungsstudie durch seine Kooperation unterstütze. Dadurch war nicht nur die Blutabnahme möglich, sondern wir konnten auch die Aktivitäts- und Ruhephasen der Teilnehmenden mittels Accelerometrie erfassen. Ein weiterer Dank geht an Katja Bolzenius, mit deren Hilfe die Datenauswertung der kontinuierlichen Glukosedaten nicht möglich gewesen wäre. Ich hätte nie gedacht, dass wir hierfür gemeinsam ein Statistikprogramm schreiben. Des Weiteren möchte ich mich bei Janina Goletzke bedanken, da sie für mich eine wertvolle Ansprechperson für die Ernährungsstudie und darüber hinaus war. Ich habe mich sehr gefreut, dass gemeinsam ein weiteres Manuskript zur ChroNu Studie zu entstanden ist. Abschließend möchte ich mich für die Unterstützung aller Co-AutorInnen bedanken, ohne die jene Manuskripte meiner Dissertation nicht so hervorragend gelungen wären.

Ein großer Dank geht natürlich an all die lieben Kolleg*Innen am Institut, vor allem an Bettina Krüger, ohne die die ChroNu Studie undenkbar gewesen wäre. Durch die Zusammenarbeit waren selbst die schwierigsten Aufgaben immer lösbar – so wie 900 Kekse backen, um 300 Probanden zu rekrutieren. Ein weiterer Dank geht auch an Judith Melcher und Jacqueline Karpenstein, die die ChroNu Studie begleitet und im Hintergrund eine unfassbare Koordination während des Projekts geleistet haben. Ihr Engagement war während der ChroNu Studie unerlässlich.

Diese Doktorarbeit ist nicht zuletzt dank dem Rückendwind meiner Familie und meinen Freunden entstanden. Ihr habt mich immer wieder ermutigt und dafür gesorgt, dass ich

aus meinem fachlichen Mikrokosmus rauskomme. Ich danke Micha für seine unfassbare Geduld, seine Unterstützung als Testproband und als jemanden, der nie den Optimismus verliert. Der letzte Dank gebührt meinen Eltern, insbesondere meiner Mutter Iris, für die keine Worte ausreichen, um mich zu bedanken.

PUBLICATIONS

Resulting from this thesis

Peer-reviewed scientific papers[1]

- **Stutz B**, Buyken AE, Schadow AM, Jankovic N, Alexy U, Krueger B. **Associations of chronotype and social jetlag with eating jetlag and their changes among German students during the first COVID-19 lockdown. The Chronotype and Nutrition study**. Appetite 2023; 180:106333

- **Stutz B**, Krueger B, Goletzke J, Jankovic N, Alexy U, Herder C, Dierkes J, Berg-Beckhoff G, Jakobsmeyer R, Reinsberger C, Buyken AE. **Glycemic response to meals with a high glycemic index differs between morning and evening – a randomized cross-over controlled trial among students with early or late chronotype**. European Journal of Nutrition 2024

Under peer-review:

- **Stutz B**[2], Goletzke J, Krueger B, Jankovic N, Alexy U, Herder C, Dierkes J, Jakobsmeyer R, Reinsberger C, Buyken AE. **Association between glucose dips and the feeling of hunger in a dietary intervention study among students with early and late chronotype – a secondary analysis of a randomized cross-over nutrition trial.**

Oral presentations

- **Stutz B**, Goletzke J, Krueger B, Jankovic N, Alexy U, Herder C, Buyken AE. **Association between glycemic dips and the feeling of hunger after a high glycemic index breakfast among students with earlier and later chronotype- a secondary analysis of the ChroNu study.** 14th European Nutrition Conference FENS: Belgrade, Serbia, 14-17th November 2023.

- **Stutz B**, Krueger B, Goletzke J, Jankovic N, Herder C, Alexy U, Buyken AE. **Glycaemic response to meals with a high glycaemic index consumed in the morning and evening differs according to individual chronotype among students with early and late chronotype- ChroNu Study**. 58th EASD Annual Meeting of the European Association for the Study of Diabetes: Stockholm, Sweden, 19 - 23 September 2022. Diabetologia 2022; 65:1–469

- **Stutz B**, Krueger B, Goletzke J, Jankovic N, Alexy U, Buyken AE. **Essen gegen die innere Uhr: Effekte einer morgens bzw. abends verzehrten Mahlzeit mit einem hohen glykämischen Index auf die Glukoseantwort bei Menschen mit früherem und späterem Chronotyp**. 60. DGE-Kongress, Bonn, 2023

[1] Full articles can be found in the appendix B-D
[2] shared first authorship with J. Goletzke

Oral presentations continued

- **Stutz B**, Krueger B, Schadow AM, Jankovic N, Alexy U, Buyken AE. **Einfluss des Chronotypen auf tageszeitliche Unterschiede im Appetit und den second meal effect nach einer Mahlzeit mit einem hohen glykämischen Index – Eine Sekundäranalyse der ChroNu Studie.** 59. DGE-Kongress, 2022

- **Stutz B**, Krueger B, Schadow AM, Jankovic N, Alexy U, Buyken AE. **Erlaubt der Lockdown ein Mahlzeitentiming nach dem circadianen Rhythmus?** 20. Dreiländertagung ‚Nutrition', Zurich, Switzerland, online, June 2021. Aktuelle Ernährungsmedizin 2021; 46:e3

Posters

- **Stutz B**, Krueger B, Goletzke J, Jankovic N, Herder C, Alexy U, Buyken AE. **Hunger and glycaemic response to meals with a high glycaemic index consumed in the morning or evening among students with earlier and later chronotype- ChroNu Study.** The 1st Gothenburg Precision Nutrition Forum, 12th September 2022

During candidature beyond this thesis

Peer-reviewed scientific papers

- Jankovic N, Schmitting S, Krueger B, **Stutz B**, Buyken AE, Nöthlings U, Alexy U. **Misalignment between timing of main energy intake and chronotype in relation to body composition during adolescence – the DONALD Study**. Eur J Nutr **63**, 253–265 (2024).

- Krueger B, **Stutz B**, Jankovic N, Alexy U, Kilanowski A, Libuda L, Buyken AE. **The association of chronotype and social jet lag with body composition in German students: The role of physical activity behaviour and the impact of the pandemic lockdown.** PLoS ONE 2023; 18:e0279620

- Goletzke J, Weber KS, Kössler T, Zaharia O-P, Bódis K, Müssig K, Szendroedi J, Burkart V, **Stutz B**, Nöthlings U, Buyken AE, Roden M; GDS Group. **Relative validity of a glycemic index extended food-frequency questionnaire.** Nutr Metab Cardiovasc Dis 2022; 32:2310–20

Under peer-review:

- Krueger B, **Stutz B**, Jakobsmeyer R, Reinsberger C, Buyken AE. **Relevance of high glycaemic index breakfast for heart rate variability among young students with early and late chronotype.**

SUMMARY

Young adults appear at high risk for an erratic meal pattern, as their delayed circadian phenotype (chronotype) potentially conflicts with social obligations. Consequently, they may eat against their inner clock, which deteriorates glucose homeostasis. Due to individual differences in chronotype, the circadian rhythm of glucose and hunger homeostasis may vary. Thus, depending on daytime and glycemic index of a meal, this could lead to differences in pronounced glucose dips (i.e. levels below baseline), which may affect hunger sensations.

Thus, the **overall aim** of this thesis was to examine the relevance of chronotype for meal timing, glycemic response, and hunger sensations among young university students.

This thesis covers three analyses based on data from the Chronotype and Nutrition Study, which collected data on chronotype and meal timing among 18-25 year-old students before and during the COVID-19 pandemic related lockdown (**analysis I**). From this cohort, those with the earliest and latest chronotype participated in a subsequent controlled cross-over nutrition trial. Participants consumed a high GI meal (GI= 72) at 7 a.m. or 8 p.m., representing a misalignment for late and early chronotypes, respectively. Glycemic response was measured using continuous glucose monitoring (**analysis II**) and subjective hunger was rated on a labelled magnitude satiety scale before each snack/meal (**analysis III**).

Analysis I (*n*= 317 cross-sectional, *n*= 156 prospective analysis) revealed that both a later chronotype and a higher social jetlag were associated with an erratic meal pattern (temporal differences in sleep/ meal timing between work- and work-free days), suggesting a more erratic meal pattern, which diminished during the lockdown. In **analysis II** (*n*= 45), persons with an early chronotype showed the expected higher glycemic responses to a high GI meal when consumed in the evening, while responses were similar in late chronotypes suggesting misalignment to an early breakfast. A secondary analysis of the nutritional trial (**analysis III;** *n*= 45) revealed more pronounced glucose dips after medium GI meals. Hunger increased throughout the day, irrespective of chronotype, yet glucose dips did not predict subsequent subjective hunger among both chronotype groups.

In conclusion, students, notably those with late chronotype, are vulnerable for a more erratic meal pattern and for a deterioration in glucose homeostasis when eating against

their inner clock. Whilst glucose dips may also occur among students, this study does not confirm a relevance of glucose dips for subjective hunger.

Practical recommendations include maintaining consistent meal timings aligned with the inner clock throughout the week. This could be promoted via flexible breaks for eating occasions and more flexibility regarding external obligations, e.g. flexible university schedules.

ZUSAMMENFASSUNG

Junge Erwachsene haben ein erhöhtes Risiko für einen unregelmäßigen Essenrhythmus, da ihr zirkadian bedingter später Phänotyp (Chronotyp) mit sozialen Verpflichtungen kollidieren kann. Dadurch essen sie möglicherweise gegen ihre innere Uhr, was die Glukosehomöstase beeinträchtigen kann. Aufgrund individueller Unterschiede im Chronotyp, kann der zirkadiane Rhythmus der Glukose- und Hungerhomöostase variieren. Folglich könnte dies je nach Tageszeit und glykämischen Index (GI) einer Mahlzeit zu unterschiedlich ausgeprägten Glukosedips (Glukosewerte unterhalb eines Ausgangsniveaus) führen, die das Hungergefühl beeinflussen könnten.

Daher war es **Ziel** dieser Arbeit, die Relevanz des Chronotyps für das Mahlzeitentiming, die Glukoseantwort und das Hungergefühl bei jungen Studierende zu untersuchen.

Diese Arbeit umfasst **drei Analysen**, die auf den Daten der Chronotype and Nutrition basieren, welche Chronotyp und Mahlzeitentiming bei Studierenden im Alter von 18-25 Jahren vor und während des COVID-19 bedingten Lockdowns erhoben hat (**Analyse I**). Aus dieser Kohorte nahmen anschließend jene mit dem frühesten und spätesten Chronotyp an einer kontrollierten cross-over Ernährungsstudie teil, in der sie eine Mahlzeit mit hohem GI um 7:00 Uhr oder 20:00 Uhr verzehrten, wodurch späte bzw. frühe Chronotypen gegen ihre innere Uhr essen. Die Glukoseantwort wurde mittels kontinuierlicher Glukosemessung (**Analyse II**) und das Hungergefühl anhand einer Sättigungsskala gemessen (**Analyse III**).

In **Analyse I** (Querschnitts- und prospektive Analyse: *n*= 317 bzw. n= 156) waren ein späterer Chronotyp und ein höherer sozialer Jetlag mit einem unregelmäßigen Mahlzeitentiming zwischen Arbeits- und arbeitsfreien Tagen assoziiert, das v.a. bei Studierenden mit späterem Chronotyp während des Lockdowns abnahm. In **Analyse II** (*n*= 45) zeigten Studierende mit frühem Chronotyp abends die erwartete höhere Glukoseantwort auf eine Mahlzeit mit hohem GI, während die Glukoseantworten bei jenen mit spätem Chronotyp ähnlich waren. Dies weist darauf hin, dass sie das Frühstück gegen ihre innere Uhr verzehrten. Eine Sekundäranalyse der Ernährungsstudie (**Analyse III**; *n*= 45) ergab, dass Glukosedips nach Mahlzeiten mit mittlerem GI ausgeprägter waren. Bei frühen und späten Chronotypen nahm das Hungerfühl im Tagesverlauf zu; die Glukosedips waren jedoch nicht mit dem Hungergefühl assoziiert.

Zusammenfassend sind Studierende, v.a. jene mit spätem Chronotyp, anfällig für einen unregelmäßigen Essensrhythmus sowie für eine beeinträchtigte Glukoseantwort, wenn sie gegen ihre innere Uhr essen. Obwohl Glukosedips auch bei Studierenden auftreten, waren sie nicht relevant für das Hungergefühl.

Im Alltag sollten Mahlzeiten am besten immer zu den gleichen Tageszeiten während der gesamten Woche und im Einklang mit der inneren Uhr verzehrt werden. Dies könnte durch flexible Essenspausen und eine höhere Flexibilität bei externen Verpflichtungen, z.B. den universitären Stundenplänen, ermöglicht werden.

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ABBREVIATIONS

AUC	Area Under the Curve
BMI	Body Mass Index
CGM	Continuous Glucose Monitoring
CONGA	Continous Overall Net Glycemic Action
COVID-19	Coronavirus Disease
CSM	Composite Scale of Morningness
DLMO	Dimlight-Melatonin Onset
En %	Energy in %
FD	Forced Desynchrony
GI	Glycemic Index
GIP	Glucose-dependent Insulinotropic Polypeptide
GL	Glycemic Load
GLP-1	Glucagon-Like Peptide 1
HbA1c	Glycated hemoglobin A1c
iAUC	Incremental Area Under the Curve
ISO	International Organization for Standardization
LMS	Labeled Magnitude Scale
MAGE	Mean Amplitude of Glucose Exursion
MCTQ	Munich Chronotype Questionnaire
MSF	Midpoint of Sleep
MSFsc	Corrected Midpoint of Sleep
MEQ	Morningness-Eveningness Questionnaire
OA	Original Article
SCN	SupraChiasmatic Nucleus
T2D	Type 2 Diabetes
TRE	Time Restricted Eating
VAS	Visual Analogue scale

1. INTRODUCTION

The global increase of Type 2 Diabetes (T2D) and obesity prevalence is a major public health concern [2,3], with a growing impact on younger adults [4–6]. Circadian misalignment, i.e. living against the inner clock, has emerged as a novel risk factor [7,8], particularly relevant for young adults due to their delayed circadian phenotype (chronotype) [9]. Thus, social schedules, which changed during COVID-19 related lockdown, may interfere with their late chronotype, potentially causing young adults to eat against their inner clock [10], which adversely affects glucose metabolism [11,12]. Moreover, eating late in the evening – characteristic among persons with late chronotype – conflicts with the diurnal deterioration of glucose tolerance [12,13] and may induce circadian misalignment among those with early chronotype. Thus, evening consumption of carbohydrates particularly with a high glycemic index (GI), i.e., causing high blood glucose levels, appears to be detrimental to glucose metabolism [14].

Furthermore, eating late in the evening coincides with the diurnal increase of hunger [15] and may contribute to the rising prevalence of obesity observed between 20 and 30 years of age [16]. Thus, factors affecting hunger are of particular interest, among which reactive hypoglycemia (glucose levels below baseline) has recently been revived [17]. As both hunger and glucose homeostasis are regulated by circadian rhythms [12,14,15,18], these rhythms likely are likely to differ among individuals with early and late chronotype.

This thesis examines the relevance of chronotype for meal timing (before and during the COVID-19- related lockdown), glycemic response when consuming a carbohydrate-rich high GI meal at socially scheduled daytimes, and subjective hunger among young and healthy university students[3]. Due to the study population, the studies cited in this thesis

[3] ChatgGPT was used to improve and check for language and readability of this thesis. ChatGPT was not used for the original articles.

primarily consider healthy adults unless otherwise stated. Given the cumulative nature of this thesis, detailed descriptions of statistical analyses, results, and related discussions are provided in the original articles (OA) in appendices B-D. A glossary of chronobiology-related terms used in this thesis can be found in the appendix A.

2. THEORETICAL BACKGROUND

2.1 Architecture and organization of the circadian system

The physiological processes of most organisms follow an endogenous rhythm [8]. This is structured in self-sustaining cycles (periods) lasting approximately 24 hours and termed “circadian” rhythm. The term derives from the Latin phrase “circa diem”, meaning “about a day” [19]. Circadian rhythms are generated by a hierarchical, multi-oscillatory network: the “central clock” (also termed central pacemaker/master clock) is located in the suprachiasmatic nucleus (SNC) and synchronizes with peripheral clocks in other brain areas and peripheral tissues of e.g. pancreas, liver, pineal gland, and muscle or adipose tissue, ***Figure 1*** [8,20]. The central clock comprises neurons in the SNC in the hypothalamus and is synchronized (entrained) predominantly by light. When light enters the eyes, photoreceptors in the retina transfer the signal to the neurons of the SCN and changes the rhythm of their clock gene expression [19]. SCN neurons transmit this rhythmic change through neurochemical transmitters to other areas of the brain, and through the autonomic nervous system, hormonal signals, and/or modulation of body temperature to other peripheral clocks [19,21]. All circadian clocks are thereby synchronized to the natural diurnal light-dark cycle brought about by the Earth´s rotation [20].

The central clock synchronizes the rhythms of peripheral clocks by a transcriptional-translational negative feedback loop [22,23]. It involves the expression of transcription factors coined “clock genes”, which initiate the expression of other clock genes. These, in turn, inhibit their own expression by repressing their transcription factors. In consequence, their gene products are degraded and a new transcriptional cycle is initiated. In this way, the negative feedback loop generates a self-sustained rhythm of the peripheral clocks, which repeats itself approximately every 24 hours, to maintain the rhythm synchronized by the central clock, and thereby provides feedback to the central

clock [24]. This complex circadian coordination is vital for optimal function of physiological and metabolic processes, thereby maintaining metabolic health [25].

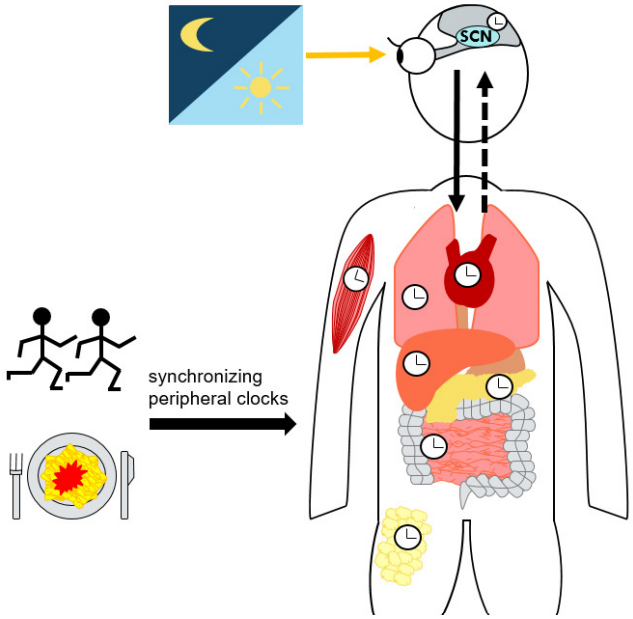

Figure 1: Architecture of the circadian system.
Light activates the central clock in the hypothalamic suprachiasmatic nucleus (SCN) via the retina. The signal is forwarded to peripheral clocks located in the cells of all tissues. Modified from [1,8].

2.1.1. Circadian misalignment

Light, food consumption, and physical activity are considered time cues because they set *phases* [1,8]. *Phases* are the "timing" of a rhythm relative to a minimum and maximum of hormonal levels, within the circadian rhythms of both the central and peripheral clocks, thus entrain (i.e. synchronize) the circadian system, ***Figure 2***. Based on the light-dark cycle, the central clock structures the circadian rhythm into day and night phases through the secretion of melatonin, i.e. low/ high levels induce the circadian day/ night, respectively. Thus, wakefulness, food consumption, and all activities are scheduled to the circadian day, while sleep, fasting, and resting occur mainly during the circadian night – a rhythm to which peripheral clocks are synchronized.

However, the rhythms between the central and peripheral clocks get out of synchronization when environmental and/or behavioral cycles change, which is termed circadian misalignment [8]. This is typical for travel associated jetlag, when the central clock is not yet aligned to the environmental light-dark cycle of the new time zone [26]. While melatonin levels remain high during the environmental day and signal the circadian night, they are low during the environmental night signaling the circadian day [8]. Roenneberg assumes that it takes the circadian system about 1 day for each time zone, i.e. 1 hour, to adjust with the new environmental light-dark rhythm [26].

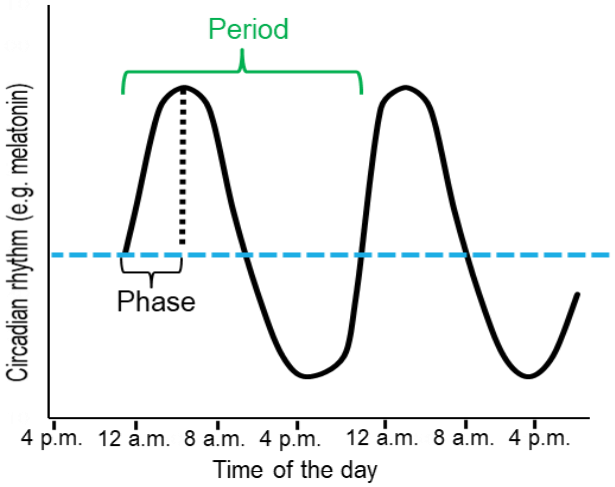

Figure 2: Structure of circadian rhythm.
A diurnal rhythm has a cycle length (period) of approximately ~24 hours, after which it repeats itself. A period is structured in phases, which is the time relative to a minimum or maximum. Modified from [1].

Peripheral clock rhythms are less robust compared to the central clock. Hence, when consuming food during the circadian night it only synchronizes the peripheral clocks without affecting the central clock [20]. This leads to phase-shift of the peripheral clocks so that they anticipate food intake at the newly set mealtime [27], whereas the central clock remains synchronized to the circadian day-night rhythm [8,20,28]. It is hypothesized that the central clock rhythm may not realign the rhythm of the peripheral

clocks set by food intake, nor does it realign the rhythm of the peripheral clocks [19,29]. However, the underlying mechanisms still need to be fully understood.

2.1.2. Markers of the circadian rhythm

Melatonin, cortisol, and core body temperature are regulated by the central clock, thus act as internal time cues as they distribute signals of the central clock to peripheral tissues, thereby synchronizing the peripheral clocks [7,20]. Therefore, they are used as circadian phase markers in research. Melatonin is the most reliable phase marker due to its robust circadian rhythm to behavioral influences, such as sleep, activity, and stress that affect core body temperature and cortisol levels, hence mask their circadian rhythm [7,30]. As this thesis focuses rather on melatonin, cortisol and core body temperature will not be reviewed. Under dim light (< 50 lux), the SCN activates the secretion of melatonin from the pineal gland, i.e. 1-2 hours before habitual sleep onset, while bright light stops the secretion [30,31]. Melatonin peaks in the first half of the sleep phase ~3-4 a.m., diminishes to baseline levels at dawn, and remains low during the circadian day.

In summary, the circadian system is a complex network of peripheral clocks that follow circadian rhythms regulated through the central clock. These clocks are sensitive to environmental and behavioral changes, potentially inducing circadian misalignment, which has emerged as risk factor for diabetes mellitus, obesity, metabolic syndrome, and cardiovascular diseases in the past decade [25].

2.2 Methods to estimate the circadian phenotype

Although light is the main time cue for circadian rhythms, individuals entrain differently to the same environmental light-dark cycle [26]. Thus, some individuals exhibit a more advanced or delayed diurnal rhythm in relation to the local time, resulting in different

circadian phenotypes, i.e. chronotypes, ranging from early chronotypes, so called “larks”, to intermediate types, and late chronotypes, so called “larks” [32]. Individual differences in the diurnal rhythm are reflected by temporal difference in melatonin onset, hence, Dim-Light Melatonin Onset (DLMO) is the most reliable method to assess chronotype [33]. Other methods include accelerometer [34], and questionnaires [35]. DLMO is examined by frequent measures of melatonin levels in blood or saliva under dim-light conditions (< 50 lux) 1-2 hours before habitual sleep onset [31]. As DLMO is laborious and expensive, questionnaires validated to correlate with DLMO were developed for estimating chronotype in epidemiologic settings [35].

Yet, the Munich Chronotype Questionnaire (MCTQ) [9], Horne-Östberg Morningness-Eveningness Questionnaire (MEQ) [36], and Composite Scale of Morningness (CSM) [37] are most commonly used [35]. The MEQ, and CSM reflect the individuals’ psychological preferences in diurnal rhythms related to behavior, such as the daytime preferences for sleep/wake [38]. The questions are answered along scales of degree, and based on the cumulative score of all questions, individuals are categorized as morning, intermediate, or evening persons.

In contrast, the MCTQ queries the actual sleep and wake times to estimate midpoint of sleep (MSF) separately for work- and work-free days [9]. However, persons may adapt their sleep and wake time based on their environment, e.g. by school or work, but may have similar behavioral preferences on how to act on ideal circumstances, e.g. during work-free days [38]. Therefore, the MCTQ corrects the MSF for sleep deficit (MSF_{sc}) – usually accumulated during workdays and compensated by sleeping-in on work-free days [26]. The distribution of chronotype according to their habitual sleep-onset and wake-up timing is illustrated in ***Figure 3*** based on the MCTQ database. Morningness/eveningness will subsequently be referred to in this thesis as early/ late chronotype, respectively.

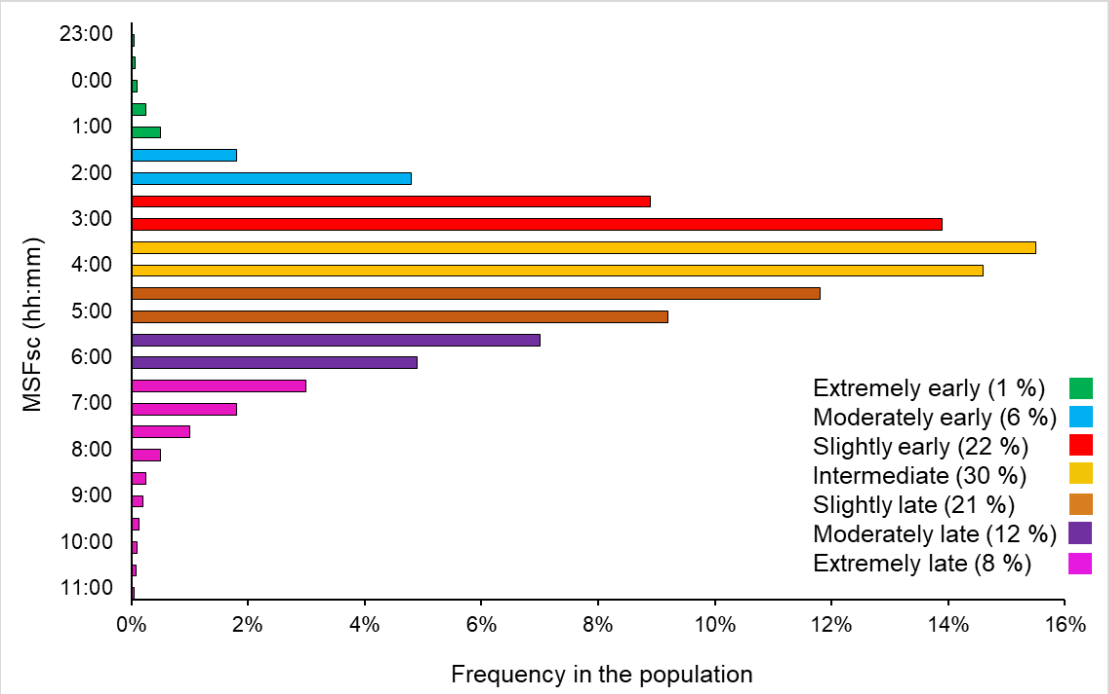

Figure 3: Distribution of chronotype based on the MCTQ database. The chronotype is defined as midpoint of sleep (MSF_{sc}) on work- and workfree days corrected for sleep depth. Modified from [26].

2.2.1. Determinants affecting chronotype

Roenneberg [26] suggests that chronotype is a biological construct as it is influenced by genetics, age, and sex. Genome-wide association studies have identified gene loci associated with chronotype and genetic variants located close to clock genes, which are assumed to be responsible for the inter-individual differences in chronotype [26,39–43]. Moreover, chronotype-associated gene loci correlate with sleep timing, e.g. individuals carrying a high number of morningness related gene loci show earlier sleep timing than those carrying less of these variants [40]. Chronotype also changes in individuals during lifetime: At childhood, individuals have an early chronotype with becoming progressively later during adolescence reaching their biologically latest chronotype at the age of 20 years [44]. From then forward, individuals become progressively earlier chronotypes again. Moreover, chronotype differs by sex [44,45] due to differences in the intrinsic circadian period [46]. Young women experience their biological latest chronotype earlier

than men (at 20 vs. 21 years, respectively). However, men tend to have later chronotype until the age of 50 years, after which differences in chronotype between men and women decrease with age.

However, chronotype is also affected by environmental light [47]. In contrast to artificial light, daylight has a stronger synchronizing effect, owing to differences in light intensities (indoor light < 400 lux vs. mid-daytime light outdoors >10.000 lux). Consequently, greater exposure to outdoor light, and less artificial light advances DLMO, while higher exposure to artificial light and spending most time indoors delays DLMO [48]. Thus, the distribution of early and late chronotypes varies between rural areas and larger cities within the same time zone [47,49]. Moreover, it was observed that increasing exposure to outdoor light in the morning and reducing light exposure in the evening for four weeks advanced DLMO and MSF_{sc} by 2 hours [50].

2.2.2. The conflict between the circadian and social clock

Social obligations, such as school or university schedules, conflict with an individual's chronotype, i.e. when an alarm clock is needed to wake up at a given time [9]. Sleep onset typically remains aligned with chronotype, resulting in sleep depth accumulating during workdays and being compensated for by sleeping-in on work-free days, when individuals are presumably able to live aligned with their inner clock. The temporal difference in the MSF between work- and work-free days is termed **social jetlag**, indicating circadian misalignment akin to the travel associated jetlag (see 2.1.1) [51]. Young adults (18-25 years old) are most vulnerable to social jetlag due to their biologically latest chronotype conflicting with early school/university starting times. Social commitments, such as late lectures at university, may also cause those young adults with early chronotype to stay up later than they prefer to. The high vulnerability to social jetlag is concerning as it is linked to increased body mass index (BMI) [52,53], waist

circumference, glycated hemoglobin (HbA1c) [53], insulin resistance [54], and a two-fold increased risk of both pre-diabetes and T2D [55].

Taken together, the chronotype differs between individuals due to various determinants, and is biologically most delayed among young adults, which may conflict with social schedules. This may result in a more pronounced social jetlag, which is associated with adverse metabolic outcomes.

2.3 Meal timing by chronotype

Considering that differences in sleep-wake timing are most pronounced between individuals with early and late chronotypes (*see **Figure 3***), it can be assumed that those with early chronotype also consume their first and last eating occasions at earlier daytimes compared to those with late chronotype. Moreover, their high vulnerability to social jetlag (see 2.2.2) may also affect their preferred meal timing. Thus, this chapter focuses on the timing of early and late eating occasions and potential misalignment among persons with early and late chronotype (for overview see ***Table 1***).

Among 19-year-old students, those consuming breakfast regularly and earlier in the morning (< 7 a.m.) were more likely persons with an early chronotype, while those who either skipped breakfast or consumed it later (>8:00 a.m.) were late chronotypes [56]. Another study among 3.304 students at similar age reported that those in the earliest chronotype quintile were more likely to consume breakfast daily and at earlier daytimes than students in the late quintile (6:35 a.m. vs. 9:19 a.m. (Q1 vs. Q5)) [57]. Moreover, students with late chronotype had dinner at later daytimes than those with early chronotype, whilst another study reported similar dinner timing [58]. Notably, late chronotype was associated with later dinner timing among students who skipped breakfast >5 times/week in that study. A recently published study among 42-year-old

adults also observed that late chronotypes engaged in late-night snacking more frequently than early chronotypes (3 vs. 2 times/week) [59]. This observation is supported by Yang and Tucker, who noticed a much higher snacking frequency after dinner (5 times/week) among 28 year old adults [60].

As hypothesized, meal timing differs between work- and work-free days. Middle-aged men consumed their first meal >1 hour later on work-free days, which was more pronounced among those with early compared to late chronotypes [61]. In contrast, studies among 20-year-old students observed a more pronounced delay of the first and, to a lesser extent, last eating occasion among those with later chronotype on work-free days [10,62]. Additionally, higher **eating jetlag**, i.e., difference in the eating midpoint between work- and work-free days, was associated with later chronotype and greater social jetlag [10].

2.4 Meal timing and associated metabolic risks

The studies mentioned above suggest that individuals with late chronotype tend to have eating patterns associated with adverse metabolic outcomes. **Firstly**, they more frequently skip breakfast, linked to an increased risk for T2D and obesity [63–66], while late-night eating is associated with similar risks [67,68]. Given that these eating patterns are commonly observed among late chronotypes (*see **Table 1***), it is plausible that they exhibit higher fasting blood glucose levels, HbA1c, and a higher risk for T2D compared to earlier chronotypes according to a meta-analysis of 37 cross-sectional studies [69]. **Secondly**, young students, notably those with late chronotype, tend to shift their breakfast to earlier times in the morning on workdays [10,62]. Eating shortly before or after the circadian sleep phase (e.g. late dinner among early chronotypes or early breakfast among late chronotypes) may entail metabolic consequences such as an increased risk of being overweight [10,70–72], elevated blood pressure, and decreased

insulin sensitivity [73,74], and having T2D [75], **Thirdly**, an early breakfast and late dinner/ snacking extend the eating duration, thereby reducing the fasting duration [10,76], presenting another metabolic burden. A prolonged eating duration (e.g. beyond 12 hours) was associated with obesity [76–78], likely due to a higher calorie intake throughout the day [79,80]. Furthermore, gluconeogenesis is stimulated beyond the eating duration, which decreases glycogen synthesis and promotes the use of glycogen instead of fat stores [28,81]. Additionally, a short fasting period reduces autophagy, which is important to enhance β-cell function. Therefore, prolonged eating duration elevates fasting and postprandial levels of both glucose and insulin, thereby increasing the risk of T2D.

In summary, persons with early and late chronotype differ in their meal timing in addition to sleep-wake rhythm. Moreover, those with late chronotype are vulnerable for eating patterns detrimental to metabolic health, such as eating against the inner clock on workdays, leading to eating jetlag.

Table 1: Cross-sectional studies examining meal timing according to their chronotype.

First author, year	Population characteristics[1]	Exposure: assessment methods[2]	Outcomes[2]	Covariates considered in analysis	Results
Lucassen, 2013 [61] 13	119 obese participants 80 early chronotypes ⌀ age: 59.1 years % female: 76% 39 late chronotypes ⌀ age: 42.7 years % female: 80% (MSF not available)	• Horne and Östberg Morning-Eveningness Questionnaire (MEQ) • 3-day dietary intake diary (one non-working and two workdays)	meal timing of the first eating occasion on work- and non-working days	n/a	**Time of first eating occasion** differed between early and late chronotype both on work- and work-free days: • Workday: 7:17±1:31 a.m. vs. 8:38±1:52 a.m. (p<0.0001) • Work-free day: 8:56±2:30 a.m. vs. 9:59±2:32 a.m. (p trend=0.08)
Nakade, 2009 [56]	800 female students ⌀ age 19.3 years	• Torsvall and Akerstedt MEQ • questionnaires on mealtime regularity in the previous 4 weeks	time and regularity of breakfast consumption	n/a	Direct associations (all p<0.0001) between: • regular breakfast consumption (always) and early chronotype • breakfast skipping and late chronotype • early breakfast time (5:00-6:59 a.m.) and early chronotype • later breakfast time (>8:00 a.m.) and late chronotype
Nitta, 2023 [59]	4626 participants ⌀ age: 42.4 years % Female: 74% ⌀ MSF_{sc}: 950 early (2.3±0:6 a.m.), 1890 intermediate (3.9±0:6 a.m.) 587 late (5.7±0:5 a.m.) chronotypes	• MCTQ • Meal timing via app-based food-logs for 1 month • Questionnaires on breakfast and late-night snack frequency (days/week)	meal timing and frequency among morning, intermediate, evening type stratified by women and men	n/	• Late chronotypes consumed breakfast and dinner later than early chronotypes (breakfast: 8:26±2:04 a.m. vs. 7:06±1:07 a.m.; p<0.001; dinner: 7:27±2:17 p.m. vs. 7:13±1:22 p.m., p<0.001)*/*** • Late chronotypes consumed breakfast less frequently than early chronotypes (5.3±2.4 vs. 6.4±1.6 times/week, p<0.001)*/*** • late chronotypes consumed late-night snacks more frequently than early chronotypes (2.9±2.9 vs. 2.0±2.9 times/week, p<0.001)*/***

Table 1: *continued.*

First author, year	Population, recruitment[1]	Exposure: assessment methods[2]	Outcomes[2]	Covariates considered in analysis	Results
Sato-Mito, 2011 [57]	3304 female students ⌀ age 18.1 years ⌀ MSF_{sc} in quintiles Q1: 2:32±0:23 a.m. Q2: 3:10±0:08 a.m. Q3: 3:37±0:07 a.m. Q4: 4:11±0:13 a.m. Q5: 5:31±0:55 a.m	Questionnaires referring to the previous 4 weeks on: • dietary behavior on weekdays sleep pattern (weekdays)	• meal timing number of skipped meals	residential block, size of residential area, current smoking (yes/no)	• earlier chronotypes (Q1) skipped breakfast less frequently than later chronotypes (<1x/week vs. 2x/week (Q1 vs. Q5), p<0.0001)*** • earlier breakfast time among earlier compared to later chronotypes (⌀6:35± 0:02 a.m. vs. 9:19±0:02 a.m. (Q1 vs. Q5), p<0.0001)*** • later dinner time among later compared to earlier chronotypes (⌀7:19±0:05 p.m. vs. 6:51± 0:06 p.m. (Q5 vs. Q1), p<0.0001)***
Teixeira, 2018 [58]	721 students ⌀ age: 20 years % female: 68% 151 early, 446 intermediate, and 124 late chronotype	Horne and Östberg MEQ Questionnaires on • sleep patterns, meal timing for weekdays and weekends) • frequency per week: breakfast, lunch, dinner	Mealtime Breakfast skipping (breakfast consumption ≤2x/week)	Linear regression: sex, age, physical activity, BMI logistic regression: age, sex, physical activity, calorie intake/kg body weight, sleep duration, SJL	• similar dinner timing among early and late chronotype (8:27±1:45 p.m. vs. 8:45±2:30 p.m., p=0.04)*** • less breakfast skippers among early compared to late chronotypes (15% vs. 27%; p=0.02) • earlier breakfast time among early compared to late chronotypes types (7:20±1:1 a.m. vs. 8:00±1:2 a.m.; p<0.001) • among breakfast skippers: negative association between chronotype and dinner time, i.e., the later chronotype the later dinner time (p=0.04)

Table 1: *continued.*

First author, year	Population, recruitment[1]	Exposure: assessment methods[2]	Outcomes[2]	Covariates considered in analysis	Results
Veronda, 2021 [62]	192 students ⌀ age: 19.4 years Sub-analysis with n=25 persons each with the earliest and latest chronotype	Composite Scale of Morningness The Chrononutrition Profile-Questionnaire	Time of first and last eating event on work- and free days	n/a	Early chronotypes consumed **first eating event** earlier than late chronotypes on both work- and work-free days: • Workday: 9:12±1:50 a.m. vs. 11:12±1:46 a.m. (p<0.001) • Work-free day: 10:00±1:25 a.m. vs. 12:20±0:58 a.m. (p=0.001) Early chronotypes consumed **last eating event** earlier than late chronotypes on both work- and work-free days: • Workday: 7:25±1:29 p.m. vs. 9:11±1:59 p.m. (p=0.001) • Work-free day: 7:52±1:32 p.m. vs. 9:50±1:52 p.m. (p<0.001)
Yang, 2021 [60]	100 participants ⌀ age: 28.4 years Female %: 63% 30 early, 34 intermediate, and 36 late chronotypes	Horne and Östberg MEQ • Questionnaires on demography, anthropometry, sleep • FFQ: snack frequency/ week (previous 4 weeks)	snack frequency and timing	race, age, BMI, sleep quality	• evening types consumed snacks more frequently after dinner than morning types (⌀ 5.3±1.6 times/week vs. 3.7±2.2 times/week, p<0.001)***
Zeron-Rugerio, 2019 [10]	1106 students ⌀ age: 21.0 years Female %:78% ⌀ MSF: 5:17±1:13 a.m. ⌀ SJL: 1.7±1.0 h	MCTQ habitual timing of breakfast/lunch/ dinner on weekends and weekdays	meal timing, eating midpoint on weekdays/weekend, eating jetlag**, breakfast and dinner jetlag	age, sex, nationality, diet quality, sleep duration, physical activity	• Association between higher eating jetlag, breakfast and dinner jetlag with later chronotype (all p<0.00001) and higher SJL (p<0.00001, p<0.00001, <0.001)

Abbreviations: ⌀ average value (mean/median as in original publication); SD, standard deviation; MEQ, Morningness-Eveningness Questionnaire, MSF, midpoint of sleep (o' clock), MSF_{sc}, midpoint of sleep corrected for sleep depth (o' clock), MCTQ, Munich ChronoType Questionnaire, BMI, Body-Mass Index, SJL, social jetlag (see 2.2.2).

[1] n number refers to participants in the final analysis

[2] Only relevant exposures and outcomes are presented * results presented for men only as results are similar for women.

** eating jetlag: difference of the eating midpoint (o' clock) between work- and work-free days.

*** for demonstration only values of earliest and latest chronotype group/quintile are shown.

2.5 Impact of the COVID-19 pandemic related lockdown on the individual's sleep and meal pattern

In early 2020, the sudden global outbreak of the COVID-19 pandemic caused many countries to implement restrictive measures e.g. closing educational institutions, restaurants, and prohibiting social gatherings during subsequent lockdown period(s) [82]. Some countries, such as France, imposed complete home confinement, allowing individuals to leave their house only for necessary activities like medical appointments or grocery shopping. Consequently, individuals relocated their work/ studies, and leisure activities to their homes [83]. The subsequent studies illustrate how this affected daily eating and sleeping patterns.

In fact, the COVID-19 related restrictions have enabled individuals to align their daily activities to their circadian rhythm on both work- and work-free days [82,84,85], resulting in reduced social jetlag [85,86]. This positive change was most pronounced among young adults [87,88] with late chronotype [85,86]. This was also observed among university students due to the closure of universities, leading to online lectures and seminars [82,89], which lasted in Germany during both summer and winter term 2020/2021 [90]. This resulted in students consuming breakfast and dinner at later daytimes, with breakfast being most delayed by ~1 hour [91]. Additionally, students appeared to have more time to consume breakfast more regularly [91–93], as lack of time is the main driver for breakfast skipping among young adults [93,94]. Moreover, meal timings may have become more regular because social commitments that influenced preferred eating times (e.g. late dinner with friends) [62] were prohibited [82], potentially contributing to reduced eating jetlag, see ***Figure 4***.

To date, only one study examined meal timing on work- and work-free days before and during the lockdown and reported fairly constant mealtimes, resulting in comparable eating jetlag among 47-year-old participants [95]. Yet, most studies have reported

changes in dietary patterns, such as higher daily energy intake [96], driven by an increased snacking frequency [97,98], particularly of high energy-dense snacks [96,97], and sweets during COVID-19 related lockdown period [98].

Taken together, university students had reduced social jetlag, yet it remains to be determined whether they also aligned their meal timings with their inner clock, potentially resulting in in decreased eating jetlag during COVID-19 related lockdown.

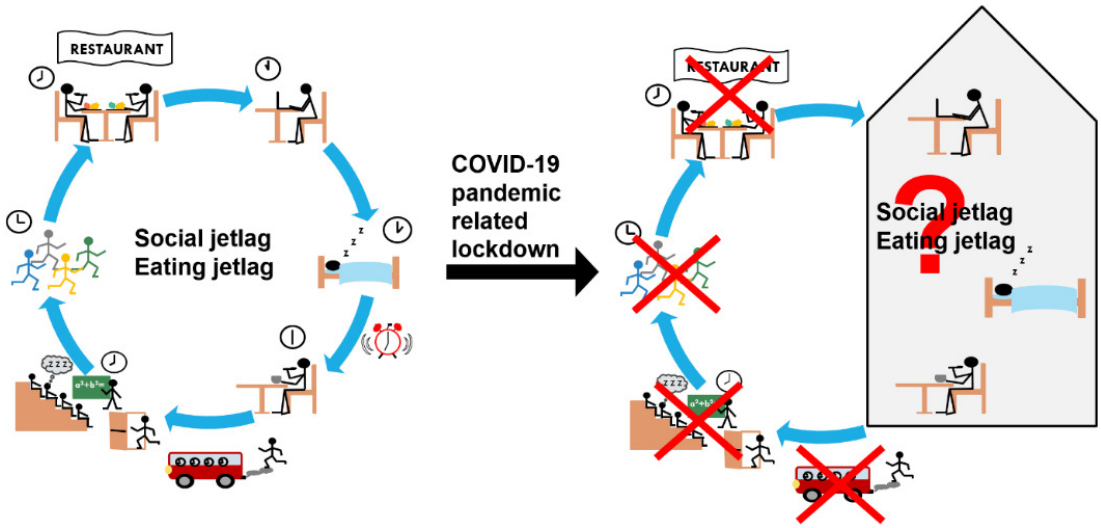

Figure 4: Impact of the COVID-19 related lockdown on the sleep- and eating rhythm among students. Before the lockdown, social obligations caused young students to live against their inner clock, resulting in social and eating jetlag [10,26]. During the lockdown, imposed restrictive measurements, e.g., closing universities and prohibition of social gatherings, may have enabled students to align daily schedules with their inner clock, thereby reducing social jetlag and presumably eating jetlag [82,84]. Figure owned by Bianca Stutz.

2.6 Temporal regulation of glucose homeostasis

Circadian rhythms of both glucose and insulin levels are well established [99,100]. Glucose tolerance decreases throughout the circadian day, driven by the circadian regulated decrease of insulin sensitivity and β-cell responsiveness to glucose, as reviewed in detail by Mason and Stenvers [8,21]. This results in a higher glucose response to a meal consumed in the circadian evening compared to the identical meal in the circadian morning [12,101], which is consistent with the diurnal differences

reported by meta-analyses of randomized controlled trials [102,103]. The underlying mechanisms of diurnal differences in glucose tolerance are crucial as chronically high glucose levels can lead to T2D [104,105]. High glucose levels may arise from reduced insulin sensitivity, for which overweight or obesity combined with high adipose fat mass are common risk factors, leading to compensatory hyperinsulinemia. Over time, pancreatic β-cells may be unable to compensate adequately for high glucose levels, leading to insufficient insulin secretion, and thus T2D [106].

Among discussed mechanisms, circadian regulated **melatonin** secretion may contribute to the diurnal decrease in glucose tolerance. Garaulet hypothesizes that the concurrence of high melatonin levels and food consumption, i.e. close to or during the circadian night, leads to postprandial high glucose levels [107]. This hypothesis is supported by the observation that bright light exposure during dinner resulted in lower melatonin levels and lower postprandial glucose levels compared to dim light exposure [108]. It is suggested that melatonin inhibits glucose-stimulated insulin secretion through binding to melatonin-receptors in the pancreatic β-cells [107,109]. However, observations on unaffected insulin levels irrespective of circulating melatonin levels argues against this pathway [108,110]. Thus, another underlying mechanism may be the decrease in peripheral insulin sensitivity induced by melatonin [110–112].

Other hormones potentially contributing to the diurnal rhythm of glucose tolerance are the incretins glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), as these decrease throughout the day [113,114]. The proposed interrelation between these incretins and glucose homeostasis stems from the observation that incretin and insulin levels were lower, whilst glucose levels were higher, following the consumption of an identical meal in the late afternoon compared to the morning [115]. Both incretins are postprandially secreted by the small intestine and affect

glucose homeostasis by inhibiting glucagon secretion and stimulating insulin secretion of pancreatic α- and β-cells, respectively [116].

Gil-Lozano suggests that the diurnal rhythm of GLP-1 and GIP secretion may be also regulated by melatonin [110]. In their study, they observed higher postprandial GLP-1 and insulin levels when melatonin levels were lower at night, induced by bright light exposure, than when melatonin levels were higher in response to dim light exposure. However, as glucose levels were high under both light exposures, the authors support the above-mentioned mechanism of melatonin decreasing peripheral insulin sensitivity.

Corresponding to glucose tolerance, **insulin sensitivity** of muscles and subcutaneous (but not visceral) adipose tissue decreases throughout the day [1]. Zhao assumes that impaired translocation of the insulin-stimulated glucose transporter (GLUT 4) to the cell surface may reduce glucose clearance at later daytimes [117], noting higher insulin-independent glucose uptake in the morning compared to evening [118]. Furthermore, Stenvers [21] and Poggiogalle [1] discuss the impact of cortisol on circadian glucose and insulin rhythm, as cortisol reduces insulin signaling and secretion. However, Morris questions the impact as they observed that the circadian rhythm of cortisol was inverse to that of glucose [12].

Taken together, glucose homeostasis displays a circadian rhythm, which is potentially affected by circadian-regulated melatonin. This raises the question whether the diurnal rhythm of glucose homeostasis differs among persons with early and late chronotype due to their individual melatonin rhythm.

2.1.1. The impact of carbohydrate quality and content on glycemic response

In line with the diurnal deterioration of glucose homeostasis as mentioned above, a higher glucose response following a high carbohydrate load in the evening compared to the morning as observed among healthy persons seems plausible [119]. These findings are underlined by a recent meta-analysis of eight intervention studies [103]. However, it is worth mentioning that both carbohydrate content and quality are relevant factors in predicting glucose and insulin response [120,121].

Carbohydrate quality is characterized by the glycemic index (GI), i.e., the glycemic potency to raise blood glucose levels [120,121]. The GI is determined using standardized procedure [122]. In brief, the GI is determined as the 2-hour postprandial glucose response, i.e., the incremental area under the curve (iAUC) ignoring glucose levels beyond baseline levels, to a food item consisting of 50 g available (digestible) carbohydrates in relation to 50 g glucose, which is defined by a GI of 100. Non-digestible carbohydrates, e.g. fiber, sugar alcohols, or inulin, are not digested or absorbed in the small intestine. The GI reflects the glycemic potency per gram carbohydrates, irrespective of the consumed amount. According to the ISO standard, the GI is defined as low (≤ 55), medium (<70), and high (≥ 70) and depends on various factors, such as ratio of starch to sugar, food structure (e.g. solid or liquid), and – to some extent – dietary fiber [123,124]. Food processing, such as refinement of grains, is another influencing factor, hence, the GI of processed foods, such as cereals and cereal products, can vary widely, ranging from high to medium and low. Legumes, fruits, dairy products, and pasta are consistently reported as low GI foods.

Furthermore, the concept of glycemic load (GL) was developed to account for both the quality and quantity of carbohydrates consumed [120,123]. The GL is crucial in determining the dietary GI of meals [125] and is calculated as the sum of GI values of each food divided by the sum of their available carbohydrates*100 [123]. The dietary GI,

in contrast to the food's GI, is categorized as low (≤ 45), medium (< 60), and high (≥ 60) [126]. As diets high in GI or GL increase glycemia, they are strongly considered as causal factors contributing to the incidence of T2D, hence, foods low in GI and GL are preferable [127].

2.1.1.1. Diurnal differences in glycemic and insulin response according to meal GI and GL

Consequently, given the diurnal decline in glucose homeostasis (see 2.1.1) large amounts of carbohydrates particularly with a high GI may need to be avoided in the evening. Gibbs [128], Haldar [129], Leung [13], and Morgan [14] investigated diurnal differences in glycemic and insulin responses to high or low GI meal consumption among healthy individuals, see ***Table 2***. All authors observed a higher glucose response in the evening compared to the morning after both high and low GI meals. Gibbs observed more pronounced glucose peaks in the evening compared to morning after high GI meal consumption [128]. Additionally, Morgan reported that the diurnal difference in glucose response were enhanced by a high GL [14]. The findings on insulin response are less consistent. Morgan observed similar insulin levels in response to a meal consisting of both high GI and GL in the morning and evening [14], supported by the findings of Gibbs [128]. In contrast, Haldar noted higher insulin response in the evening compared to morning, irrespective of high or low GI [129]. Leung, who only served low GI meals, reported that insulin levels were higher in the evening compared to morning but similar after meal consumption in the evening and at midnight [13]. Low GI meals also caused delayed insulin peak both in the evening and at midnight night but not in the morning.

In summary, diurnal deterioration of glucose response is enhanced by a meal with both high GI and GL. The diurnal differences in insulin response seem unrelated to meal GI.

Table 2: Intervention studies comparing diurnal differences of glycemic and insulin parameters to low and high GI meals.

First author, year,	Population characteristics	Study design	Intervention	Diet	Outcomes[2]	Results
Gibbs, 2012 [128]	n=10 (90% female) • ⌀ age 25.5 years • ⌀ BMI: 21.9 kg/m^2	Randomized cross-over controlled trial 2 days wash-out period	Low GI (37) and high GI (73) meal consumed at: • 8:00 a.m. • 8:00 p.m.	**Low GI (GI=37)** • Kellog' s (all ban), semi-skimmed milk, plums **High GI (=73)** • Kellog' s, rice krispies, semi-skimmed milk, low fat cheese, half fat cheese ➔ Both meals were similar in energy from macronutrients	2-hour pp • Glucose (iAUC†, peak values) • Insulin levels	**2-h-pp glucose:** • ↑ iAUC after both high (p= 0.003) & low GI (p< 0.0001) in the evening vs. morning • ↑ peak after high GI in the evening vs. morning (p<0.0002) • ↔ peaks after low GI between morning & evening **2-h-pp insulin:** • ↑ ⍉ levels after low GI meal in the morning vs. evening (p=0.04) • ↔ ⍉ levels after high GI meals in the morning vs. evening
Haldar, 2020 [129]	n=34 (62% female) • ⌀ age 56.8 years ⌀ BMI: 22.3 kg/m^2	Randomized cross-over controlled trial 3 days wash-out period	Low GI†† (55) and high GI (92) meal consumed at: • 9:00 a.m. • 6:30 p.m.	**High GI:** • Rice (GI= 92), chicken, leafy vegetables **Low GI:** • Rice (GI= 55), chicken, leafy vegetables	2-hour pp • Glucose (iAUC†, mean levels) • Insulin (iAUC, mean levels)	**2-h-pp glucose:** • ↑ glucose iAUC (p<0.0001) after both high & low GI meal in the **evening vs. morning** • ↑ glucose iAUC (p<0.0001) after **high GI vs. low GI** meal both in the morning & evening **2-h-pp insulin:** • ↑ insulin iAUC (p<0.05) after both high & low GI meal in the **evening vs. morning** • ↑ insulin iAUC (p<0.0001) after **high GI vs. low GI meal** both in the morning & evening

Table 2: *continued*.

First author, year	Population characteristics	Study design	Intervention	Diet	Outcomes[2]	Results
Leung, 2017 [13]	n=10 (80% female) • ⌀ age 23 years • ⌀ BMI: 22.6 kg/m^2 n=5 participants completed both high and low GI interventions	cross-over controlled trial	Low GI (<55[†††]) consumed at: • 8:00 a.m. • 8:00 p.m. • 12:00 p.m. High GI (100) consumed at: • 8:00 a.m. 8:00 p.m.	**High GI:** • Pure glucose solution (consumed in form of an OGTT) **Low GI:** Tomato-based vegetarian pasta dish (consisting of low GI ingredients)	**High GI** • 2-hour pp glucose (iAUC[†]) **Low GI:** • 3-hour pp glucose (iAUC[†]) 2-hour pp insulin (early phase (0-30 min) and late phase	**Postprandial glucose:** • ↑ iAUC 2-hour pp high GI meal in the morning vs. evening (p=0.007) • ↑ iAUC 3-hour pp in the evening (p=0.008) and at midnight (p=0.02) vs. morning • ↔ ⌀ iAUC 3-hour pp between evening & midnight **2-h-pp insulin (only after low GI):** • ↑ iAUC in the evening & at midnight vs. morning (both p=0.008) • ↔ ⌀ iAUC between evening and midnight • ↔ ⌀ early phase insulin between morning, evening, midnight • Delayed late phase insulin peak in the evening (p=0.018) and at midnight (p=0.017) vs. morning
Morgan, 2012 [14]	n=6 (70% female) • ⌀ age 30 years • ⌀ BMI: 21.6 kg/m^2	Randomized cross-over controlled trial 7 days washout	Meals were consumed at: 9:30 a.m. (breakfast) 1:30 p.m. (lunch) 8:30 p.m. (dinner) High GI (~84) or low GI (~34) meals served at all mealtimes within one day with highest GL in the i) morning **OR** ii) evening	**High GI arm:** **Breakfast (higher GL):** Fruit loaf, margarine, skimmed milk, cheese, fruit low fat yoghurt, Mars bar, Glucose **Dinner (lower GL):** sultana bran*, skimmed milk, Glucose, cheddar **Low GI arm:** **Breakfast (higher GL):** Pumpernickel, margarine, semi-skimmed milk, apple, fruit yoghurt, fruit& nut **Dinner (lower GL):** all-bran*, semi-skimmed milk, orange juice	**Glucose:** • 2-hour pp levels • $_{total}$AUC/hour (⌀ of 20 hours) **Insulin:** • 2-hour pp levels • 2-hour pp $_{total}$AUC/hour (⌀ of 2 hours) • 2-hour pp HOMA 2-hour pp levels refer to blood sampling in intervals: 0, 30, 60, 120 min	• ↑ glucose $_{total}$AUC/hour when high GI& GL meal was consumed in the evening compared to all other meals consumed in the morning or evening (p<0.05) • ↑ pp insulin $_{total}$AUC/hour after high GI&high GL meal in the evening compared to low GI meals consumed in the morning or evening (p<0.05) • ↑ pp insulin $_{total}$AUC/hour after high GI&high GL meal in the morning compared to low GI&GL in the evening • ↑ pp HOMA after high GI& GL meal in the evening compared to low GI meals consumed in the morning and evening (p<0.05), but not in the high GI& GL meal in the morning

Abbreviations: BMI, Body Mass Index, pp, postprandial, iAUC, incremental area under the curve, OGTT, oral glucose tolerance test, GL, glycemic load, HOMA, homeostatic model assessment (index of insulin resistance).

Abbreviations: BMI, Body Mass Index, pp, postprandial, iAUC, incremental area under the curve, OGTT, oral glucose tolerance test, GL, glycemic load, HOMA, homeostatic model assessment (index of insulin resistance).
† iAUC calculated based on the trapezoidal rule.
†† corresponds to GI of rice, as no meal GI is provided by the researchers.
††† corresponds to GI of each meal ingredient, as meal GI was not calculated. *Kellogg's
⌀ average value, mean or median as provided in the original publication.
[1] sample included in the final analysis
[2] Only relevant exposures and outcomes are presented
[3] ↔: no statistically significant changes
[4]↑: significant increase

2.1.1.2. Impact of GI on reactive hypoglycemia and hunger

Foods with high GI rapidly increase blood glucose levels, which then decline steeply, as the rapid blood glucose rise induces hyperinsulinemia and suppresses glucagon secretion [130]. As this physiological state maintains, even though glucose has already been absorbed, blood glucose levels fall rapidly even beyond baseline levels within 2-hours after food consumption, a condition termed "reactive hypoglycemia", see ***Figure 5***. According to the *"glucostatic theory"*, low glucose levels signal biological lack of energy, which is enhanced by both suppressed gluconeogenesis and lipolysis [131–134]. This induces the secretion of counter-regulatory hormones, which stimulate the feeling of hunger and promote food intake. Consequently, consumption of high GI foods can lead to higher daily energy intake, thereby increasing the risk for overweight, as reviewed [132,134].

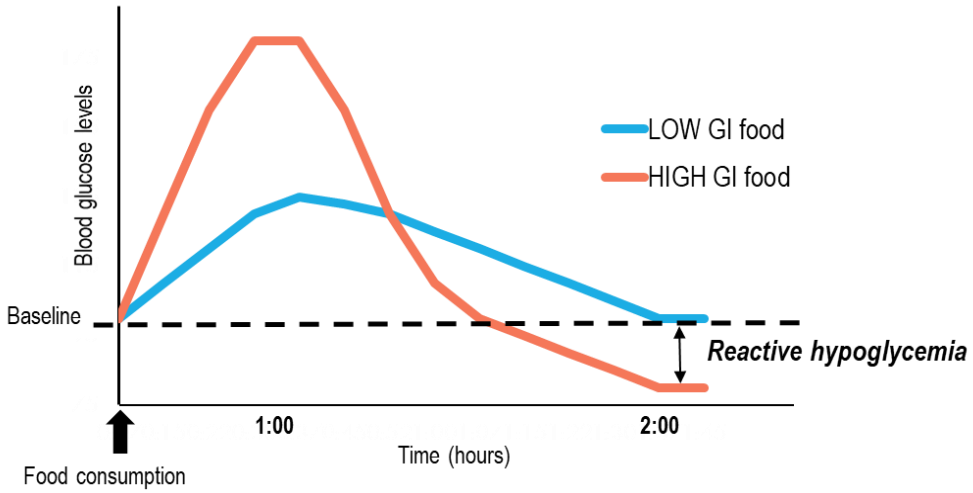

Figure 5: Consumption of high GI foods can cause reactive hypoglycemia. Compared to foods with low GI (≤ 55), food items with high GI (≥ 70) [126] cause a steep increase of blood glucose levels inducing hyperinsulinemia and suppression of glucagon secretion [130]. As this maintains although glucose has already been absorbed, glucose levels decrease rapidly and can fall beyond baseline levels, termed "reactive hypoglycemia". Modified from University of Sydney [135].

The glucostatic theory is, however, controversially discussed because results from subsequent studies have not consistently support this theory [136–139]. Lately, Mayer's

theory regained interest, when the impact of glucose on hunger was investigated among 1.070 healthy participants of the PREDICT study [17]. Among different glucose parameters examined, only glucose dips occurring 2-3 hours after breakfast were associated with subjective hunger feeling and subsequent food intake. The researchers further report that the associations were most pronounced after the consumption of an oral glucose tolerance test solution, that is defined by a GI of 100. In contrast, a meta-analysis of nine randomized cross-over studies reported no differences between high and low GI meals consumed for breakfast on subsequent energy intake [140]. Thus, the impact of the GI as predictor of subjective hunger still remains controversial [141–143].

In summary, high GI meals were observed to predict subjective hunger by inducing glucose dips. Considering the reviewed literature of chapter 2.6, the daytime when consuming a high GI meal may lead to diurnal differences in reactive hypoglycemia, potentially also in subjective hunger, due to the diurnal deterioration of glucose metabolism. Yet, the diurnal effect of high GI meal consumption on subjective hunger and glucose response has not been investigated by chronotype.

2.7 Temporal regulation of hunger and related hormones

Given the fact that glucose metabolism affects subjective hunger as mentioned above, the metabolic control of hunger appears crucial for regulating food consumption, and, consequently, preventing obesity [144]. As this thesis focuses on subjective hunger, it has to be differentiated from appetite, as often used synonymously. While hunger signals energy status, appetite is a psychological stimulus occurring irrespective of energy status [145]. Appetite is the desire to eat certain food and describes the sensory sensation for food attributes, e.g. sweet or salty [146]. This chapter will briefly address hunger regulation, and focus on the diurnal variation of hunger, which may differ by chronotype.

2.1.2. Physiological regulation of hunger

From a physiological point of view, hunger is the homeostatic drive to eat [144]. It signals lack of energy, indicated by e.g. an empty stomach, to the regulatory centers of energy intake in the hypothalamus [7,24,147]. This signal is reinforced by ghrelin secreted in the stomach and metabolic signals, such as low blood glucose levels, which contribute to the stimulation of hunger and initiate the eating process by stimulating neurons in the hypothalamus [147]. During the eating process, satiation increases by both physical distension of the stomach and blood osmotic load, which induces meal termination. Satiety (fullness) finally stops the eating process and is regulated by the gut hormones, such as GLP-1. These gut hormones also activate neurons in the hypothalamus, which induce satiety through of further hormonal signals. Insulin, leptin, GLP-1, glucose, and amino acids regulate the post-absorptive phase of long-term satiety [24,147]. This cycle is termed **satiety cascade** [145].

2.1.3. Temporal rhythm of hunger and related hormones

A circadian rhythm of subjective hunger is well established among healthy individuals, as it increases throughout the day and decreases during the night irrespective of food intake [7,15,18,27]. Thus, a circadian regulation of hunger related hormones is discussed as the underlying mechanisms. Among these, a diurnal increase of **ghrelin** levels that has been observed throughout the day and a decrease during the night, ***Table 3***, [148]. Moreover, postprandial ghrelin levels were higher in response to identical meals consumed in the circadian evening than morning [149,150]. The circadian regulation of ghrelin is emphasized by the observation that ghrelin-responsive neurons in the brain receive direct synaptic signals from the central clock [24]. There are conflicting reports regarding circadian regulation of **leptin**. While Shea observed a circadian peak at 7 a.m. and trough at 3 p.m. [100], Rynders did not observe circadian differences although both

studies used a constant routine protocol [148]. Thus, it is assumed that leptin secretion may be affected by sleep-wake/ eating-fasting rather than in a circadian manner [148,149]. Regarding satiety hormone peptide YY, a decrease across circadian daytime and increase across circadian night was observed [148]. While evidence for a circadian rhythm of GLP-1 is lacking [7], a decrease of GLP-1 levels throughout the day was described previously (see 2.6).

Furthermore, subjective hunger and related hormones show rhythmic patterns in anticipation of food at expected daytimes [137,151], a behavioral cycle driven by peripheral clocks in the brain that are regulated by the central clock [23,24].

Table 3: Diurnal differences of subjective hunger and related hormone levels.

Subjective hunger and related hormones	Morning	Evening
Subjective hunger	↓	↑
Ghrelin	↓	↑
Leptin	↓	↑
Peptide YY	↑	↓
GLP 1	↑	↓

Abbreviations: GLP-1, Glucagon-like-peptide.
↑: high levels; ↓: low levels

2.5.2.1 Diurnal rhythm of hunger by chronotype

Given the circadian regulation of hunger and related hormones (2.1.3) and differences in meal timing (2.3), subjective hunger may vary across the day by chronotype. Persons with late chronotype may experience greater hunger at later daytimes, as they consume main daily calories later in the day compared to early chronotypes [152].

To date, three studies have examined the relationship between chronotype and hunger by daytime with all performed in a young study population aged 18-25 years, ***Table 4*** [153–155]. In the cross-sectional study of Young, a later chronotype was associated with increased subjective hunger in the evening while earlier chronotype was related with

higher hunger in the morning [154]. In intervention studies, i) hunger was examined before and after wakefulness for one night [155], and ii) fullness to test meal in the morning and late afternoon [153]. In the study of Beaulieu, participants with early and late chronotype consumed a standardized meal between 8-10 a.m. or 4-6 p.m. [153] Perceived fullness to test meal was higher among early than late chronotype but independent of meal timing. Reiter compared hunger and snack intake before and after one night of complete wakefulness among early and late chronotypes [155]. There was no association between chronotype and hunger or snack consumption nor an interaction between chronotype and these outcomes.

In summary, the circadian rhythm of hunger seems unrelated to chronotype. However, subjective hunger may differ in response to a meal consumed in the morning or evening among persons with early or late chronotype considering that glucose homeostasis, which affects subjective hunger (see 2.1.1.2), is circadian regulated. For instance, those with early chronotype may have higher glucose tolerance in the morning, leading to fast decline in glucose levels even below baseline, hence increases hunger

Table 4: Studies on the relationship between chronotype and hunger.

First author, year,	Population characteristics[1]	Study design	Exposure: assessment methods[2] / intervention	Outcomes[2]	Results
De Yong, 2022 [154]	n=150 students[1] • ⌀ 19.55 years old • 77% women • ⌀ BMI: 25.0 kg/m^2	Cross-sectional	• Morningness-Eveningness-Questionnaire • Night eating questionnaire	• lack of hunger in the morning • increased hunger in the evening	• early chronotype associated with increased hunger in the morning • late chronotype associated with increased hunger in the evening
Beaulieu, 2020 [153]	n=44 participants[3] ⌀ 18-25 years Early chronotype (n=22): • ⌀ 64% women • ⌀ BMI: 24.1 kg/m^2 Late chronotype (n=22): • ⌀ 64% women • ⌀ BMI: 24.9 kg/m^2	Counter-balanced cross-over	• Chronotype assessment by Morningness-Eveningness-Questionnaire Meal consumption: i.) 8-10 a.m. ii.) 4-6 p.m. Standardized test meal: 195 g baked beans, 60 g medium whole-meal toast • 1 week wash-out	• ⌀ test meal fullness after consumption	**Fullness to test meal:** • ↑ fullness in the morning than evening (p=0.02) • ↑ fullness among early chronotype than late chronotype (p=0.04) irrespective of meal timing
Reiter, 2022 [155]	n=72 participants[1] • 50% women • ⌀ 23.1 years old • ⌀ BMI: 21.5 kg/m^2 • Early chronotype (n=24) • intermediate chronotype (n=23) • late chronotype (n=24)	Intervention	Chronotype assessment by DLMO • Sleep (3 a.m.-12 a.m.), wake phase (12 a.m.-8 a.m.) • Breakfast* (12:20 a.m. & 7:20 a.m.), dinner* (9:50 p.m.) • Snacks: 3:10 p.m.; 7:40 p.m.; 11:50 p.m.; 3:30 a.m. • Hunger measurement: 12:20 a.m.; 9:50 p.m.; 7:20 a.m. • Snack choices: i) peaches and/or pears, ii) fruit yoghurt, iii) apricot/ muesli bar, iv) no snack	• Hunger, prospective food consumption, snack consumption (visual analog scale) • Snack consumption	• chronotype was not associated with any of the outcomes • no interaction between chronotype and time of hunger assessment

Abbreviations: BMI, Body Mass Index, DLMO, dim light melatonin onset; * standardized, no further information provided.

⌀ average value, mean or median as provided in the original publication

[1] n number and characteristics refer to initial recruitment and not of final analysis as no other presented

[2] Only relevant exposures and outcomes are presented

[3] n number and characteristics refers to participants in the final analysis

2.8 Methodological approaches to examine circadian rhythms

As outlined in 2.1.1, external (environmental (light/dark) and behavioral (sleep-wake, eating/fasting)) cycles affect circadian rhythm, hence, they must be tightly controlled to measure their impact on the circadian rhythms of biological and psychological parameters [1,7,8]. Thus, the following study protocols were developed and are referred to in chapters 2.9 and 2.10. Owing their robust rhythm, circadian markers (see 2.1.2) are measured simultaneously to interpret the circadian rhythm on studied parameters.

The **circadian alignment/misalignment protocol** and **forced desynchrony (FD) protocol** both shift external cycles thereby investigating their impact on circadian phases of studied parameters, ***Figure 6a) and b)***, respectively [1]. In the **circadian alignment/misalignment protocol**, external cycles are first aligned with the diurnal rhythm and then abruptly shifted by 12 hours, so participants sleep during the daytime and are awake during the nighttime, ***Figure 6a) i+ii)***. This enables to measure the relative impact of the circadian system versus external cycles. During the **FD protocol**, participants stay in dim light (~2 lux) during the wake phase. The external cycles are shifted across a recurrent advanced (< 24 hours) or delayed (> 24 hours) circadian “day”, while maintaining a 1:2 sleep-wakefulness ratio in terms of time [1,8]. As the circadian system cannot synchronize to these short/ long “days” in dim light conditions, it follows its endogenous rhythm. This separates the impact of the circadian system from environmental and behavioral effects on the investigated parameters, allowing to measure the parameters’ response to the impact of external cycles across all circadian phases [8]. In contrast to the **FD protocol**, the **circadian alignment/misalignment protocol** maintains a 24-hour period and wakefulness occurs under varied light conditions (90-450 lux) [1]. Of note, both protocols allow to study the impact of environmental and behavioral cycles when misaligned but also when aligned to the endogenous circadian rhythm [1,8].

The impact of external cycles can also be assessed by comparing levels of biological and psychological parameters during a constant routine protocol before and after circadian misalignment [156]. The **constant routine protocol** assesses the contribution of the circadian system on the diurnal rhythm of biological and psychological parameters as it eliminates, holds constant, or equally distributes all external factors over at least one circadian cycle (≥ 24-hour) [7], ***Figure 6* c)**.To this end, participants stay consistently awake for ≥ 24 hours in a semi-recumbent position under constant dim light (< 8 lux), and thermoneutral ambient temperature [1,7]. Energy intake is maintained through hourly isocaloric snacks or continuous infusion. Under these conditions, it is considered that the rhythm of a parameter is exclusively generated by the endogenous circadian system [1].

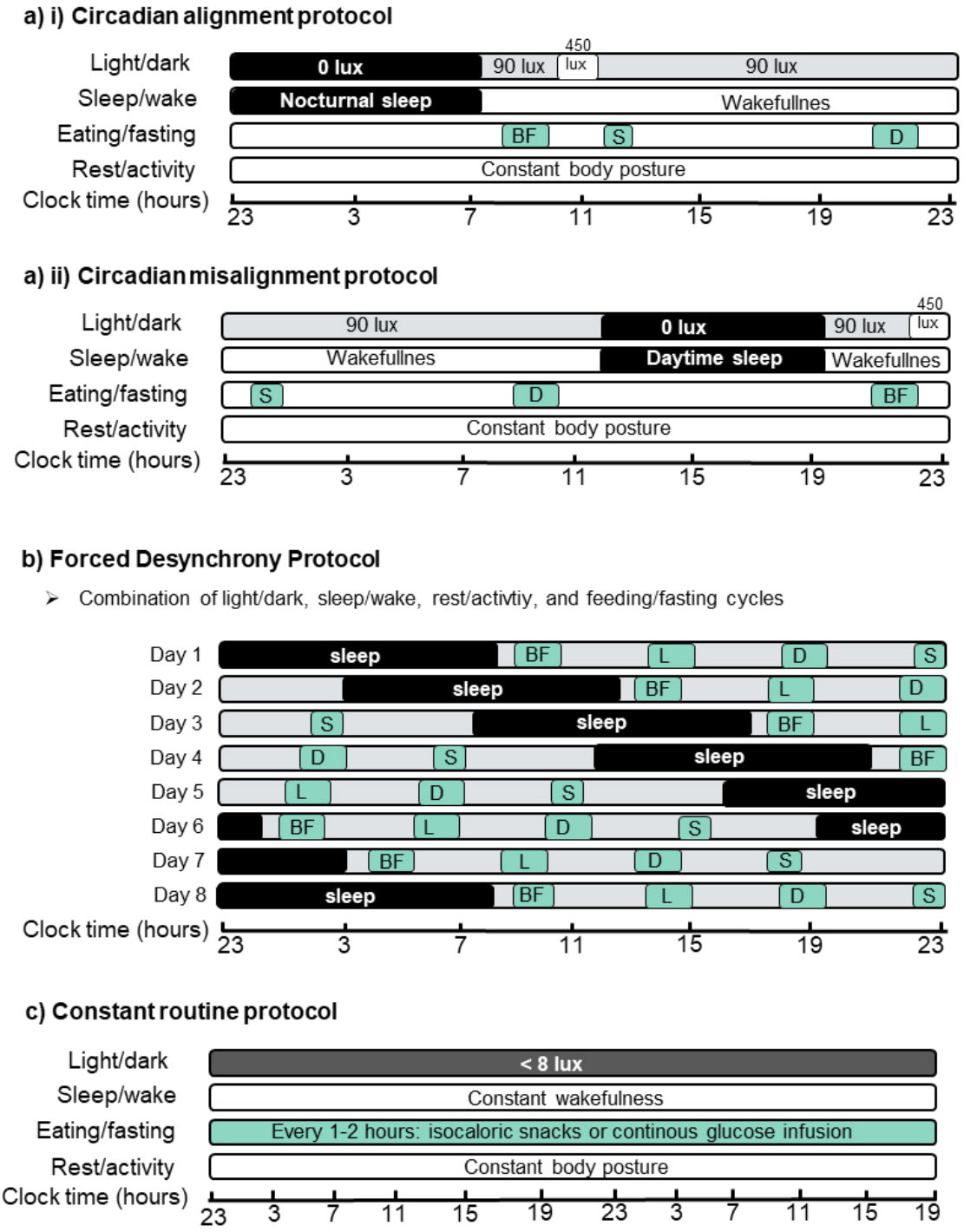

Figure 6: Study protocols to determine circadian rhythms of physiological and psychological parameters in humans. a) Constant routine protocol is used to measure the circadian contribution on the rhythm of parameters when environmental and behavioral cycles are kept constant, while the circadian alignment/ misalignment protocols, and the Forced Desynchrony Protocol (b i) + b) ii), c), respectively) shift theses cycles to examine the effects of environmental and behavioral cycles on circadian rhythms. Adapted from [1]. Abbreviations: BF, breakfast, L, lunch, D, dinner, S, snack.

2.9 Impact of circadian misalignment on glucose and insulin metabolism

Given the fact that young adults tend to live against their inner clock [10,26], they are exposed to a high risk for adverse glucose homeostasis [53,157] and T2D [55]. Therefore, this chapter focuses on the impact circadian misalignment on both glucose and insulin metabolism, which was investigated with the use of the protocols mentioned above (see 2.8). Two of the studies reviewed [158,159] have been included in a recent meta-analysis, which, however, only focused on insulin sensitivity as outcome [160].

To date, mainly Scheer's research group has focused on circadian misalignment among young (~27 years-old), healthy participants using the FD [11,156] or the circadian alignment/ circadian misalignment protocol (see 2.8) [12,159], ***Table 5***. Except for their first study, the same test meals were served, and participants consumed the food items from high to low GI within these meals [12,156,159].

In their first study, Scheer examined the effects when progressively shifting behavioral rhythms through all circadian phases using a 28-hour FD protocol. Compared to circadian alignment, postprandial and 24-hour levels of glucose and insulin were higher in response to misalignment (fourth day when sleep and meal timing was shifted by 12 hours). In a subsequent study, they aimed to investigate the impacts of circadian phases (circadian morning vs. evening) and of circadian misalignment separately on glucose tolerance [12]. Thus, they used the circadian alignment/ misalignment protocol in a cross-over design. Compared to circadian alignment, postprandial (average of two identical meals consumed at 7 a.m. and 7 p.m.) glucose peak and area under the curve (AUC) were higher in response to circadian misalignment. Moreover, compared to circadian alignment, both AUC and secretion rate of late-phase insulin (30-120 min. after meal consumption) were postprandially higher as well as both 24-hour glucose and insulin AUC in the misalignment condition. Based on the same study, Qian (2018) found β-cell

function was unaffected – indicative of early-phase insulin secretion – and insulin sensitivity reduced – indicative of higher late-phase insulin levels.

Based on these findings, i.e., circadian misalignment deteriorates glucose and insulin metabolism, the researchers aimed to examine whether it is preferable to avoid eating during the circadian night even when being awake and restrict eating to the circadian day when sleeping [156]. Thus, a 28-hour FD protocol was combined with an inversed sleep-wake-rhythm. Indeed, restricting food consumption to the circadian day (for which participants were awakened while sleeping) did not affect postprandial and 28-hour levels of glucose and insulin. However, food consumption during the circadian night and fasting during the circadian day caused higher glucose and lower early-phase insulin (timespan from meal initiation to 30 min. postprandial) levels postprandially, and inversed glucose rhythm. Of note, circadian rhythms of melatonin and cortisol remained robust, although peaks and nadirs being flattened [11], irrespective of shifts in behavioral cycles in these studies [12,156].

Unlike these studies, Gonnissen delayed (“day”= 27 hours) and advanced (“day”= d 21 hours) the circadian phase for three days [151]. Although this study includes a short sleep duration (7 hours sleep during 21 hours) sleep deprivation was prevented by keeping a constant 1:2 sleep-wake ratio in terms of time. Compared to control (24-hour day), postprandial and mean (all measurements pre/ post meal consumption) glucose levels were higher but insulin levels did not change in response to phase delay. In contrast, mean and postprandial insulin levels were higher, but glucose levels were unchanged in response to phase advance. Additionally, compared to the first day of phase advance, postprandial glucose and insulin levels differed by mealtime in response to the third day, However, such comparison is not reported for phase delay and the authors also do not describe composition of tests meals. Furthermore, postprandial levels were based on only one measurement after each meal. As similar macronutrient

compositions can provoke different glucose excursions measured at the same time point [161], reliability of postprandial results remains controversial.

Of note, circadian rhythms of melatonin and cortisol remained robust, although peaks and nadirs being flattened [11], irrespective of shifts in behavioral cycles in these studies [12,151,156].

In summary, circadian misalignment impairs glucose tolerance by decreasing insulin sensitivity and/or insulin secretion, ***Figure 7.*** This raises the question of whether this also affects persons with late chronotype when they consume an early breakfast and, vice versa, when those with early chronotype consume a late dinner.

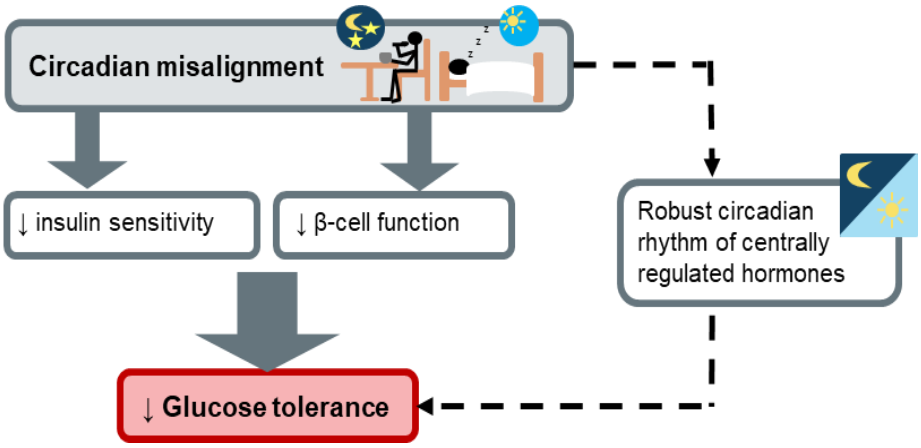

Figure 7: Impact of circadian misalignment on glucose and insulin metabolism. Circadian misalignment, i.e. misalignment between the central pacemaker and behavioral/environmental rhythms [8], decreases glucose tolerance by reduced insulin sensitivity and/or by reduced β-cell function (see 2.8). Study results summarized in 2.8 suggest that this may be caused by the robust circadian rhythm of centrally regulated melatonin or cortisol. Figure owned by Bianca Stutz.

Table 5: Intervention studies examining the effect of circadian misalignment on glycemic and insulin parameters.

First author, year	Population characteristics[1]	Study design	Intervention	Diet	Outcomes[2]	Results
Chellapppa, 2021 [156]	**Nighttime meal control (NMC):** • n=10 (40% female) • ⌀ age 27.0 years • ⌀ BMI: 22.5 kg/m^2 **Daytime meal intervention (DMI):** • n=9 (30% female) • ⌀ age 26.2 years • ⌀ BMI: 23.0 kg/m^2	Randomized parallel single-blinded controlled trial 10 days of intervention	Chronological order: 1. **2 days CRP* in circadian alignment (baseline a)** 2. **1 day: 28-h FD protocol (baseline b):** sleep/wake duration: 9:20/18:40 h:mm; 3 lux light during wake time 3. **4 days: 28-h FD&** **(i) NMC:** eating during circadian night **(ii) DMI:** eating restricted to circadian day 4. 3 days: **post-misalignment CRP**	Isocaloric meals **since wakefulness**: 0:10 h (breakfast), 4:10 h, 8:10 h, 12:10 h (dinner) (except during CRP) **1st and 4th 28-h day: 2 test meals** (0:10 h & 12:10 h since wakefulness) chosen by the participants for all tests and consumed in the same order: a) Glucola[7], bagel with butter, cereals with milk& sugar, egg, peanuts or b) Glucola, bagel with butter, cereal with milk& sugar, turkey sausage, almonds	FD protocol: • levels and AUC‡ of glucose, early- and late-phase[6] insulin CRP: • Diurnal glucose and insulin levels	**4th day vs. 1st (baseline b) of 28-h FD:** **3-h-pp glucose levels:** • ↑[3] glucose levels and AUC in NMC group after breakfast† (p=0.002) • ↔[4] glucose levels and AUC after dinner in both groups **3-h-pp insulin levels:** • ↓[5] early-phase insulin after breakfast (p=0.01) in NMC group • ↔ early-phase insulin (dinner), late-phase insulin and AUC (breakfast& dinner) in both groups **⌀ 24-h levels:** • ↑ glucose levels in NMC group only (p=0.003) • ↔ insulin profile (both groups) **CRP alignment (baseline a) vs. post-misalignment:** • reversed diurnal glucose rhythm in NMC group only (p=0.003) • ↔ diurnal insulin rhythm and insulin levels in both groups

Table 5: *Continued.*

First author, year	Population characteristics[1]	Study design	Intervention	Diet	Outcomes[2]	Results
Gonnissen, 2012 [151]	n= 13 • 46% female • ⌀ age: 24.3 years • ⌀ BMI: 23.6 kg/m²	Randomized single-blinded cross-over controlled trial 3 days of each condition	3 cycle conditions: **i.) 24-h control cycle** (8 h sleep/ 24 h) **ii.) 21-h cycle** (7 h sleep/ 21 h) **ii.) 27-h cycle** (9 h sleep/ 27 h) All conditions: >400 lux light during wake time ≥4 weeks wash-out between cycles	Meal timing o´ clock on 3rd cycle day: **24-h cycle:** • Breakfast: 8:30 a.m. • Lunch: 1:30 p.m. • Dinner: 6:30 p.m. **21-h cycle:** • Breakfast: 1:30 a.m. • Lunch: 5:30 a.m. • Dinner: 9:30 p.m. **27-h cycle:** • Breakfast: 3:30 p.m. • Lunch: 9:30 p.m. • Dinner: 3:30 a.m. Daily diet: 12% protein, 55% CH, 33% fat	• glucose and insulin levels (samples: pre- (-5 min.) and post-meal (35 min.) **a)** ⦰ pre- and post-meal (here termed "diurnal") **b)** ⦰ pre-meal **vs.** ⦰ post-meal (here termed "postprandial")††† • HOMA-IR (⦰ pre- and post-meal)	**27-h vs. 24-h cycle (3rd day)**: • ↑ mean†† & pp glucose levels (p=0.02; p<0.001) • ↔ mean & pp insulin levels **21-h vs. 24-h cycle (3rd day)**: • ↑ mean and pp insulin levels (p=0.04; p=0.02) • ↔ mean and pp glucose levels **1st vs. 3rd day (21-h cycle)**:** • ↑ pp glucose levels after breakfast (p=0.01) • ↑ pp insulin levels after dinner (p=0.03) • ↑ ⦰ HOMA-IR (p=0.03)
Morris, 2015 [12]	n= 14 • 42% female • ⌀ age: 28 years • ⌀ BMI: 25.4 kg/m²	Randomized cross-over controlled trial 8 days of intervention	i.) **circadian alignment 8 days**: sleep phase 11 p.m.-7 a.m. ii.) Circadian alignment (days 1-3) followed by **circadian misalignment** (days 4-8): sleep: 11 a.m.- 7 p.m. Both conditions: 90 lux light during wake time ⦰ ≥4 weeks wash-out	Meal/snacks **since wakefulness** (both conditions): **1st and 3rd test day (≙ days 5&7):** **1 h**, 5 h, **13 h (test meals)** All other days: 1 h, 5 h, 8 h, 13 h **details on test meals** (see [156]	• 2-h-pp levels/ AUC‡ of glucose, early and late phase insulin levels (⦰ of test meals) • Fasting and 2-h-pp AUC‡ of insulin secretion rate (ISR) (⦰ of test meals) • 24-h AUC of glucose & insulin • fasting glucose and insulin levels	**Circadian misalignment vs. alignment:** ⦰ **2-h-pp of test days 1&3:** • ↑ glucose AUC (p=0.0003) • ↑ peak glucose (p=0.03) • ↔ early-phase insulin AUC and ISR AUC • ↑ late-phase insulin AUC (p=0.006) and late-phase ISR (p=0.001) • ↔ fasting glucose, insulin, ISR levels ⦰ **24-h of test days 1&3:** • ↑ glucose and insulin AUC (both p≤ 0.013)

Table 5: *Continued.*

First author, year	Population characteristics[1]	Study design	Intervention	Diet	Outcomes[2]	Results
Qian, 2018 [159]	Participants and study details above, see Morris et al. 2015				• insulin sensitivity • β-cell function • disposition index (proportion of insulin secretion to insulin resistance)	**Circadian misalignment vs. alignment** (⌀ pp responses to test meals on 1st & 3rd test day): • ↓3-h-pp insulin sensitivity (p=0.0007) • ↔ ↓3-h-pp β-cell function and disposition index
Scheer, 2009 [11]	n=10 • 50% female • ⌀ age 25.5 years • ⌀ BMI: 25.1 kg/m^2	Uncontrolled trial 10 days of intervention	After 2 adaption days: • **7x cycles** (≙ 8 days) **28-h FD** (9:20 h sleep/ 28 h) • **1.8 lux** light during wake time	Meal/snacks **since wakefulness** on all days: 1 h (breakfast), 5 h (lunch), 11.5 h (dinner), 15.5 h (snack) isocaloric meals/ snacks (25% fat, 50% CH, 25% protein)***	• pp and fasting glucose and insulin levels • circadian (24-hours) glucose and insulin rhythm	**Circadian misalignment vs. alignment** (4th day 28-h FD): **All meals:** • ↑⌀ 3-h pp glucose levels **Breakfast (9 a.m. vs. 9 p.m.):** • ↑ ⌀ 2-h pp glucose levels (p=0.03) • ↑ ⌀ 2-h pp insulin levels (p=0.04) • ↔ fasting glucose and insulin levels **⌀ 24-h levels:** • ↑ glucose levels (p<0.001) ↑ insulin levels (p=0.006)

Abbreviations: BMI, Body Mass Index, RCT, randomized control trial, NMC, Nighttime meal control, DMI, daytime meal intervention, FD, forced desynchrony, pp, postprandial, AUC, area under the curve, HOMA-IR, homeostatic model assessment of insulin resistance, CH, carbohydrates, CRP, constant routine protocol

⌀ average value, mean or median as provided in the original publication.

*Constant routine: constant wakefulness in semi recumbent position and hourly snacks in dim light environment [1].

**No results available for 27-hour cycle.

***No further information on meals/snack provided, e.g. whether the meals were identical to the meals used in later studies [12,156].

† First meal after extended fasting during sleep.

†† mean of all measurements pre/ post meal consumption

††† "Time" was not explicitly defined by the authors, hence, it was interpreted based on the results shown.

‡ Using trapezoidal method.

[1] sample included in the final analysis

[2] Only relevant exposures and outcomes are presented.
[3] ↑: statistically high/ increased,
[4] ↔: no statistically significant changes
[5] ↓: statistically low/ decreased
[6] early-phase insulin: timespan from start of the meal until 30 min. postprandial; late-phase insulin: timespan from 30-120 min. postprandial
[7] Glucola: pure glucose dissolved in water (GI=100) [162,163]

2.10 Impact of circadian misalignment on subjective hunger and related hormones

Given the circadian regulation of subjective hunger and related hormones (see 2.1.3), the association between circadian misalignment, indicated by social jetlag, and higher ghrelin levels (hunger hormone) seems plausible [162]. This may explain the link between social jetlag and obesity [52,163]. This chapter reviews studies, among which Gonnissen [151] was previously reviewed (see 2.9) as they also examined glucose metabolism, investigating the impact of circadian misalignment on subjective hunger and related hormones.

Gonnissen [151] investigated subjective hunger, satiety, and related hormones pre-/post breakfast, lunch, and dinner during phase advance and phase delay, ***Table 6***. Compared to 24-hours (control), mean hunger and satiety ratings were similar in response to both advanced and delayed phases. Compared to control, mean hunger and satiety ratings were similar in response to both advanced and delayed phases. No further meal- (breakfast, lunch, dinner) or time-specific (pre-/post meal) data were not provided. GLP1, ghrelin, and leptin levels shifted within advanced and delayed meal timings, underlining their meal related regulation. Moreover, compared to control, only mean GLP-1 levels were lower in response to phase delay the other hormones investigated were similar in response to phase advance. Qian determined subjective hunger and ghrelin level response to identical meals with estimated GI food items when following circadian alignment and misalignment protocol (based on [12] study (see ***Table 5***)) [150]. Compared to circadian alignment, hunger and fullness ratings were unchanged but postprandial ghrelin levels were higher – irrespective of meal consumption in the circadian morning vs. evening – in response to misalignment. Additionally, the circadian differences of postprandial hunger, i.e. increased hunger in the morning compared to evening, were robust but less pronounced in response to misalignment.

In addition to circadian regulation, Gonnissen [151] and another study of McHill [164], which considered sleep restriction, noted a meal dependency of subjective hunger and fullness. Building upon these findings and drawing from his own observations, Isherwood speculated that hunger sensations and related hormones display a characteristic meal pattern in anticipation to food irrespective of circadian misalignment [137].

In summary, the circadian rhythm of hunger feelings and related hormones is unaffected by circadian misalignment, hence, it remains to be determined whether diurnal differences in subjective hunger are affected by circadian misalignment and among early and late chronotypes.

Table 6: Intervention studies examining the effect of circadian misalignment on subjective hunger and related hormones.

First author, year	Population characteristics[1]	Study design	Intervention	Diet	Outcome: Primary endpoints[2]	Results
Gonnissen, 2012 [151]	13 participants • 46% female • ⌀ age: 24.3 years • ⌀ BMI: 23.6 kg/m²	Randomized single-blinded cross-over controlled trial 3 days of each condition	**3 conditions:** **i.) 24-h control cycle** (8 h sleep/ 24 h) **ii.) 21-h cycle** (7 h sleep/ 21 h) iii.) **27-h cycle** (9 h sleep/ 27 h) ≥4 weeks wash-out between cycles	Meal* timing (o´ clock) 3rd cycle: **24-h cycle:** • Breakfast: 8:30 a.m. • Lunch: 1:30 p.m. • Dinner: 6:30 p.m. **21-h cycle:** • Breakfast: 1:30 a.m. • Lunch: 5:30 a.m. • Dinner: 9:30 p.m. **27-h cycle:** • Breakfast: 3:30 p.m. • Lunch: 9:30 p.m. • Dinner: 3:30 a.m.	Pre-/post-meal: • ghrelin, leptin, GLP-1 levels • subjective hunger and fullness (visual analogue scale (VAS))	**21-h vs. 24-h cycle (3rd day)**: • ↔[3] ⧁ hunger and fullness ratings • GLP-1, ghrelin, leptin levels **shifted with meal pattern** • ↔ ⧁ GLP-1, ghrelin, leptin levels **27-h vs. 24-h cycle (3rd day)**: • ↔ ⧁ hunger and fullness ratings • GLP-1, ghrelin, leptin levels **shifted with meal pattern** • ↔ ⧁ ghrelin levels • ↓ ⧁ GLP-1 levels (p=0.02)
Qian, 2019 [150]	14 participants • 42% female • ⌀ age: 28 years • ⌀ BMI: 25.4 kg/m²	Randomized cross-over controlled trial 8 days of intervention	iii.) **circadian alignment 8 days**: sleep phase 11 p.m.-7 a.m. iv.) Circadian alignment (days 1-3) followed by **circadian misalignment** (days 4-8): sleep: 11 a.m.-7 p.m. Both conditions: 90 lux during wake time ⧁ ≥4 weeks wash-out	Meal/snacks **since wakefulness** (both conditions): **1st and 3rd test day (≙ days 5&7):** **1 h**, 5 h, **13 h (test meals)** All other days: 1 h, 5 h, 8 h, 13 h Test meals (a) or b) identical for all tests) consumed in the following order: [8] Glucola, bagel with butter, cereals with milk& sugar, egg, peanuts **or** [9] Glucola, bagel with butter, cereal with milk& sugar, turkey sausage, almonds	On test days 1+3: • Fasting (-5 min.) and pp (55 min., 115 min. after test meal) hunger, fullness using VAS • Fasting (-7 min.) and pp ghrelin levels (60 min, 120 min after test meal)	**Circadian misalignment vs. alignment:** • ↔ ⧁ fasting and pp hunger and fullness • ↑ ⧁ pp ghrelin levels (p=0.04) • ↔ ⧁ fasting ghrelin levels • Similar results on 3rd test day **Differences between circadian morning and evening after circadian misalignment:** • ⧁ ↓ pp hunger (p=0.02) • ⧁ ↓ pp ghrelin levels (p=0.05) • ↔ ⧁ fasting hunger and ghrelin levels

Abbreviations: BMI, Body Mass Index, h, hours, FD, forced desynchrony, CCD, chronic circadian disruption, CSR, chronic sleep restriction, VAS, visual analogue scale.

* no information meal composition available.
** meal timing data extracted from [164].
*** no analysis of postprandial hunger/fullness.
∅ refers to mean or median of original publication.
[1] sample included in the final analysis
[2] Only relevant exposures and outcomes are presented
[3] ↔: similar values
[4] ↑: statistically high/ increased
[5] ↓: statistically low/ decreased

2.11 Conclusive considerations

Young adults are vulnerable to discrepancies between their inner clock and socially determined schedules due to their biologically delayed chronotype, leading to phenomena termed social jetlag and eating jetlag. The COVID-19 pandemic related lockdowns allowed individuals to align daily schedules with their inner clock. Yet, it remains to be determined whether this affected eating jetlag and how chronotype relates to potential changes on social jetlag and eating jetlag.

Furthermore, glucose tolerance deteriorates throughout the day. Additionally, circadian misalignment, indicated by social and eating jetlag, adversely affects glucose homeostasis. Thus, consumption of carbohydrate-rich meals with high GI appears problematic, particularly when consumed late in the evening or against the inner clock. It is unknown whether the consumption of an early breakfast entails circadian misalignment for individuals with late chronotype, whilst this could also be attributed to persons with early chronotype when consuming dinner late in the evening.

Moreover, hunger is circadian regulated and increases throughout the day, however, irrespective of chronotype according to literature. Of note, consumption of high GI foods can lead to a rapid decline in glucose levels, even below baseline (glucose dips), thereby potentially increasing subjective hunger after consumption. Thus, glucose dips after a high GI meal may be more or less pronounced when consumed in alignment or against the inner clock, potentially leading to varying levels of subjective hunger. It remains to be determined whether subjective hunger differs in response to a high GI meal consumed in the morning or evening among persons with early or late chronotype considering the circadian rhythm of glucose tolerance.

Therefore, the interrelations between meal timing, GI, and hunger among persons with early or late chronotype are yet to be stablished.

3. AIMS AND RESEARCH QUESTIONS

In this thesis, three aims were formulated to fill in the research gaps outlined above, thereby examining the relevance of chronotype for meal timing, glycemic response, and hunger among young students.

AIM 1: Examine the associations of chronotype and social jetlag with eating jetlag and their changes during the 1st COVID-19 pandemic related lockdown.

Research questions:

1.1 Is chronotype and/or social jetlag associated with erratic meal pattern reflected by eating jetlag before the COVID-19 pandemic?

1.2 Are chronotype, estimated before the COVID-19 pandemic, and/or changes in social jetlag during the lockdown associated with concurrent changes in eating jetlag?

1.3 Do students with later chronotype and/or those with larger changes in social jetlag between the time before and during the lockdown have greater changes in eating jetlag?

AIM 2: To investigate the glycemic response to a high GI meal consumed in the morning or in the evening in two samples of students either with early or late chronotype.

Research question:

*2. Does the **2-hour postprandial and 24-hour glycemic response** to a carbohydrate-rich meal from higher GI sources consumed early in the morning (7 a.m.) or late in the evening (8 p.m.) differ in two samples of students with either early or late chronotype?*

AIM 3: To assess diurnal glucose dips after medium and high GI meal consumption and their association with the feeling of hunger among young adults with early and late chronotype.

3.1 To describe the diurnal profile of hunger and glycemia when a high or medium GI meal was served as breakfast and on a day when the identical high or medium GI meal was served as dinner among persons with either early or late chronotype.

Research questions:

3.2 Are glucose parameters including glucose dips different following a high GI vs. medium GI meal among persons with either early or late chronotype?

3.3 Are glucose parameters including glucose dips different between breakfast vs. dinner among persons with either early or late chronotype?

3.4 Is there an association between glucose parameters including and the feeling of hunger following breakfast[4]?

All aims were based on data from the Chronotype and Nutrition (ChroNu) study described in chapter 4. The research aims were addressed in three original articles, each providing detailed information on the methods and statistical analyses, and can be found in the appendices (see

Table 7).

Table 7: Research aims assessed by analysis I-III.

Aim	Analysis	Location
1	I: Meal timing according to chronotype	Appendix B
2	II: Glycemic response by early and late chronotype	Appendix C
3	III: Glycemic response and hunger by early and late chronotype	Appendix D

[4] Hunger/fullness was not inquired after dinner.

4. GENERAL METHODOLOGY

The research questions were examined on the basis of data from the ChroNu study that was conducted from September 2019 to December 2022. The ChroNu study aimed i) to characterize students aged 18–25 years from Paderborn University according to their chronotype **(study 1)** and ii) to select those with the earliest and latest chronotype for participation in the controlled nutrition trial **(study 3)**. Additionally, a follow-up of the screening was conducted during the 1st COVID-19 pandemic related lockdown in Germany **(study 2)**. An overview of the ChroNu study is shown in ***Figure 8***. The ChroNu study was approved by the Ethics Committee of Paderborn University and all participants signed written informed consent prior to participation in each study. This chapter provides an overview on the study design of the ChroNu study.

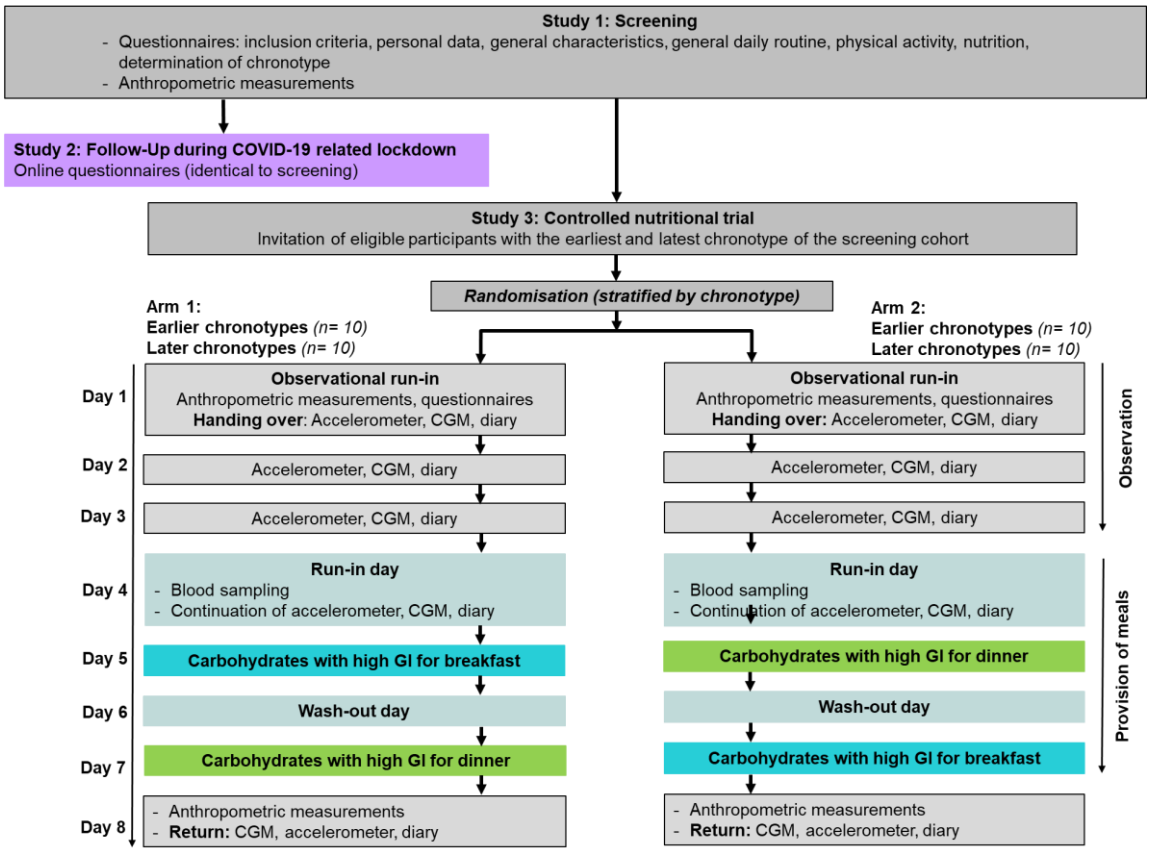

Figure 8: ChroNu Study overview.

4.1. Screening (study 1) and Follow-up (study 2)

For the screening, body size was measured using an ultrasonic measuring station (seca 287 dp) from SECA and waist circumference was measured midway between the lowest rib and the iliac crest. Body composition was obtained with the use of Bioimpedance Analysis (mBCA 515, SECA). Afterwards, participants filled in online questionnaires via REDCap [165], which referred to the previous month, on the timing of their daily routine, meal/snack consumption, physical activity, and sleep/wake pattern separately for work- and free days to account for chronotype specific differences. The chronotype was defined according to the participants´ MSF_{sc} using the MCTQ [9]. Social jetlag and eating jetlag were calculated as the temporal difference between midpoint of sleep or eating midpoint on workdays and work free days [9,10]. The screening was conducted from September 2019 to January 2020.

From June to July 2020, all participants were re-contacted via e-mail and asked to fill in the same online-questionnaires as assessed during screening to capture potential changes in meal and sleep patterns during the 1st COVID-19 related lockdown in Germany **(study 2)**. The lockdown started in mid-March 2020 and all cultural and educational institutions – including schools and universities – were closed while pharmacies, post offices, and grocery stores remained open [82]. When the follow-up during the COVID-19 related lockdown was conducted, certain restrictions e.g. closing fitness clubs and restaurants had already been eased locally while universities were still closed until autumn 2020 [166].

Data of **study 1** was used to determine the association of chronotype and social jetlag with eating jetlag before the 1st COVID-19 related lockdown. Potential changes during the lockdown were examined based on **study 1 & 2** (see OA1, Appendix B). Descriptive data are presented in sex-specific tertiles of chronotype. For analyses of chronotype and outcome variables, MSF_{sc} before the lockdown was used as continuous variable.

4.2. Controlled nutrition trial (study 3)

The controlled nutrition trial was conducted to determine the glycemic response to a high GI meal consumed early in the morning (7 a.m.) and late in the evening (8 p.m.) among two samples with early and late chronotype. The early and late meal timing is supposed to interfere with the circadian rhythm of students with late and early chronotype, respectively (for details, see OA2, Appendix B). Random assignment of participants to arm 1 (high GI meal morning/evening) or 2 (high GI meal evening/morning) was stratified by sex and chronotype and conducted externally (University of Bergen). Researchers were blinded to the participants´ chronotype only since the study involved provision of meals/snacks.

4.2.1. Study schedule

Therefore, eligible participants with the earliest and latest chronotype based on their MSF_{sc} were selected from the screening cohort **(study 1)** and invited for participation, ***Figure 8***. The trial started with a 3-day observational run-in phase followed by four days of the controlled nutrition trial. On day 1, participants filled-in online questionnaires via REDCap [165] and anthropometric measurements were conducted as described in 4.2. Furthermore, they received a continuous glucose monitoring device (CGM) (G6, Dexcom) to record their glycemic response. The CGM measures subcutaneous interstitial glucose concentrations continuously and sends a mean glucose value every 5 minutes to a receiver via Bluetooth [167]. During the trial (days 4-8), the receiver was blinded to the participants. Additionally, participants received an accelerometer (E4 wristband, Empatica SRI, Italy) to objectively monitor their sleep-wake times and thus corroborate their chronotype.

During the observational run-in, participants were asked to maintain their daily routines and sleep/wake rhythm. On day 3, participants were asked to abstain from food/drinks

after 10 p.m. to ensure a ≥10 hour fasting period. In the morning of run-in (day 4), fasting blood samples were collected and participants received breakfast and mid-morning snack. Participants returned to the study center for a freshly prepared warm lunch and received an afternoon snack, dinner, breakfast, and midmorning snack for consumption at home until lunch next day. This procedure continued until day 7 when participants received their afternoon snack and dinner. On day 8, participants returned the devices and anthropometric measurements were conducted. During the controlled trial, participants were instructed to consume food/snacks at predefined times and to abstain from any other foods/drinks than provided. Furthermore, participants were asked to record their timing of sleep and meal/snack consumption, and daily activities in a diary throughout the trial.

4.2.2. Assessment of hunger

To determine the association between glycemic response and the diurnal feeling of hunger/fullness (see OA3), which is a secondary analysis of the controlled nutrition trial, participants were further inquired to mark their feeling of hunger/fullness on a labelled magnitude satiety (LMS) scale [168] in their diary before consuming every meal/snack, ***Figure 9***. The scale is subdivided by 11 descriptive phrases and anchored at the end by “Greatest imaginable hunger” (score=−9,5 cm) and at the top by “Greatest imaginable fullness” (score=+9,5 cm). The distances on the scale were measured from the midpoint (“neither hunger nor full”, which denotes a value of 0 cm) in centimeters. For this study aim, the scale was freely translated into German.

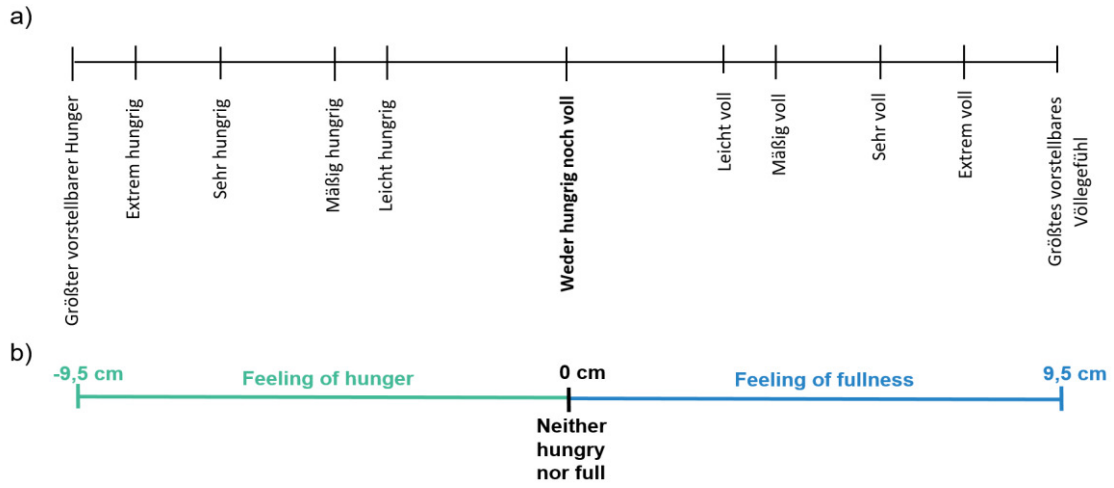

Figure 9: Labelled magnitude scale to assess subjective hunger/fullness. (a) German translation of the scale from [168]. Distances measured from the center (neither hunger nor full) to the marking of subjective hunger/fullness. (b) Negative values denote a feeling of hunger with a maximum score of -9.5 cm ("greatest imaginable hunger"). Positive values with a maximum score of +9.5 cm ("greatest imaginable fullness") indicate feeling of fullness ("greatest imaginable fullness"). Neither hungry nor full is denoted 0 cm.

4.2.3. Meals and snacks

All meals/snacks had medium GI (GI 46-59) except for the high GI meal with estimated GI of 72 consumed in the morning (7 a.m.) or evening (8 p.m.) separated by one wash-out day (day 6). On the intervention days (days 5+7), high GI meal provided the largest proportion of available carbohydrates while on the run-in/wash-out days lunch was the meal with the highest proportion. The estimation of the foods´ GI was performed according to a procedure described previously [169]. In brief, preference was given to food items with a published GI [123,170] and when more than one GI value was available a mean GI was assigned.

To maintain body weight, participants followed an isocaloric diet and avoided vigorous physical activities. The macronutrient distribution (daily consumed energy in %; En%) was similar on all study days. The diets of the intervention and the run-in/wash-out days were designed to comply with the recommendations of the German Nutrition Society, containing 53 En% from available carbohydrates, 14 En% from protein, 30 En% from fat, and 3 En% from dietary fiber [171].

5. ORIGINAL ARTICLES

OA1: Associations of chronotype and social jetlag with eating jetlag and their changes among German students during the first COVID-19 lockdown. The Chronotype and Nutrition study.

Stutz B[5], Buyken AE, Schadow AM, Jankovic N, Alexy U, Krueger B.

Appetite 2023; 180:106333; doi.org/10.1016/j.appet.2022.106333

Due to their biologically later chronotype, young students are vulnerable to a discrepant sleeping pattern between work- and free days, coined “social jetlag” (SJL). This study examined whether a later chronotype and/or a larger SJL are related to an analogous discrepancy in meal timing (eating jetlag (EJL)) and whether chronotype and/or changes in SJL during the first COVID-19 related lockdown in Germany associated with changes in EJL. Baseline data were collected from September-January 2019-20 among 317 students (58% females) aged 18 – 25 years of which a total of 156 students (67% females) completed an online follow-up survey in June-July 2020 (i.e. the 1st lockdown). Data were collected on daily routines, timing of meals/snacks, and physical activity. Chronotype was determined using the Munich ChronoType Questionnaire; SJL and EJL correspond to the difference in midpoint of sleep/eating duration between work- and free days. Multivariable linear regression revealed that students with a later chronotype or a larger SJL experienced a larger EJL ($p_{adjusted}$=0.0124 and $p_{adjusted}$<0.0001, respectively). A later chronotype at baseline and reductions in SJL during lockdown were associated with concurrent reductions in EJL ($p_{adjusted}$=0.027 and $p_{adjusted}$<0.0001). In conclusion, students with a later chronotype exhibit a more erratic meal pattern, which associates with SJL. During lockdown, flexible daily schedules allowed students to align the meal timing with their inner clock.

[5] Contribution of B. Stutz: Planning and conduction of screening (together with Krüger), data assessment, statistical analysis (together with by A.E. Buyken), interpretation of study results (together with co-authors) and drafting of the original draft (supervised by A.E. Buyken).

OA2: Glycemic response to meals with a high glycemic index differs between morning and evening – a randomized controlled trial among students with earlier or later chronotype.

Stutz B[6], Krueger B, Goletzke J, Jankovic N, Alexy U, Herder C, Dierkes J, Berg-Beckhoff G, Jakobsmeyer R, Reinsberger C, Buyken AE.

European Journal of Nutrition 2024, under production

PURPOSE

Glycemic response to the same meal depends on daytime and alignment of consumption with the inner clock, which has not been examined by individual chronotype yet. This study examined whether the 2-h postprandial and 24-h glycemic response to a meal with high glycemic index (GI) differ when consumed early or late in the day among students with early or late chronotype.

METHODS

From a screening of 327 students aged 18–25 years, those with early (n=22) or late (n=23) chronotype participated in a 7-day randomized controlled cross-over intervention study. After a 3-day observational phase, standardized meals were provided on run-in/washout (days 4 and 6) and intervention (days 5 and 7), on which participants received a high GI meal (GI=72) in the morning (7 a.m.) or in the evening (8 p.m.). All other meals had a medium GI. Continuous glucose monitoring was used to measure 2-h postprandial and 24-h glycemic responses and their variability.

RESULTS

Among students with early chronotype 2-h postprandial glucose responses to the high GI meal were higher in the evening than in the morning (iAUC: 234 (±92) vs. 195 (±91) (mmol/L) x min, p=0.042). Likewise, mean and lowest 2-h postprandial glucose values were higher when the high GI meal was consumed in the evening (p<0.001; p=0.017). 24-h glycemic responses were similar irrespective of mealtime. Participants with late chronotype consuming a high GI meal in the morning or evening showed similar 2-h

[6] Contribution of B. Stutz: selection of eligible participants (together with B. Krüger, A. E. Buyken), conduction of the trial (planning, coordination, data collection (together with B. Krüger)), development of diet, preparation of meals/snack; conduction of statistical analysis (together with G. Berg-Beckhoff, K. Bolzenius, A.E. Buyken) interpretation of study results (with co-authors) and drafting of the original draft (supervised by A.E. Buyken).

postprandial (iAUC: 211 (±110) vs. 207 (±95) (mmol/L) x min, p=0.9) and 24-h glycemic responses at both daytimes.

CONCLUSIONS

Diurnal differences in response to a high GI meal are confined to those young adults with early chronotype, whilst those with a late chronotype seem vulnerable to both very early and late high GI meals. Registered at clinicaltrials.gov (NCT04298645; 22/01/2020).

OA3: Association between glucose dips and the feeling of hunger in a dietary intervention study among students with earlier and later chronotype- a secondary analysis of a randomized cross-over nutrition trial

Stutz B[7]*, Goletzke J*, Krueger B, Jankovic N, Alexy N, Herder C, R. Jakobsmeyer, C. Reinsberger, Buyken AE.

*shared first authorship

Under review

Meals with high glycaemic index (GI) can cause hypoglycemia, thus increasing postprandial hunger. Since the circadian rhythm differs intra-individually, we describe glucose dips after high/medium GI breakfast/dinner consumption among students with earlier and later chronotype and examine their relation to the feeling of hunger. This is a secondary analysis of a randomized cross-over nutrition trial among 18-25-year-old students with earlier (n=22) or later (n=23) chronotype. Glucose dips were calculated as the difference between the lowest glucose value recorded 2-3 hours postprandially and baseline and presented as percentage of average baseline level. Associations between glucose dips and the feeling of hunger were analyzed using multilevel linear models.

Glucose dips occurred more frequently after a medium GI meal among both chronotype groups (p=0.03). For earlier chronotypes, glucose dip values were lower after breakfast than after dinner (-4.9 % vs. 5.5 %, p=0.001). Hunger increases throughout the day among both chronotypes but glucose dips were not related to the feeling of hunger following breakfast. Interestingly, medium GI was associated with lower glucose dip values 2-3 hours postprandially, particularly in the morning among earlier chronotypes. These glucose dips did not predict hunger after breakfast irrespective of meal GI and chronotype.

[7] Contribution of BS: selection of eligible participants (together with B. Krüger, A. E. Buyken), conduction of the trial (planning, coordination, data collection (together with B. Krüger)), development of diet, preparation of meals/snack, interpretation of study results (with co-authors) and drafting of the original draft (together with J. Goletzke and supervised by A.E. Buyken).

6. DISCUSSION

In this section, a comprehensive discussion and overall interpretation of the original research results will be conducted, particularly emphasizing the practical relevance of the findings in the context of public health nutrition. Detailed discussions of the underlying mechanisms of research results can be found in the subsequent articles (Appendix B-D). Methodological considerations regarding selected outcomes for all OAs are discussed to emphasize challenges to be considered in future studies.

6.1 Synopsis of research results

The overall aim of this thesis was to investigate the relevance of chronotype for meal timing, glycemic response and hunger sensations among 18-25-year-old students of Paderborn University. The results of each research objective are placed in the context of existing knowledge in which also presents additional research questions that emerge from these results. The first research aim was to examine the associations between chronotype and social jetlag with eating jetlag before the COVID-19 related lockdown, and prospective changes during the lockdown (see chapter 3). The findings of this study underline that students exhibited discrepancies in meal timing between work-, and workfree days **before the COVID-19 related lockdown**, leading to eating jetlag (OA1) [172], ***Figure 10.*** As anticipated, eating jetlag was more pronounced among those with later chronotype, as they also showed greater social jetlag also associated with eating jetlag. The phenomenon of eating jetlag was mainly driven by late-night snacking and breakfast, that was either skipped, possibly due to dinner consumption and snacking late in the evening or consumed earlier in the morning on workdays compared to free days. While this was most pronounced among students with later chronotype, almost 74% of the study population consumed breakfast against their inner clock on workdays. **During the lockdown**, there was a significant decrease in eating jetlag notably among students

with later chronotype, who also experienced the greatest reductions in social jetlag. Similarly, the decrease in social jetlag was linked to reduction in eating jetlag, Figure 10. Of note, eating jetlag predominantly decreased due to fewer students skipping breakfast and delayed breakfast timing on workdays. These changes were again most pronounced among those with later chronotype.

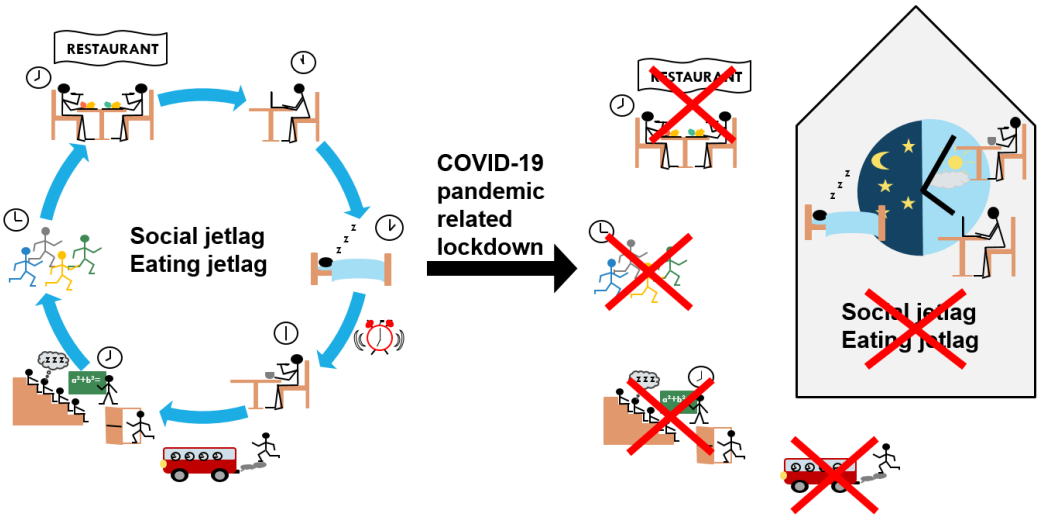

Figure 10: Alignment of sleep- and eating rhythm with the inner clock during the COVID-19 related lockdown. While university students consistently slept and ate against their inner clock due to daily schedules before the lockdown, resulting in social jetlag and eating jetlag [10,26], closure of university and (social) restrictions related to the COVID-19 pandemic [82] enabled students to align their sleep and eating pattern with their circadian rhythm, resulting in reduced social jetlag related to decreased eating jetlag (see OA1). Figure owned by Bianca Stutz.

Based on these findings, glycemic response to a meal consumed at socially scheduled daytimes, potentially interfering with circadian rhythmicity, was separately investigated in two groups of students with either early or late chronotype. The findings from **research aim 2**, which determined the glycemic response to a high GI meal consumed in the morning or in the evening among students with early or late chronotype, are concerning. They indicate that consuming carbohydrate-rich high GI meal against the inner clock causes adverse 2-hour postprandial glycemic responses, i.e. meal consumption at 7 a.m. for late chronotypes and at 8 p.m. for early chronotypes (OA2). Notably, diurnal differences in postprandial glycemia, i.e. a higher glucose response to the evening meal

compared to morning, were only observed among **students with early chronotype**, but not among those with late chronotype.

Students with late chronotype showed similar high 2-hour postprandial and 24-hour glycemic responses to morning and evening high GI meals. This was somewhat unexpected as late chronotypes were assumed to tolerate meals consumed in the evening compared to morning due to their delayed circadian rhythm. Thus, individuals with late chronotype may bear a double metabolic burden: consuming high-GI meals early in the morning exposes them to circadian misalignment, as confirmed by high melatonin levels at ~7 a.m., while late evening meals (or snacks (OA1)) interfere with diurnal deterioration of glucose metabolism (OA2). Noteworthy, melatonin levels, regulated by the master clock and assumed to decrease glucose tolerance [107], correlated with higher 2-hour postprandial glycemic response following the high GI meal consumption in the morning. Yet, it remains to be clarified whether a diurnal difference in glycemic response between morning and evening is evident when a high GI meal is consumed later in the morning (e.g. 11 a.m.) compared to the evening.

Students with early chronotype showed the expected decline in glucose homeostasis throughout the day [12,13]. Importantly, the elevated mean and 24-hour glucose levels highlight the prolonged impact of consuming a high GI meal late in the evening on glucose homeostasis (OA2). In addition to the diurnal decline, meal consumption at 8 p.m. may have induced some degree of circadian misalignment, as it was scheduled close to habitual sleep onset, and hence potentially interfered with DLMO of early chronotypes.

While high postprandial glucose levels, as observed in research aim 2, can result in reactive hypoglycemia after high GI meals [132], it seems contradictory that glucose dips after medium GI meal were more pronounced compared to high GI meals – irrespective of consumption time and chronotype (OA3). However, even low GI food items were observed to induce reactive hypoglycemia following glucose spikes, which seems to

depend on the food structure (i.e. liquid vs. solid), and sugar components [126]. Glucose dips were observed after a medium GI breakfast among students with early chronotype. However, these were not related to subjective hunger following breakfast – irrespective of meal GI or chronotype. Thus, glucose dips may have been insufficiently physiologically low to elicit hunger feelings among the young and healthy study population (OA3). Of note, the hunger feeling increased throughout the day – irrespective of breakfast GI – among both early and late chronotypes. This may be problematic, particularly for students with late chronotype who habitually have a delayed sleep onset in the evening [26]. Consequently, the latter are more susceptible to increased late-night snacking, as underlined by findings of research aim 1 (OA1), potentially adversely affecting glycemic response (OA2). Moreover, participants with late chronotype felt full before their midmorning snack, likely scheduled close to the end of their biological night, when circulating levels of ghrelin are low [7]. This may explain the high frequency of breakfast skipping among persons with late chronotype, as observed before the COVID-19 related lockdown in relation to research aim 1 (OA1).

Considering all findings, students, particularly those with late chronotype, exhibited eating jetlag, primarily caused by frequent shifts in breakfast timing on workdays against their inner clock (OA1). Such circadian misalignment causes adverse glucose response (OA2). Additionally, students with early or late chronotype experienced an adverse glycemic response to food consumption at 8 p.m. (OA2), for which students with late chronotype may be vulnerable due to habitual late dinner timing and increased snacking potentially enhanced by circadian regulated increase of subjective hunger (OA3).

Table 8: Overview of current research, research gaps, information added by this thesis, and future research questions.

Research aim (A)/ Original article (OA)	What is already known?	What are the research gaps?	What does this thesis add to the current knowledge?	Which additional research questions arise from the added evidence and how could they be approached?
	Details subchapters 2.2-2.8		Details 6.1 and in the appendices B-D	Partly further discussed in 6.2
A1/ OA1 [172]	• Students aged 18-25 years have their biologically latest chronotype • The chronotype-dependent late sleep and eating rhythm collides with social constraints of daily life **Before COVID-19 related lockdown:** • Students face **erratic shifts** between living against their inner clock on workdays and in alignment on work-free days resulting in: ➢ Social jetlag ↑ ➢ Eating jetlag ↑ **During COVID-19 related lockdown:** • Sleep-wake-rhythm aligned with the inner clock: ➢↓social jetlag	• Considering **snacking** in eating jetlag A **prospective study** examining changes due to the COVID-19 pandemic related lockdown: ➢ *Are later chronotype and/or larger changes in social jetlag associated with greater changes in eating jetlag?*	**Before COVID-19 related lockdown:** ➢ Eating jetlag is only significant when considering snacking ➢ Eating jetlag is mainly driven by late-night snacking and breakfast ➢ The later the chronotype the larger social jetlag and eating jetlag ➢ The larger social jetlag the larger eating jetlag **Changes during COVID-19 related lockdown:** ➢ ↓ eating jetlag ➢ ↓ social jetlag	➢ *How to enable more flexibility for students to live aligned with their inner clock at university when experiencing again social jetlag and eating jetlag since life returned to the pre-pandemic state?* **Hypothesis:** A mix of remote and in-person courses may enable more flexibility. ➢ *Does exposure to eating jetlag at young adulthood increase the risk of developing adverse cardiometabolic health effects (e.g. obesity, T2D) later in life?*
A2/ OA2	• Diurnal decline of glucose tolerance ➢ identical meals cause higher postprandial glucose levels in the evening compared to morning • eating late in the evening: ↑ risk for higher fasting blood glucose, HbA1c	➢ *Do socially scheduled meals interfere with circadian rhythmicity of persons with early or late chronotypes?*	➢ **Late chronotypes:** similar high 2-hour and 24-hour glycemic responses in the morning and evening due to: ➢ Circadian misalignment (early morning) ➢ Diurnal decline in glucose homeostasis (late evening)	➢ *What is the optimal eating window during the day for persons with late chronotype?* **Hypothesis:** Persons with late chronotype have a short eating window due to circadian misalignment in the morning leading and deterioration of glucose homeostasis in the evening.

Table 8: *continued.*

Research aim (A)/ Original article (OA)	What is already known?	What are the research gaps?	What does this thesis add to the current knowledge?	Which additional research questions and gaps arise from the added evidence?
	Details subchapters 2.2-2.8		Details 6.1 and in the appendices B-D	Partly further discussed in 6.2
	• eating against the inner clock, as indicated by eating jetlag, adversely affects glucose response	➢ *Does the 2- hour postprandial and 24-hour glycemic response to a high GI meal consumed early in the morning or late in the evening differ in two samples of students with early or late chronotype?*	➢ **Early chronotypes:** ↑ 2-hour and 24-hour glycemic response in the evening compared to morning due to: ○ Diurnal decline in glucose homeostasis & circadian misalignment (late evening)	➢ *What is the impact of late eating for early chronotypes? Do they experience an increased metabolic stress due to the diurnal deterioration and circadian misalignment at the same time?*
A3/ OA3	• high GI food items can lead to reactive hypoglycemia ➢ ↑ feeling of hunger ➢ ↑ food consumption • Both glucose homeostasis and feeling of hunger are regulated circadian • Persons differ in their feeling of hunger and fullness by their chronotype in the morning	➢ *Does the diurnal profile of glycemia and hunger differ according to breakfast GI among early or late chronotypes?* ➢ *Are glucose parameters different following a high GI vs. medium GI meal among early or late chronotype?* ➢ *Are glucose parameters different between breakfast vs. dinner among early or late chronotype?* ➢ *Are glucose parameters associated with the feeling of hunger following breakfast?*	➢ Hunger increases throughout the day – irrespective of breakfast GI and chronotype ➢ glucose dips can also occur after medium GI meals – irrespective of mealtime and chronotype ➢ glucose dips occur rather in the morning and only after medium GI breakfast among early chronotypes ➢ glucose dips (reactive hypoglycemia) do not associate with increased hunger feelings per se	➢ *Is it possible to reduce diurnal increase in hunger?* **Hypothesis:** Hunger increases throughout the day irrespective of changes in daily eating patterns. ➢ *What nutrition recommendations can be suggested for students, who stay up late due to their late chronotype and/or studying, to increase satiety in the evening?* **Hypothesis:** Carbohydrates with low GI appear promising to promote satiety. ➢ *At which physiological glucose levels is reactive hypoglycemia associated with subjective hunger?*

Social jetlag: temporal difference in midpoint of sleep between workdays and work free days [26]. Eating jetlag: temporal difference in eating midpoint between workdays and work-free days [10].
↑: increase; ↓: decrease

6.2 Considerations arising from the findings of this thesis

This section focuses on potential recommendations of the thesis' findings and addresses selected research questions and hypotheses mentioned in **Table 8**.

6.2.1. How can consistent eating patterns be enabled among students?

Given the assumption that eating jetlag disrupts metabolic rhythmicity [20,77], thereby increasing the risk of adverse cardiometabolic health effects, including higher BMI [10,74], increased body fat [173], higher HbA1c, and elevated blood pressure [74], it underscores the significance of maintaining consistent mealtimes throughout the week [172], as observed during the COVID-19 related lockdown (OA1). This is of great importance now that social dynamics have returned to their pre-pandemic state, again affecting sleep timing, notably among persons with late chronotype [174], and hence, potentially meal timing.

Compared to other meals, breakfast is consumed less regularly or against the inner clock (OA1), with both adversely affecting glycemia [11,12,63,64], among students with later chronotype on workdays. Thus, allowing flexible breaks at university may enable students to consume breakfast at the same time as on work free days. Universities could also offer low to medium GI foods in the morning to encourage students to opt for a late breakfast without risking high postprandial glucose levels.

A further option may be a mix of remote/online and in-person courses, enabling students to study partly online from home. Our findings (OA1) and those of others emphasize [82,86,89,175] that remote study enabled students to align their schedules with their inner clock during the COVID-19- pandemic related lockdown period (s). Although returning to in-persons classes [176] meets the preference among students, many favor a combination of online and in-person classes according to a survey in the UK [177]. The implementation of hybrid teaching could alleviate the need for students to attend classes

early in the morning or late evening, and in-person classes could be scheduled towards the middle of the day. This may enable young students to better align their meal patterns (particularly breakfast) with their chronotype and contribute to maintaining metabolic health (OA1).

6.2.2. Meal timing by chronotype – what can be advised?

Our findings indicate that nutrition recommendations should differ by chronotype. For **students with early chronotype**, advising an early breakfast and avoiding food consumption at 8:00 p.m. or later would better align with their circadian rhythm to maintain glycemic health.

For **students with late chronotype**, the situation appears more complex, as both meals consumed at 7:00 a.m. and 8:00 p.m. caused similar adverse glycemic responses (see 0). This raises a question regarding an optimal eating window throughout the day for this population, which also appears of narrow time-range. Students with late chronotype may adopt a 16:8 fasting-eating rhythm, e.g. scheduling their eating window to late daytimes from 11 a.m. – 7 p.m. However, such a late eating window does not seem to improve or maintain glucose homeostasis compared to an early eating window (i.e. early morning until early afternoon) [178,179]. In fact, Allison observed adverse effects on glucose homeostasis following a late (12 a.m. – 11 p.m.) compared to earlier (8 a.m. –7 p.m.) window [73]. Studies on TRE have not yet considered chronotype, with only one study protocol currently addressing this aspect (ChronoFast trial) [180].

To date, studies examining chronotype-adjusted nutrition interventions are scarce and primarily focused on weight loss [181–183]. Marzi [183] and Munoz [181] shifted main energy intake to an earlier eating window (until lunch) among both persons with early and late chronotype, while persons with late chronotype still consumed more of their daily calories in the later eating window compared to those with early chronotype. Munoz

observed decreased fasting insulin levels and Mazri reported improved insulin resistance among both groups with energy distribution adjusted to the chronotype. Only Mazri considered meal timing, i.e., last energy intake at least 1 hour before sleep time, and additionally noticed an advanced sleep timing and reduced social jetlag among late chronotypes [183]. Strojiny only examined the impact of the same fixed meal timing schedule for both early and late chronotypes (breakfast at 7:30 a.m. and dinner at 5 p.m.), however, they do not inform about diurnal energy distribution. In their study, only those with early chronotype had a greater decrease in HbA1c [182].

The above mentioned studies examined that a chronotype-adjusted diet may have positive effects on glycemia in healthy overweight/ obese middle-aged adults. However, the metabolic response to meal timing among persons with different chronotypes are less explored. According to our observations, eating dinner late in the evening causes high postprandial glucose levels among persons with early chronotype (see ***Table 8***), potentially due to the diurnal deterioration of glucose homeostasis while simultaneously presenting some degree of circadian misalignment. For those with late chronotype, consuming a meal early in the morning also induces circadian misalignment due to their high melatonin levels (OA2). Thus, it remains to be determined when students should actually eat to avoid circadian misalignment. Observational studies suggest eating close to the circadian phase, either too early in the morning or too late in the evening, increases the risk of being overweight and [10,184] decreases insulin sensitivity, and elevates blood pressure [74]. Rather than focusing on the clock time of meal consumption, subsequent studies highlight the relationship to melatonin rhythm, however, again only focusing on body weight. For instance, consuming a high number of daily calories close to DLMO has been found associated with increased body fat and BMI [184]. [185] reported similar observations, but only among those with the latest DLMO, i.e. persons with latest chronotype. A later study of McHill suggests avoiding high carbohydrate intake in the late afternoon as well as main daily energy intake at 7 p.m. to maintain body weight

[186]. These studies strongly suggest that the timing of the last daily eating occasion and main energy intake need to be considered in relation to the individual circadian phase, which is hardly feasible in daily practice.

Another approach may be to recommend timing of the first and last meal in relation to sleep timing, as suggested by Xiao [71]. Xiao observed that consuming the main energy intake and carbohydrates two hours before bedtime increased the likelihood of being overweight/obese only in individuals with late chronotype. Conversely, main energy intake two hours after waking decreased the likelihood of being overweight/ obese only in early chronotypes. In practice, this implies that students need to know their chronotype or their MSF according to the findings of Zeron-Rugerio [187], i.e. scheduling the last eating occasion not later than 6 hours before MSF.

Hence, advising consistent alignment of the first eating occasion with timing on work-free days throughout the week may be a feasible approach to avoid interference of food consumption with high melatonin levels, while the timing of the last eating occasion needs further investigation.

6.2.2.1. Risk of adverse glucose levels due to melatonin intake

Considering the assumed adverse impact of melatonin on glycemic response [107], as supported by our results (OA2), the increasing trend of melatonin-containing supplement intake may be concerning [188]. In recent years, such supplements have been increasingly used to address insomnia without the use of prescription in certain countries [189]. In the European Union, supplements containing melatonin a maximum concentration of 1 mg can be freely purchased [190], whilst there are no regulations in the United States [191]. The intake of melatonin, either by prescription or as supplement, has particularly increased students, which use melatonin during and after exam periods,

[192,193], e.g. to advance sleep onset or improve sleep quality [194]. Of note, sleep onset has been found to be advanced by maximum 30 minutes [195]. According to a recent cross-sectional Spanish study among 6798 students 21% of students consumed melatonin and was the second most consumed psychoactive drug [193]. However, melatonin dosage can be easily exceeded due to is its convenient availability (e.g. fruit gums, sprays), which is concerning considering that an exogenous dose below 1 mg has been found to be as effective as higher concentrations of melatonin [195]. Moreover, wrong timing of exogenous melatonin can disrupt circadian rhythms [196]. Thus, the intake of exogenous melatonin should be considered with caution, and it is advisable to avoid simultaneous food consumption to prevent glucose spikes [107].

6.2.3. Is it possible to reduce diurnal increase in hunger?

Since glucose dips were not associated with subjective hunger (see Table 8), they appear negligible for subjective hunger among young and healthy students. However, the diurnal increase of hunger observed among both chronotype groups (OA3) may be concerning, considering the rising prevalence of obesity observed between 20 and 30 years of age [16]. Notably students with late chronotype seem more susceptible for increased energy intake in the evening due to later sleep onset than earlier chronotypes [26]. However, irrespective of chronotype, particularly exam periods may be critical as students extend their study hours into the late night [197], potentially resulting in increased energy intake through late-night snacking [80] due to increased hunger [15]. Additionally, sleep deprivation (< 7 hours sleep) [198], which is in general highly prevalent among students [199], may pose another risk for obesity [200]. It is hypothesized that increased hunger and energy intake resulting from sleep deprivation are due to an increase in energy expenditure and altered levels in hunger-related

hormones [7,80]. It thus seems plausible that sleep deprivation leads to a higher eating frequency, however, also a higher energy intake in the evening was reported [80,201].

Of note, sleep can be interrelated with circadian misalignment (see 2.2.2), the latter of which does not affect the circadian rhythm in hunger and related hormones under adequate sleep duration (see 2.10). However, studies controlling for sleep deprivation while investigating circadian misalignment also observed that hunger and related hormones ghrelin and leptin display an unchanged circadian rhythm [18,164,202,203]. On the other hand, in a study with unlimited access to food, an excessive caloric amount consumption (~4000 kcal/ 24 hours) following both conditions of circadian alignment and misalignment with sleep restriction was observed [204]. Moreover, compared to the aligned condition, more calories were consumed after 7 p.m. in response to misalignment and sleep restriction. Therefore, while the circadian rhythm of hunger sensations and related hormones is unaffected by both circadian misalignment and sleep restriction, hunger sensations appear overall elevated under sleep deprivation.

It remains to be determined whether subjective hunger may be reduced to prevent increased energy intake in the evening. Yet, only few studies investigated influences on diurnal hunger rhythm [27,205,206]. Among these, Jakobowicz [205] and Ruddick-Collins [206] suggest that consuming main daily energy intake in the morning reduces subjective hunger throughout the day, as observed in persons with overweight/obesity and with/without metabolic syndrome. Given the fact that this is characteristic for persons with early chronotype [61,207] it may be speculated that they are less hungry in the evening compared to the morning. On the other hand, Wehrens [27] observed that circadian rhythm of subjective hunger remained robust irrespective of whether shifting breakfast, lunch, and dinner to earlier or later times of the day. In line, another study did not observe any differences in subjective hunger and related hormones as well as energy intake throughout the day when having the first eating occasion (consisting of ≥700 kcal

of daily caloric intake) in the morning [208]. Consequently, eating patterns seem to have a minor, if any, effect on hunger sensations [209]. Furthermore, we observed that subjective hunger increased among both early and late chronotype groups throughout the day although meals and snacks were i.) balanced in energy intake accounting for sex and BMI, ii.) consumed regularly throughout the day, and iii.) most of daily energy intake was consumed until the afternoon (OA2).

Considering the robust circadian rhythm of hunger, it remains to be clarified what can be advised to eat in the evening, particularly when students stay-up late to study, e.g. during exam period [197]. Recommending consumption of low GI carbohydrates appears promising for promoting satiety [142] while preventing glucose peaks in the evening [14,129].

6.3 Methodological considerations

This chapter discusses the study design and population used to examine the research aims, and the methods applied to measure the respective research aim outcomes.

6.3.1 Study design

All research aims (see chapter 3) were investigated within a closed cohort, meaning participants were recruited only once and subsequently contacted for participation in the online survey during the COVID-19 related lockdown (see 4.2) and the nutrition trial (see 4.2.1). The study design of the research aims will be reviewed in the following.

6.3.1.1. Research aim 1

The associations of chronotype and social jetlag with eating jetlag before and during the COVID-19 related lockdown were examined by observational **prospective** study design (OA1). This design allowed to determine causation, in contrast to cross-sectional studies, as the exposure (e.g. social jetlag) precedes the outcome (eating jetlag) [210,211]. Hence changes in exposure are independent of outcome. Furthermore, due to the lower risk of recall bias in the prospective design, we were able to conduct a more detailed comparison of changes in eating jetlag compared to a retrospective study design, which relies on self-perceived changes, as used by many during COVID-19 lockdown [92,95,212–215].

6.3.1.2. Research aim 2

To determine the glycemic response to a meal consumed in the morning and evening among two chronotype groups, a cross-over design appeared most feasible in practice (see OA2). Firstly, as participants in both chronotype groups received the same interventions (high GI in the morning & high GI in the evening), but in a randomized order (morning x evening/ evening x morning), they acted as their own control [216,217]. Consequently, intervention effects are compared within a person**,** which removes inter-

individual variability, as occurs in between-group comparisons, balances distribution of covariates, and reduces confounding. Thus, if we would have aimed to compare glycemic response in the morning and evening between early and late chronotype groups, this would have quadrupled the sample sizes in each group to achieve statistical power, necessitating screening a significantly larger sample (approximately 1200 students) [218]. In contrast to a parallel design, we had to consider an adequate wash-out period between interventions (i.e., one day) to avoid carry-over effects from the first into the second intervention, ensuring analysis of the impact of both interventions separately [216,219].

A parallel study design would not have been the right approach for our research aim as participants would have been allocated to only one intervention [210,211,217], e.g. high GI in the morning or in the evening. Comparing intervention effects between groups can pose a high risk of confounding (see 6.3.2), e.g. when participant characteristics vary between groups and sample size is not sufficient irrespective of randomization [210]. Thus, according to Wellek, a parallel design would have required a study population six times larger than that needed for a cross-over study to achieve the same intervention effects according to [216].

As our study aimed to investigate diurnal differences of glucose response to socially scheduled meals by chronotype, we did not control for sleep-wake or light-dark rhythms, which are known to affect glucose metabolism [8,21]. Thus, we cannot conclusively determine whether these diurnal differences result from such external influences or whether they are exclusively generated by the circadian system. On the other hand, Morris [12] demonstrated that the diurnal rhythm in glucose tolerance is robustly regulated by the circadian system irrespective of external influences. Nevertheless, studies using the constant routine or FD protocol (see 2.8) may verify whether persons with early and late chronotype differ in their circadian rhythm of glucose homeostasis.

6.3.1.3. Research aim 3

The association between glucose dips and the feeling of hunger was a secondary analysis of the randomized cross-over nutrition trial (OA3). Consequently, this analysis was based on observational and explorative data and may have lacked statistical power to detect significant associations. Nevertheless, the study design was appropriate to assess hunger sensations, given the variability in subjective perception both between individuals and interventions, as it enables analysis within a person [145,209,220]. Of note, day-to-day variations in the subjective perception of hunger and effects of external stimuli can confound correlations [146,220]. Thus, identical test meals need to be consumed in duplicate on different test days for repeated measures to compare the subjective estimations of hunger/fullness in response to the meals within the same participant [17,145], which was not conducted in our study. Furthermore, to examine diurnal differences, data on subjective hunger/fullness feelings should have been collected before breakfast/dinner (e.g. -15 min), at the time of consumption, and in regular intervals after meal consumption (e.g. 30 min. intervals over a 240 min. timespan). This would have provided data on minimum and maximum hunger feelings in relation to glucose data. This approach was limited due to the secondary nature of this study, as we only collected data just before meal/snack consumption. This also resulted in lack of data collection regarding hunger and fullness sensations after dinner.

6.3.2 Statistical considerations

For analysis I and III (OA1 & OA2), confounding of the cause-effect relationship between exposure and outcome had to be considered [211]. A confounder is causal to the outcome independent of the exposure and is further associated with the exposure even in absence of the outcome. To avoid random confounding, we evaluated the

confounders' aetiology in the exposure-outcome association before analysis, including only variables that either improved the exposure´s regression coefficient [221], or significantly predicted the outcome [222]. Furthermore, the relation between exposure and outcome can be enhanced or mitigated, termed *interactions* [211]. Consequently, we separated our analysis in research aim 1, as we observed sex-differences in the association of social jetlag and eating jetlag at screening (OA1). Due to the cross-over design we performed multilevel linear regression (proc mixed models) considering the dependence between repeated measures, e.g. glucose parameters morning vs. evening, within a person and to account for variations between measures within the person for both research aims 2 & 3 [223].

6.3.3 Study population

Our study population is well-defined and comprises of healthy university students aged 18-25 years with defined chronotype, and normal body weight. Consequently, our results may not extend to older, less healthy, or obese people as well as persons other than students. As expected, the majority of the cohort were women, as often observed in health studies [224]. The controlled nutrition study was conducted with participants based on the earliest and latest chronotype within the screened cohort. Compared to the literature, the study sample, on which the results of this thesis are based on, comprises individuals with moderately early or late chronotype rather than persons with extreme early and late MSF_{sc} (< 1:00 a.m. and > 6 a.m., respectively), (OA2) [26].

6.3.4 Methodological Assesments

6.3.4.1 Assessment of chronobiologic predictor

Chronotype was estimated based on the participants' MSF_{sc} using the MCTQ (see 4.1) [26]. Other commonly used questionnaires, such as the MEQ and CSM (see 2.2), were

not suitable for our purpose, as these do not inquire about sleep and wake times, but daytime preferences for sleep (see 2.2). Consequently, we could not have estimated the students' social jetlag [26], indicating circadian misalignment and a predictor for eating jetlag (OA1). Moreover, the MEQ determines chronotype based on pre-defined scores and as such, individual categorization within the study group is not intended [36]. As in previous studies, this may have led to an uneven distribution among chronotype groups for research aim 1, as in previous studies [58,225]. Furthermore, as we aimed to schedule the high GI meal against the inner clock (research aim 2), we had to select participants with the current earliest and latest MSF_{sc} within the screened cohort (see 4.2). During the controlled nutrition trial, we confirmed participants' chronotype using both sleep times records in a diary and an accelerometer (see 4.2), due to the potential for over- or underestimation of self-reported sleep and wake times [226,227]. Moreover, parallel recording was reported to demonstrate good correlation, provide more accurate values [50,228–230], and associate with DLMO [34]. Indeed, MSF_{sc} calculated based on data recorded by accelerometry and diary entries show quite good agreement with a mean difference of 09:54 m:ss, i.e., 0,7% (see ***Appendix Table 2***).

6.3.4.2 Psychological disturbances as potential predictor for erratic eating patterns

During the 1st COVID-19 related lockdown, we observed decreased snacking frequency among students in contrast to most studies but reporting negative impacts on eating behaviors, such as loss of eating control [213,231–234] and increased snacking frequency [97,98]. These discrepancies may stem from differences in country and the time of survey administration [235]. These studies focused on the early stage of pandemic restrictions (March – May 2020), characterized by mandatory self-isolation at home and high uncertainty [82], potentially increasing vulnerability to emotional eating [236,237]. In contrast, we collected data when social restrictions had already been eased

locally [166], potentially resulting in reduced psychological distress [238] and thus decreased snacking frequency. Though we did not measure psychological distress as to not overload the questionnaire, the following sections highlight the psychological impact on regular eating patterns during the COVID-19 related lockdown.

Loss of eating control, food craving, or increased snacking are reactions to negative or positive emotions and not to a biological lack of energy [145] and are termed emotional/ stress eating [235]. Stress is the individual's perception of being overwhelmed or able to master a challenging situation. This largely depends on coping skills and trait-like characteristics, such as self-esteem [235,239]. Students, in general, constitute a highly vulnerable group to psychological distress [240], with depression and anxiety affecting almost one-fifth of students [241]. This is attributed to adapting to new environments, dealing with academic pressure, and/or financial problems [242]. As these circumstances have worsened since the outbreak of the COVID-19 pandemic [243,244], an increase in anxiety and depression, stress [237,239,245], and/or insomnia (i.e. sleep disturbances) [91,246], which are often interrelated [239,247,248], was observed among students. Consequently, this led to increased emotional eating behaviors [234,235,239,244]. Of note, psychological disturbances are often associated with lower resilience and negative coping strategies, such as denial and avoidance of challenging situations [249,250]. As emotional eating can increase daily energy intake, it potentially increases the risk for obesity [235], ***Figure 11***.

6.3.4.2.1 Predictors of psychological disturbances among students during COVID-19 related lockdown

During COVID-19 related lockdown predictors associated with psychological disturbances among students have predominantly arisen from cross-sectional studies and are: younger age [234,251–253], being in the first semesters, or being

undergraduates [234,254,255], female sex [234,237,238,245,246,256], financial [243,244,257], academic [257,258], and family problems [255,257], as well as feelings of loneliness [259–261].

Graduate students appear to experience less psychological distress. This may be attributed to their potentially enhanced coping skills, which are crucial for mental health [256,262], as well as their better self-estimation of academic achievements, and an increased self-efficacy in their studies [239]. Consequently, they may exhibit greater resilience compared to younger and undergraduate students [234,251,263]. Furthermore, students predisposed to psychological disturbances [245] and facing academic challenges prior to the lockdown experienced enhanced disturbances during lockdown [257,258]. Students reported increased stress as they felt overloaded with work, the latter of which was greatly affected by the shift from in-person to distance learning as many students struggled to adapt to this new format [255].

During COVID-19 related lockdown, adults with late chronotype showed lower resilience [174,264], increased insomnia, and more depressive symptoms than those with early chronotype, irrespective of education status [264,265]. According to a cross-sectional study among 19.267 adults from 12 countries, those with late chronotype reported more mental health issues and lower well-being [266]. Additionally, analysis of four international cohorts indicated those with late chronotype were more likely to be emotional eaters before lockdown [267]. It is also plausible that young students with late chronotype may have experienced more lockdown-associated psychological disturbances, leading to increased emotional eating.

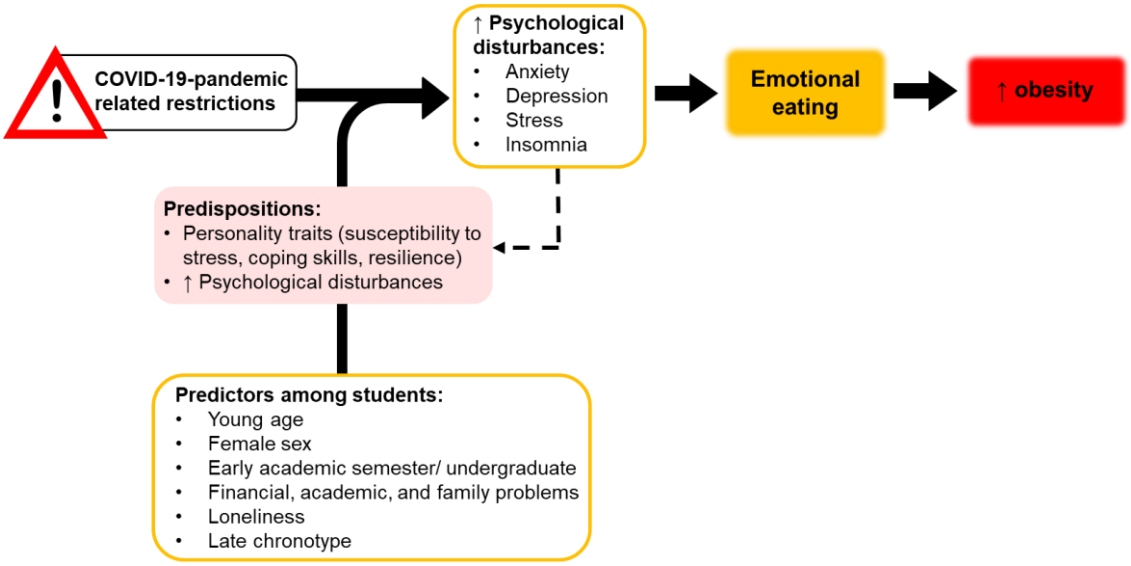

Figure 11: COVID-19-pandemic related restrictions increased psychological disturbances leading to emotional eating, thereby increasing the risk for obesity. Among students, predictors were associated with increased psychological disturbances, enhanced by the individuals' predispositions [235,239,248]. Vice versa, psychological disturbances, such as depression and insomnia, are associated with adverse personality traits, i.e. low resilience, and coping skills [249,250]. Figure owned by Bianca Stutz.

In summary, students are a highly vulnerable group to psychological distress, which increased during the COVID-19 related lockdown, leading to an increase of habits related to emotional eating. Thus, assessing psychological distress may have provided us more insight into whether less psychological distress among our study population contributed to the development of more regular eating habits.

6.3.4.3 Outcome measurements

6.3.4.3.1 Eating jetlag – Definition of meals and snacks

For research aim 1, participants reported consumption and timing of breakfast, lunch, and dinner (see OA1). However, the conventional three meals-a-day pattern is often absent, with more than three daily *eating occasions/ events* common [76,77]. Hence, the terms *eating occasions/ events* appear more appropriate to characterize students' eating patterns. Consequently, we also included snacks in our analysis of eating jetlag, and our findings emphasize the significance of snacks in relation to eating jetlag. Additionally,

the terms *eating occasions/ events* provide an objective approach, recognizing that individuals define meals differently depending on their sociocultural background [268]. Furthermore, inquiring on the timing of eating occasions relative to the individual circadian phase appears to be equally important for metabolic health as examining meal consumption or skipping (research aim 2). Given the absence of three meals-a-day pattern [76,77], participants may have found it challenging to differentiate between meals and snacks, such as mistaking breakfast for midmorning snacks, leading to biased categorization of breakfast skipping. This highlights the lack of a clear distinction in research [269,270], yet meals and snacks are either i) subjectively defined by participants, ii) pre-defined by researchers, or iii) retrospectively classified [268]. In our study, we inquired about snacks consumed between meals without further definition, potentially leading to heterogeneous interpretations of snacking [268], which may have biased findings on eating jetlag. Objective approaches, e.g. retrospective classifications, wherein researchers classify participants' eating occasions after data collection, appear to be the less biased approach. Retrospective classifications include 24-hour dietary recalls, dietary records, or food diaries [270,271], and new technologies, such as digital food diaries using mobile phone apps [59], which allow participants to take photos of consumed meals and snacks [76,77], may provide more precise data. However, as these methods are expensive and time consuming, they were less suitable for our study. Consequently, the risk of bias may be tolerated in epidemiological settings [271].

6.3.4.3.2 Glycemic response

The controlled nutrition trial primarily aimed to compare diurnal differences of postprandial glucose levels in response to the intervention meal (research aim 2), as high glucose values are crucial for T2D risk [272]. Thus, parameters, such as $iAUC_{net}$ and AUC_{total}, have not been applicable as they also consider the area beyond baseline

in contrast to iAUC [273]. However, AUC values do not identify glucose fluctuations, i.e., glycemic variability, which is found to be more deleterious for cardiovascular health than consistently high glucose levels even, in healthy individuals [272,274]. Since the availability of CGMs, measures of glycemic variability have regained interest, leading to development of new parameters, such as continuous overall net glycemic action (CONGA) [275]. However, many measures of glycemic variability correlate with each other [276], likely due to their consideration of mean glucose levels [277]. Hence, different measures of glycemic variability may not necessarily provide distinct or substantially different information [275]. Consequently, we examined conservative variables (mean, standard deviation, highest, and lowest glucose value), except for 24-hour mean amplitude of glucose excursion (MAGE), i.e. excursions >1.0 standard deviation of mean glucose level [277]. Given debate regarding the significance of glucose excursions >1.0 standard deviation for metabolic health compared to postprandial excursions, e.g. iAUC, MAGE may not have provided additional information for 24-hour glycemia.

6.3.4.3.3 Assessment of subjective hunger

For research aim 3, we collected data on hunger using LMS scale before participants consumed any meal/snack (see 4.2.2). This scale belongs to the labeled magnitude scales, anchored by the greatest feelings of hunger/fullness, and subdivided by perceptions describing different intensities [220]. Since the semantic meaning of the descriptions and the intensity of hunger/fullness differs inter-individually, participants should be trained in using the scale to ensure that all agree on the descriptors' semantic meaning and express the same perceptions [278]. However, as we saw a clear trend of hunger increasing throughout the day, training may have only improved precision of recordings. Given that labeled magnitude scales are often tailored for specific study

purposes, such as the LMS scale used from Zalifah (2008) to measure perceived satiety (LMS scale), a universal scale is lacking [168,220,279]. Compared to the LMS, the VAS is anchored by the greatest feeling of hunger/fullness without further descriptions along the scale [145]. Thus, the VAS does not present the risk of participants' responses clustering around the descriptors on the scale [279]. On the other hand, it is argued that the LMS scale is easier to use due to the descriptors along the scale than VAS, as observed in a previous study. The main advantage of VAS is its reproducibility and validity with identical meals [146], potentially contributing to higher reliability of our findings.

6.3.4.3.4 Measurement of hormones

In the controlled nutrition trial, we did not measure appetite or satiety hormones, e.g. ghrelin, GLP-1, and leptin, which also exhibit a circadian rhythm [20]. This omission limited interpretation of our findings in relation to the participants´ circadian rhythmicity at the time of intervention. Importantly, we measured melatonin in a subsequent analysis (OA1) from fasting plasma samples collected sequentially on day 4, starting with the first participant at 7 a.m. and concluding with the last participant in the row by ~7:30 a.m. (OA2). Such temporal differences in blood collection can result in high variation in the measured melatonin levels. Hence, it is best to measure melatonin repeatedly at the same daytime in each participant and within the study group [280]. Additionally, melatonin levels vary significantly between individuals. Therefore, melatonin should be measured only at critical thresholds when secretion increases, as determined by DLMO, or decreases, such as 1-2 hours after wake-up [31]. Currently used test methods, such as radioimmunoassay and enzyme-linked immunosorbent assay kits, measure melatonin levels both in saliva and plasma, but vary in detection sensitivity, particularly detection of low melatonin levels during the daytime [280]. Plasma melatonin is preferred

for assessing total levels and inferring pineal gland production, due its binding to proteins. Saliva, on the other hand, contains unbound melatonin, i.e. 30% of total plasma melatonin, and is useful for detecting concentrations changes.

To determine whether intervention meals were consumed against the inner clock, participants could have collected saliva samples at home, e.g., every 30 minutes for 1-2 hours when consuming the intervention meals in the morning and evening [280]. Unfortunately, melatonin measurement was not considered in our study planning.

7. CONCLUSION AND OUTLOOK

In conclusion, students, notably those with late chronotype, are vulnerable for a more erratic meal pattern and for adverse glucose response when eating against their inner clock. Whilst glucose dips also occurred, we cannot confirm a relevance of glucose dips for subjective hunger. Of note, hunger increased throughout the day, irrespective of chronotype. Based on these findings, some aspects require further investigation.

Firstly, longitudinal research is needed to investigate the impact of erratic meal patterns during young adulthood for the development of cardiometabolic diseases, such as T2D or obesity. In this context, future studies should explore the feasibility of implementing more flexible study formats, e.g. a combination of online and in-person courses at universities. Additionally, it is crucial to determine whether such a flexible study environment enables students to align better with their inner lock, as seen during COVID-19 related lockdown.

Our findings reveal that the diurnal rhythm of glucose metabolism differs among persons with early and late chronotype. Thus, future studies must consider the participants' chronotype to interpret findings without selection bias. We speculate that previous intervention studies, often scheduling study visits in the early morning, may have inadvertently enrolled persons with early or intermediate chronotypes rather than persons with late chronotype.

Moreover, as we examined diurnal differences of glucose response by chronotype, studies controlling for behavioral and environmental cycles may verify whether these differences are exclusively generated by the circadian system [8,21]. Furthermore, studies using the FD protocol (see 2.8) may provide more insight on the optimal eating window particularly for persons with late chronotype, who seem to face a dual risk of adverse glycemic response when eating early in the morning and late in the evening. Of note, while epidemiological studies indicate a higher risk of adverse health impacts

among individuals with late chronotype compared to those with early chronotype [69,281], the circadian rhythms of metabolic responses need more investigations.

Furthermore, strategies are necessary to compensate for increased hunger in the evening, thereby preventing glucose peaks and weight gain. This is relevant for young students, notably those with late chronotype, as they may stay up late to study, e.g. during exam periods, and thus are vulnerable to increased late-night snacking.

APPENDIX A

Glossary of chronobiology related terms

Appendix Table 1: Glossary of chronobiology related terms.

Behavioral rhythm	Sleep-wake, fasting-eating, rest/exercise cycles.
Chronotype	Circadian phenotype, which differs between individuals.
Circadian day/night	Defines the circadian phase during which melatonin levels are low (day) or high (night).
Circadian rhythm	Endogenous generated diurnal rhythm that repeats itself every ~24-hours. This rhythm is self-sustaining irrespective of environmental or behavioral influences.
Constant Routine protocol	Experimental protocol removing the rhythm of environmental and behavioral influences to measure circadian rhythms of biological parameters. This is enabled by keeping environmental and behavioral influences constant over ≥ 24 hours.
Cycle	See *period*
Diurnal (or daily day-night) rhythm	Circadian, environmental and behavioral rhythms drive diurnal rhythms of biological and physiological parameters and repeat itself every ~24-hours. The diurnal rhythm of the circadian system is reflected by cyclic phases of circulating melatonin, which are affected by light.
Entrainment	Synchronization of a rhythm to behavioral or environmental cues (e.g. synchronization of the circadian rhythm to day-night rhythm).
Environmental rhythm	Light-dark/ day- and night cycles.
Forced Desynchrony (FD) protocol	Experimental protocol disentangling the circadian rhythm from behavioral and environmental rhythms (e.g. light-dark/ sleep-wake/ eating-fasting cycles) to measure biological parameters in response behavioral/ environmental rhythms across all circadian phases. This allows to separately determine the effects of circadian/ behavioral and/or environmental rhythms as well as circadian alignment/ misalignment.
Misalignment (or desynchrony)	Differences in phases between two rhythms, i.e. misalignment between environmental (light-day/day-night), behavioral (eating-fasting/sleep-wake cycle) and the circadian rhythm, e.g. light exposure during the circadian night.
Period	Cycle length: time it takes a rhythm to repeat itself (~ 24-hours).
Phase	A period is structured in phases, which is the time relative to a key point within a cycle (e.g. minimum, maximum).
Time cue	An external cue (e.g. light, sleep, food consumption) that entrains (synchronizes) the phase of a circadian rhythm.

References: [1,8,26]

APPENDIX B

OA1

Appetite 180 (2023) 106333

Contents lists available at ScienceDirect

Appetite

journal homepage: www.elsevier.com/locate/appet

Associations of chronotype and social jetlag with eating jetlag and their changes among German students during the first COVID-19 lockdown. The Chronotype and Nutrition study

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ARTICLE INFO

Keywords:
Eating jetlag
Erratic meal pattern
Chronotype
Social jetlag
COVID-19

ABSTRACT

Due to their biologically later chronotype, young students are vulnerable to a discrepant sleeping pattern between work- and free days, coined *social jetlag* (SJL). This study examined whether a later chronotype and/or a larger SJL are related to an analogous discrepancy in meal timing defined as *eating jetlag* (EJL) and whether chronotype and/or changes in SJL during the first COVID-19 related lockdown in Germany associated with changes in EJL. Baseline data were collected from September 2019–January 2020 among 317 students (58% females) aged 18–25 years of which a total of 156 students (67% females) completed an online follow-up survey in June–July 2020 (1st lockdown). Data were collected on daily routines, timing of meals/snacks, and physical activity. Chronotype was determined using the Munich ChronoType Questionnaire; SJL and EJL correspond to the difference in the daily midpoint of sleep/eating duration between work- and free days. Multivariable linear regression revealed that students with a later chronotype or a larger SJL experienced a larger EJL ($p_{adjusted}$ = 0.0124 and $p_{adjusted}$<0.0001). A later chronotype at baseline and reductions in SJL during lockdown associated with concurrent reductions in EJL ($p_{adjusted}$ = 0.027 and $p_{adjusted}$<0.0001). In conclusion, students with a later chronotype exhibit a more erratic meal pattern, which associates with SJL. During lockdown, flexible daily schedules allowed students to align the meal timing with their inner clock.

1. Introduction

The relevance of the eating pattern on the individual's circadian rhythm has been highly discussed lately: meal timing was found to differ between work- and free days resulting in an "eating jetlag" (EJL) – also called "metabolic jetlag" – reflecting the extent to which an individual is eating against the own circadian rhythm (Gill & Panda, 2015; Makarem et al., 2021; Thomas et al., 2020; Zerón-Rugerio et al., 2019). A recent study reports that individually preferred eating times commonly differ largely from the actual meal timing in daily life of students (Veronda & Irish, 2021). Of note, EJL seems to be most pronounced among those with a later diurnal phenotype – i.e. chronotype – as reported by a study among Spanish and Mexican students (Zerón-Rugerio et al., 2019). Although the associated metabolic risks still have to be fully elucidated, recent studies indicated that food consumption shortly before or after the own circadian sleep phase (e.g. late night snacking among earlier chronotypes or early breakfast among later chronotypes) may entail metabolic consequences such as an increased risk for overweight (McHill & Wright, 2017; Zerón-Rugerio et al., 2019), decreased insulin sensitivity, and elevated blood pressure (Allison et al., 2021; Makarem et al., 2021).

Students are particularly vulnerable to live against their inner clock since humans experience their latest chronotype at the age of 20–21 years (Roenneberg et al., 2004) and university commonly starts at relatively early times of the day. This further results in a phenomenon coined "social jetlag" (SJL), likewise defined as the difference in the midpoint of sleep between work- and free days. Later chronotypes are more likely to have a larger SJL (Roenneberg et al., 2019), yet – while plausible – associations between chronotype and/or SJL and EJL remain to be established.

Abbreviations: SJL, social jetlag; EJL, eating jetlag.

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https://doi.org/10.1016/j.appet.2022.106333
Received 29 December 2021; Received in revised form 18 August 2022; Accepted 28 September 2022
Available online 4 October 2022

The exponential outbreak of COVID-19 has caused sudden stark changes in every day's life: many countries imposed restrictive measures, e.g. closing education institutions, restaurants, and fitness centres obliging citizens to isolate themselves at home (Stafford, 2020). Consequently, leisure activities, studying, and working were relocated to the individual's home, which has in fact enabled many individuals to adjust daily work and social schedules to their circadian rhythm, resulting in a reduced SJL particularly among young adults (Korman et al., 2020; Stafford, 2020). Changes in dietary patterns due to COVID-19 related lockdown have also been described, yet primarily with respect to a more pronounced consumption of snacks (Alfawaz et al., 2021; Deschasaux-Tanguy et al., 2021; Gallo et al., 2020), confectionaries (Huber et al., 2021), and sweets (Deschasaux-Tanguy et al., 2021). It remains to be clarified whether more erratic meal timings as reflected by larger EJLs were also reduced during the lockdown in the particularly vulnerable group of students and how chronotype or changes in SJL were associated with changes in EJL.

Therefore, we aimed to assess the association of chronotype and SJL with the extent of erratic meal patterns reflected by EJL in a sample of students aged 18–25 years before the COVID-19 pandemic. Secondly, we examined whether chronotype at baseline and/or changes in SJL during lockdown were related to concurrent changes in EJL. We hypothesized that students adjusted their dietary habits on workdays to those on free days, which would result in a reduced EJL. In line with this, we expected greater changes in EJL among students with a later chronotype at baseline and/or those with larger changes in SJL between baseline and lockdown.

2. Methods

2.1. ChroNu study

The ChroNu (Chronotype and Nutrition) study is a cohort study that commenced at Paderborn University (Germany) in September 2019. This study aimed to collect data on the timing of students' daily routines, meal consumption and physical activities as well as their circadian phenotype during their studies. Participants were recruited through posters, flyers, and online advertisement (e.g. social media). Eligibility criteria considered healthy students aged 18–25 years and being fluent in German from all faculties of Paderborn University. Students enrolled in study courses of the research group, regularly working shifts at night or having travelled >1-time zone in the past three months (McHill & Wright, 2017) were excluded, as were those being pregnant or lactating, taking antidepressants, hypnotic and/or sedative medication. From September 2019 to January 2020 students were interviewed for eligibility in person by the study team and asked to fill in questionnaires online via the data capture tool RedCap at the study centre. During the 1st COVID-19 pandemic lockdown, all participants were re-contacted via e-mail and asked to fill in the same questionnaires online on RedCap as assessed at baseline. All questionnaires referred to the past four weeks. In Germany, education institutions (including universities and schools) and cultural institutions were closed mid-March 2020 except for grocery stores, pharmacies, and post offices which remained open; social gatherings were banned and two people from two households only were allowed to meet in public and private (Staller & Randler, 2020). From June to July 2020 – when the follow-up was conducted online- certain restriction measures had already been eased locally like opening restaurants, bars, and fitness centres (Mitteldeutscher Rundfunk, 2020) but universities remained closed until autumn 2021. Data were collected and managed using RedCap online data capture tools hosted at Paderborn University (Harris et al., 2009). Informed consent was obtained from all participants in written form at the baseline visit and online prior to the survey. The study was approved by the Ethics Committee of Paderborn University and registered at clinicaltrials.gov (NCT04302922).

2.2. Study population

In total, 327 students (58% females) were included in the baseline recruitment, yet seven persons were excluded based on the eligibility criteria (n=6: regular night work, n=1: taking antidepressants). Reports on eating duration <4 h on workdays, i.e. shorter than the shortest period of time-restricted eating (4:20 h) (Cienfuegos et al., 2020) were considered implausible (n=3). Hence, the analysis was performed in 317 students. During the COVID-19 pandemic lockdown, 192 online survey entries were recorded. Of those, 27 surveys were incomplete, four participants filled in the survey twice, and two further entries did not match with the baseline IDs. Three participants got further excluded due to the eligibility criteria (n=2: regular night work; n=1: taking antidepressants), thus resulting in 156 participants included in the follow-up analysis.

2.3. Chronotype and SJL

The chronotype was assessed by the Munich ChronoType Questionnaire (MCTQ) (Roenneberg et al., 2003). In brief, the MCTQ inquires sleep time separately for work- and free days. Free days refer to days when neither studying nor working is scheduled, while workdays refer to those days on which students either study and/or work. The individual chronotype is calculated as the midpoint of sleep (MSF) between sleep-onset and sleep-offset and corrected for accumulated sleep debt during workdays (MSF_{sc}). SJL represents the actual temporal difference between the midpoint of sleep on workdays and free days (Roenneberg et al., 2019).

2.4. Characteristics on eating pattern

Habitual consumption (yes/no) and timing of breakfast, lunch, dinner and snacks were separately inquired for work and free days. Skipping breakfast/lunch/dinner was defined as no consumption of the corresponding meal. Meals and snacks were defined individually by the participants. EJL was calculated as previously suggested by Zerón-Rugerio (Zerón-Rugerio et al., 2019). Briefly, EJL describes the temporal difference between the midpoint of eating on workdays and free days. The daily eating midpoint is calculated based on the timing of the first and the last meal. Furthermore, the jetlag for each meal was assessed as the temporal difference in the midpoint of the corresponding meal between work- and free days. One participant reported identical timing for breakfast and lunch on work- and free days (8:30 a.m. and 11:00 a.m., respectively). In this case, meal timing was considered for breakfast only.

The definition of EJL by Zerón-Rugerio only considers main meals (Zerón-Rugerio et al., 2019), but since snacks may be consumed in place of meals (e.g. skipping breakfast in favour of snacking later) or after the last meal, i.e., late night snacking among later chronotypes (Xiao et al., 2019), we considered whether snacks were consumed (yes/no) in the morning (9:00–11:30 a.m.), afternoon (13:30–18:00), and at night (≥19:00) to estimate the eating midpoint and thus determine a total EJL also accounting for snacking. To this end, we defined snack time as the midpoint in the above given time frames (e.g., 10:15 a.m. for morning snack consumed between 9:00 a.m. and 11:30 a.m.). If snack at night (i.e. snack after 19:00) was reported, we calculated an individual midpoint between 19:00 and the time when getting ready to sleep as obtained from the MCTQ (*"When are you ready to fall asleep?"*) (Roenneberg et al., 2003). Hence, we focused on the analysis of the total EJL, yet also report data on the main meal EJL (Zerón-Rugerio et al., 2019) for comparative purposes in sensitivity analyses. We further estimated the duration of nightly fasting as the timespan between the last meal/snack and first meal/snack.

Table 1
General characteristics stratified by sex-specific tertiles of chronotype at baseline (n=317).

		Chronotype		
	n	T1 *(n=105)*	T2 *(n=107)*	T3 *(n=105)*
Sex (females, n (%))	183	61 (58)	62 (58)	60 (57)
Age (years)	317	22 (20.0; 23.0)	22 (20.0; 24.0)	21 (20.0; 23.0)
Smoking (n (%))[a]	31	6 (6)	12 (11)	13 (12)
Days of classes at university (n)	317	4 (3; 5)	4 (3; 5)	4 (4; 5)
Start at university (h:mm)	303	9:51 (9:00; 10:50)	10:12 (9:15; 10:09)	10:23 (9:30; 11:12)
End at university (h:mm)	303	15:48 (15:03; 16:31)	15:48 (14:52; 16:46)	15:36 (14:33; 16:30)
Average travel time to university and back during week (h:mm)	317	00:40 (0:20; 1:20)	00:40 (0:23; 1:20)	0:30 (0:20; 1:00)
Job (n (%))[b]	198	70 (67)	72 (67)	56 (53)
Living form (n (%))				
Shared apartment	150	46 (44)	49 (46)	55 (52)
Single apartment	57	13 (12)	20 (19)	24 (23)
Other (with parents/partner/own family)	110	46 (44)	38 (36)	26 (25)
Screen time >4 h/day (h:mm)				
Workdays	165	46 (44)	60 (56)	59 (56)
Free days	130	32 (30)	39 (36)	59 (56)
Physical activity (n (%))[c]				
High (≥5 days/week)	68	26 (25)	23 (22)	19 (18)
Low (≤2 days/week)	112	28 (27)	39 (36)	45 (43)
Exercise intensity (n (%)) [d]				
High (≥2 h/week)	184	70 (67)	55 (51)	59 (56)
Low (<1 h/week)	51	13 (12)	17 (16)	21 (20)
Exercise on workdays (n (%))				
Early (6:00–14:00)	95	38 (36)	34 (32)	23 (22)
Late (≥14:00)	265	87 (83)	90 (84)	88 (84)
Exercise on free days (n (%))				
Early (6:00–14:00)	141	60 (57)	45 (42)	36 (34)
Late (≥14:00)	226	64 (61)	79 (74)	83 (79)

Abbreviation: T, tertile; n, sample size.
[a] Smoking (yes/no).
[b] Job (yes/no).
[c] Physical activity: every activity resulting in sweating or heavily breathing.
[d] Exercise: regular training sessions. Data are frequencies, or medians (Q1, Q3).

2.5. Daily activities

Data on smoking (yes, no, sometimes) was inquired. Furthermore, with respect to the student's schedule at university start and end times of attended lectures on the corresponding weekdays were inquired at baseline; in the online survey, students were asked to report the schedule of attended online classes. Average travel time to and from university was queried at baseline only. At baseline and follow-up, participants were asked whether they had a job (yes/no) and whether they lived in in a flat-sharing community, single apartment, with parents, partner, or their own family. Similarly, participants were asked at both time points on their daily active screen time (computer, TV, smartphones, excluding e-books) separately for work- and free days (>6 h/day, 4–6 h/day, 3–4 h/day, 1–2 h/day, 30–60 min/day, ≤30 min/days, not at all, I do not know). Data on physical activity (7, 6, 5, 4, 3, 2, 1 or 0 day(s)/week) and exercise (no exercise, <1 h/week, 1–2 h/week, 2–4 h/week, >4 h/week) were collected using the German health questionnaire adapted from the German Health Interview and Examination Survey for Adults (Krug et al., 2013). Whereas questions on exercise referred to regular training sessions, questions on physical activity considered all activities associated with breathing heavily or sweating. We further queried the time frames in which exercise was usually performed separately for work- and free days: morning (6:00 a.m.–11:00 a.m.), noon (11:00 a.m.–14:00), afternoon (14:00–18:00), evening (18:00–21:00), and/or at night (21:00–6:00 a.m.).

2.6. Statistical analyses

Potential confounders considered in the analyses were defined as follows: Smoking was categorized in smokers (yes or sometimes) and non-smokers (no). Average start and end times of attended lectures were calculated by adding up all data given for the respective days and dividing them by the number of days on which lectures were attended. Travel time forth and back to university were added up to obtain total travel time. If participants did not attend lectures or were studying entirely from home, timing of attended lectures and total travel time were set to zero. In the follow-up, travel time was not assessed and thus baseline data were set to negative values to describe for changes in the follow-up. Living form was grouped in flat-sharing community, single apartment, and other (living with parents/partner/own family). High screen time was categorized as screen time >4 h/day (yes/no). Days of physical activity were categorized as high (≥5 days/week) or low (≤2 days/week) and intensity of exercise as high (≥2 h/week) and low (<1 h/week), respectively. Timing of exercise was grouped in "early" combining time frames in the morning and middays (6:00 a.m.–11:00 a.m., 11:00 a.m.–14:00) and "late" summarizing time frames in the afternoon, evening, and at night (14:00–18:00, 18:00–21:00, 21:00–6:00 a.m.). Data on snacking in the morning or evening on work- and free days were summarized because snacking habits did not differ significantly between work- and free days.

Descriptive data are presented as medians (Q1, Q3) for continuous variables and percentages for categorical variables in sex-specific tertiles of chronotype (MSFsc). Changes in categorical variables were determined as changes in category (baseline minus follow-up), i.e., a negative value indicate a decrease in the respective category. The hypotheses underlying the following analyses (see introduction) were specified before carrying out the statistical analysis according to a pre-specified analytic plan: 1) Association of chronotype or SJL (exposure variables) with total EJL (outcome) at baseline, and 2) Association of the chronotype at baseline or changes in SJL (exposure variables) during lockdown with concurrent changes in total EJL (outcome). Chronotype at baseline (rather than changes in chronotype) was related to changes in total EJL since chronotype is considered a biological construct (Roenneberg et al., 2019) and it was assumed that this would remain stable

Table 2
Circadian characteristics, meal intake, and meal timing by sex-specific tertiles of chronotype at baseline (n=317).

		Chronotype		
	n	T1 *(n= 105)*	T2 *(n=107)*	T3 *(n=105)*
MSFsc (h:mm)	317	3:35 (3:10; 3:50)	4:35 (4:22; 4:50)	5:35 (5:20; 6:00)
Time when falling asleep (h:mm)				
Workdays	317	22:45 (22:30; 23:15)	23:50 (22:50; 24:00)	24:00 (23:30; 1:00)
Free days	317	23:15 (23:00; 23:59)	1:30 (24:00; 1:00)	1:35 (1:00; 2:15)
Wake-up time (h:mm)				
Workdays	317	7:00 (6:30; 7:30)	7:30 (7:00; 8:00)	8:00 (7:30; 9:00)
Free days	317	8:00 (7:30; 9:00)	9:00 (8:30; 9:45)	10:00 (9:30; 10:45)
Social jetlag (h:mm)	317	0:50 (0:25; 1:15)	1:07 (0:46; 1:35)	1:35 (0:57; 2:10)
Breakfast timing (h:mm)				
Workdays	234	8:00 (7:30; 8:30)	8:12 (7:55; 8:55)	8:30 (8:15; 9:30)
Free days	254	9:00 (8:45; 10:00)	10:00 (9:00; 10:00)	11:00 (10:00; 11:15)
Lunch timing (h:mm)				
Workdays	296	13:00 (12:30; 13:00)	13:00 (12:30; 13:15)	13:00 (12:30; 13:30)
Free days	248	13:00 (13:00; 14:00)	13:30 (13:00; 14:00)	14:00 (13:00; 15:00)
Dinner timing (h:mm)				
Workdays	309	19:00 (18:30; 19:30)	19:00 (18:30; 20:00)	19:30 (19:00; 20:00)
Free days	309	19:00 (18:30; 19:30)	19:30 (19:00; 20:00)	19:30 (19:00; 20:00)
Breakfast jetlag (h:mm)	212	1:10 (0:30; 1:45)	1:30 (1:00; 2:00)	1:30 (1:00; 2:45)
Lunch jetlag (h:mm)	236	0:30 (0:00; 1:00)	0:30 (0:00; 1:00)	1:00 (0:00; 2:00)
Dinner jetlag (h:mm)	302	0:00 (−0:30; 0:30)	0:00 (−0:30; 0:30)	0:00 (−1:00; 0:43)
Eating midpoint (h:mm)				
Workdays	317	13:45 (13:20; 14:20)	14:22 (13:45; 15:22)	15:15 (14:07; 16:00)
Free days	317	14:30 (14:00; 15:00)	15:00 (14:22; 15:45)	16:16 (15:07; 17:00)
Total eating jetlag (h:mm)	317	0:30 (0:00; 1:11)	0:37 (0:00; 1:12)	1:00 (0:11; 1:52)
Main meal eating jetlag (h:mm)[a]	317	0:30 (0:00; 1:05)	0:37 (0:00; 1:00)	0:40 (−0:04; 1:28)
Breakfast skipping (n (%))				
Workdays	83	17 (16)	35 (33)	31 (30)
Free days	63	11 (10)	27 (25)	25 (24)
Lunch skipping (n (%))				
Workdays	21	6 (6)	8 (7)	7 (7)
Free days	69	13 (12)	17 (16)	39 (37)
Snacking in the morning (n (%))	112	37 (35)	41 (38)	34 (32)
Snacking in the evening (n (%))	136	34 (32)	35 (33)	67 (64)
Duration of nightly fasting (h:mm)				
Workdays	317	13:00 (11:30; 14:15)	13:30 (12:00; 14:45)	13:00 (12:00; 14:15)
Free days	317	14:00 (12:45; 15:00)	14:30 (13:15; 15:15)	14:00 (12:30; 15:10)

Abbreviations: T, tertile; n, sample size; MSFsc, midpoint of sleep corrected.
*Dinner skipping was minimal (i.e. <5%).
[a] Main meal eating jetlag (Zerón-Rugerio et al., 2019). Data are frequencies, or medians (Q1, Q3).

during the COVID-19 related lockdown. Multivariable linear regression models were used to analyze these associations considering p-values <0.05 statistically significant. Since men and women differ in their chronotype (Roenneberg & Merrow, 2007) we conducted tests for interaction between the exposure-outcome associations, which indicated a sex difference in the association between SJL and total EJL at baseline (p= 0.0307) only. Hence, multivariable linear regression for this exposure-outcome relation was also performed stratified by sex. Model building was performed for the primary exposure, i.e., chronotype or SJL in their relation to total EJL (Model 1). Model 2 was adjusted for sex and age (or age only in sex-stratified analyses). Model 3 considers additional potential confounders as outlined above using a hierarchical approach (Victora et al., 1997) to avoid overadjustment potentially resulting from the inclusion of too many variables and/or collinearity arising from the fact that the considered covariates reflect similar constructs. Potential confounding covariates considered for inclusion in the hierarchical approach were (1) external obligations (days of attending lectures (n), travel time to and from university (h:mm), job (yes/no)), and (2) behavioral variables (physical activity high/low, exercise intensity high/low, early/late timing of exercise and high screen time separately for work- and free days respectively as well as smoking (yes/no)). Only variables that either modified the exposure's (i.e. chronotype/SJL) regression coefficient by ≥10% (Maldonado & Greenland, 1993) or significantly predicted the outcome variable (i.e. total EJL) (Kirkwood & Sterne, 2003) were considered.

Sensitivity analyses repeated the analyses outlined above using main meal EJL at baseline as outcome to enable comparison of the results with data from Zerón-Rugerio (Zerón-Rugerio et al., 2019). Statistical analyses were performed using SAS procedures (SAS version 9.4; SAS Institute, Cary, NC, USA).

3. Results

Students in the latest chronotype tertile (T3) were more likely to smoke and report a high screen time (≥4 h/day) on free days, while those in the earliest chronotype tertile (T1) were physically more active (≥5 days/week) and exercised more frequently at early times (6:00 a.m.–14:00) of the day (Table 1). Moreover, students in the earliest tertile attended university lectures more frequently at earlier daytimes.

Table 2 shows the circadian characteristics and eating patterns by sex-specific tertiles of chronotype at baseline. Chronotype ranged from a midpoint of sleep at 3:35 a.m. in T1 to 5:35 a.m. in T3. Those with the latest chronotype had the largest SJL and consumed most meals at later times of the day on both work- and free days when compared to earlier chronotypes. Among all chronotypes, breakfast time was delayed notably on free days when compared to workdays resulting in the largest meal jetlag for breakfast. Likewise, students reported breakfast skipping less frequently on free days. Overall, later chronotypes had a later eating midpoint which differed most between workdays and free days resulting in a greater total EJL compared to earlier chronotypes. Total EJL was more pronounced when snacking was considered since students with later a chronotype snacked more frequently in the evening.

In the multivariable regression analysis, both chronotype and SJL were associated with total EJL in the crude and adjusted models:

Table 3
Adjusted mean total eating jetlag in sex-specific tertiles of chronotype and social jetlag at baseline (n=317).

	Chronotype					SJL			
	T1	T2	T3	P_{trend}		T1	T2	T3	P_{trend}
MSFsc (h:mm)[a]	3:35 (3:10; 3:50)	4:35 (4:22; 4:50)	5:35 (5:20; 6:00)		**SJL (h:mm)**	0:30 (0:17; 0:42)	1:07 (1:00; 1:15)	2:00 (1:45; 2:30)	
Model 1[b]	0.5 (0.3–0.7)	0.5 (0.3–0.7)	1.0 (0.7–1.2)	**0.0008**	**Model 1**	0.4 (0.1–0.6)	0.6 (0.4–0.8)	1.0 (0.8–1.2)	**<0.0001**
Model 2	0.5 (0.3–0.7)	0.5 (0.3–0.8)	1.0 (0.7–1.2)	**0.0015**	**Model 2**	0.4 (0.1–0.6)	0.6 (0.4–0.8)	1.0 (0.8–1.2)	**<0.0001**
Model 3	0.6 (0.3–0.8)	0.5 (0.3–0.7)	0.9 (0.7–1.1)	**0.0124**	**Model 3**	0.6 (0.3–0.9)	0.8 (0.5–1.0)	1.1 (0.9–1.4)	**<0.0001**

Abbreviations: T, tertile, MSFsc, midpoint of sleep corrected, SJL, social jetlag. Linear trends (P_{trend}) were obtained in linear regression models with MSFsc and SJL as continuous variable.

[a] Values are medians (Q1, Q3) of MSFsc and SJL (h:mm).

[b] Values are presented as adjusted least square means (95% Confidence Interval (CIs)) of MSFsc and SJL. **Model 1** is unadjusted. **Model 2** adjusted for sex and age. **Model 3** additionally adjusted for days of lectures at university, exercise at early daytimes (6:00–14:00) on free days, and smoking (yes/no).

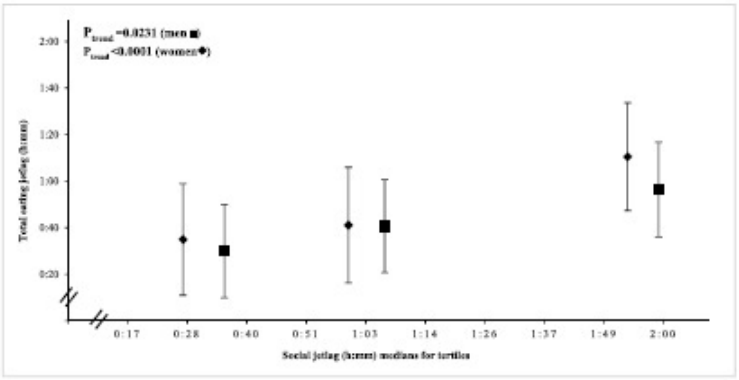

Fig. 1. Association between total eating jetlag and social jetlag stratified by sex at baseline (men n=134; women n=184). Total eating jetlag in students by tertiles of social jetlag. Men ■ and women ◆. Data are presented as least-square means and 95% CI adjusted for age, transport time to university and back, and exercise at early daytimes (6:00 a.m.–14:00) on free days in men and for age, days of lectures at university, transport time to university and back, high physical activity (≥5 days/week), and smoking (yes/no) in women.

students with a later chronotype or greater SJL experienced a larger total EJL irrespective of potential confounders (Table 3, models 1–3). In sex-stratified analysis, the independent association between total EJL and SJL was more pronounced among women (Fig. 1; Table 2, supplemental data).

In the follow-up examination, baseline characteristics of participants and non-participants were similar, yet participation rate was higher among females (67% vs. 33%) (Table 1, supplemental data). From baseline to follow-up, the MSF_{sc} was reduced among the latest chronotype only (T3), while SJL decreased in all tertiles (Table 4). All students consumed breakfast and lunch at later times on workdays resulting in reduced total EJL and less breakfast skipping. In particular, students with a later chronotype shifted breakfast to later times on workdays and earlier daytimes on free days and thus experienced a greater reduction of breakfast jetlag and an earlier eating midpoint on free days. Furthermore, snacking in the evening declined notably among those in the latest chronotype tertile.

Compared to baseline, students with a later chronotype experienced a greater reduction in total EJL independent of potential confounders during COVID-19 related lockdown (Table 5). Similarly, a greater reduction in SJL was independently associated with a greater reduction in total EJL. In sensitivity analysis, SJL – but not the chronotype – was associated with main meal EJL irrespective of potential covariates (Table 3, supplemental data).

4. Discussion

This study confirmed our hypothesis that students with a later chronotype are more vulnerable to an erratic meal pattern resulting in a greater discrepancy between the timing of their meals consumed on work- and on free days as illustrated by a larger total EJL among later chronotypes than earlier chronotypes. As expected, total EJL is closely related to SJL, for which later chronotypes are also more susceptible. During the COVID-19 lockdown, total EJL was reduced particularly among later chronotypes, hence the more flexible daily schedules allowed for an alignment of meal pattern with their inner clock. Likewise, a decreased SJL was associated with reductions in erratic meal pattern – i.e. total EJL.

In the population studied, differences in meal pattern between work- and free days were most pronounced for breakfast: while breakfast is skipped more frequently on workdays its timing is later on free days, which was most pronounced among students with a later chronotype. One reason may be that later chronotypes visited lectures starting later in the morning encouraging them to skip breakfast in favour of lunch at the cafeteria. Moreover, in line with previous studies (Garaulet et al., 2013; Reutrakul et al., 2014; Roβbach et al., 2018; Teixeira et al., 2018) evening snacking was more frequent among later chronotypes, which may also contribute to breakfast skipping especially when dinner or snack are consumed late in the evening (Okada et al., 2019).

Yet, most students in our study reported having breakfast (n=234 (74%)) which was consistently scheduled against their inner clock on workdays as indicated by the largest jetlag of all meals. Evidence from other studies support our findings that breakfast timing differs most between work- and free days (~1 h) and mainly drives the EJL while the timing of lunch and dinner usually remain fairly constant throughout the week (Gill & Panda, 2015; Makarem et al., 2021; Zerón-Rugerio et al., 2019). Furthermore, a previous study among 18–25 year old students living in Mexico or Spain also found that EJL was larger among those with a later chronotype and a larger SJL (Zerón-Rugerio et al., 2019). In our study, chronotype was only associated with total EJL which also

Table 4
Changes in social jetlag, eating jetlag, meal timing, and snacking from baseline to follow-up (n=156).

Change in		Chronotype		
	n	T1 (n=51)	T2 (n=53)	T3 (n=52)
MSF_{sc} (h:mm)	156	0:02 (−0:22; 0:47)	−0:02 (−0:30; 0:22)	−0:37 (−01:03; 0:20)
Sleeping time (h:mm)				
Workdays	156	0:15 (−0:15; 0:50)	0:25 (0:00; 0:55)	0:15 (−0:30; 0:52)
Free days	156	0:15 (−0:15; −0:41)	0:00 (−0:30; 0:30)	−0:30 (−1:14; 0:22)
Wake-up time (h:mm)				
Workdays	156	0:00 (−0:15; 0:45)	0:30 (−0:15; 1:00)	0:02 (−0:30; 1:00)
Free days	156	0:00 (−0:45; 0:30)	0:00 (−0:30; 0:30)	−0:30 (−1:30; 0:26)
Social jetlag (h:mm)	156	−0:16 (±0:36)	−0:26 (±0:38)	−0:54 (±1:00)
Breakfast (h:mm)				
Workdays	105	0:30 (0:00; 1:00)	0:30 (0:00; 1:00)	1:00 (0:52; 1:30)
Free days	113	0:00 (−0:30; 0:30)	0:00 (0:00; 0:30)	−0:30 (−1:01; 0:00)
Lunch (h:mm)				
Workdays	124	0:30 (0:00; 1:00)	0:15 (0:00; 1:00)	0:55 (−0:15; 1:30)
Free days	109	0:00 (0:00; 0:30)	0:00 (−0:30; 0:30)	0:00 (−1:00; 2:00)
Dinner (h:mm)				
Workdays	144	0:00 (−0:30; 0:00)	0:00 (−0:30; 0:30)	0:00 (−1:00; 1:00)
Free days	145	0:00 (−0:19; 0:30)	0:00 (−0:30; 0:18)	0:00 (0:35; 0:30)
Breakfast jetlag (h:mm)	85	−0:30 (−1:00; 0:00)	−0:30 (1:01; 0:00)	−1:30 (−2:54; −0:05)
Lunch jetlag (h:mm)	87	0:00 (−0:32; 0:20)	−0:29 (−1:00; 0:15)	−1:00 (−1:30; 0:15)
Dinner jetlag (h:mm)	99	0:00 (−0:15; 0:30)	0:00 (−0:30; 0:30)	0:00 (−0:30; 1:00)
Eating midpoint (h:mm)				
Workdays	156	0:00 (−0:52; 0:30)	0:26 (-0:22; 0:45)	0:15 (−1:00; 1:15)
Free days	156	0:00 (−1:00; 0:30)	0:00 (−0:30; 0:15)	−0:30 (−1:20; 0:41)
Total eating jetlag (h:mm)	156	−0:07 (−0:37; 0:30)	−0:15 (−0:43; 0:07)	−0:26 (−1:39; 0:34)
Main meal eating jetlag (h:mm)[a]	156	−0:07 (−0:30; 0:33)	−0:15 (−0:45; 0:00)	−0:29 (−1:28; 0:37)
Breakfast skipping (n (%))				
Workdays	32	−2 (−4)	−2 (−4)	−7 (−14)
Free days	28	0 (0)	−3 (−6)	0 (0)
Lunch skipping (n (%))				
Workdays	25	−2 (−4)	6 (11)	10 (19)
Free days	31	2 (4)	4 (8)	−8 (−15)
Snacking in the morning (n (%))	46	−5 (−10)	−6 (−11)	−8 (−15)
Snacking in the evening (n (%))	41	−11 (−22)	−2 (−4)	−14 (−27)
Duration of nightly fasting (h:mm)				
Workdays	156	0:45 (−0:30; 2:00)	0:15 (−0:15; 1:30)	0:55 (−0:20; 2:30)
Free days	156	0:25 (−0:30; 1:30)	0:00 (−0:30; 1:00)	0:00 (−1:00; 1:26)

Abbreviations: T, tertile; n, sample size; MSF_{sc}, midpoint of sleep corrected.
*Dinner skipping was minimal (i.e. <5%).
[a] Main meal eating jetlag (Zerón-Rugerio et al., 2019). Data are frequencies, or medians (Q1, Q3).

accounted for snacking. This is in contrast to the findings from Zerón-Rugerio et al. who reported associations based on meal timing only. These differences could stem from cultural differences in dinner time which is usually later than 21:00 in Spanish and Mexican populations (Zerón-Rugerio et al., 2019) whilst our study population had dinner not later than 20:00 even in the latest chronotype tertile both on work- and free days. Yet, in our population, 43% students reported snacking after 19:00 and this was most frequent among those with later chronotype. It has been proposed that late night energy intake accompanied by a socially determined early breakfast reduces the overnight fasting period and might increase the risk of obesity (Palla & Almoosawi, 2019). However, compared to other studies, in our cohort duration of nightly fasting was relatively long and similar on work- and free days (~13:00 h on workdays and ~14:00 h on free days compared to approx. ~9:00 h (Gill & Panda, 2015; Gupta et al., 2017) presumably due to later breakfast timing and/or breakfast. This may reflect some circadian flexibility of daily meal timing among all chronotypes in our cohort.

Accumulating evidence suggests that erratic meal timing, as reflected by EJL, is associated with adverse cardiometabolic health effects such as increased body fat (Thomas et al., 2020), higher BMI (body mass index) (Makarem et al., 2021; Zerón-Rugerio et al., 2019), elevated blood pressure, and higher HbA1c (Makarem et al., 2021). An EJL may be interpreted as a "metabolic time zone crossing" on workdays (Gill & Panda, 2015) potentially disrupting metabolic processes (e.g. glucose metabolism) (Challet, 2019). Hence, while food is consumed in synchrony with the master clock in the suprachiasmatic nucleus on free days, consumption during the circadian sleep phase on workdays (e.g. early breakfast among later chronotypes) entrains the peripheral clocks located in liver, muscles, adipose tissue etc. This will not only result in a desynchronisation with the master clock, which remains entrained by the light-dark rhythm (Challet, 2019), yet also phase-shift peripheral clocks anticipating food intake at the newly set meal timing on subsequent days including free days (Chaix et al., 2019). In our study, individuals with the latest chronotype experienced a total EJL of 1 h, corresponding to a metabolic crossing of 1 time zone (Evans & Davidson, 2013). This may have adverse long-term consequences as indicated by Zeron-Rugerio who reported that a main meal EJL ≥3.5 h was associated with 1.34 kg/m^2 higher BMI (Zerón-Rugerio et al., 2019). Of note, the sex-differences in the association of SJL with total EJL suggested by the formal tests for interaction (p= 0.0307) appear to be largely driven by a broader range of the total EJL among women resulting in a more pronounced association with SJL than among men. Hence, our data support a similar public health relevance of the associations in both sexes. While more research need to investigate the consequences of EJL on metabolic health, a regular eating pattern during circadian wake phase may help to maintain a robust circadian rhythm (Zerón-Rugerio et al., 2020). This could be achieved by flexible breaks for eating occasions between lectures, more flexible work/school schedules or enable home office/studying online which also saves time when not commuting to university/work.

Our study demonstrates that students aligned their meal timing with their circadian rhythm during lockdown as indicated by a significant decrease in total EJL particularly among later chronotypes. Again, this appears to be largely driven by breakfast habits and/or timing since

Table 5
Mean change in total eating jetlag (follow-up minus baseline) by sex-stratified tertiles of chronotype at baseline and changes in social jetlag (n=156).

	Chronotype at baseline					Changes of SJL			
	T1	T2	T3	P_{trend}		T1	T2	T3	P_{trend}
MSF_{sc} (h:mm)[a]	3:27 (3:07; 3:42)	4:30 (4:05; 4:47)	5:35 (5:21; 6:05)		SJL (h:mm)[a]	0:01 (-0:15; 0:22)	-0:23 (-0:41; -0:12)	-1:12 (-1:42; -0:40)	
Model 1 [b]	0.0 (-0.4-0.4)	-0.2 (-0.6-0.2)	-0.5 (-0.9- -0.7)	**0.0482**	**Model 1**	0.0 (-0.4-0.4)	0.0 (-0.4-0.3)	-0.6 (-0.1-1.2)	**<0.0001**
Model 2	0.0 (-0.4-0.4)	-0.3 (-0.7-0.1)	-0.5 (-0.9- -0.1)	**0.0642**	**Model 2**	-0.1 (-0.5-0.3)	-0.1 (-0.5-0.3)	-0.6 (-1.0- -0.2)	**0.0001**
Model 3	0.2 (-0.3-0.6)	-0.1 (-0.5-0.4)	-0.5 (-0.9-0.0)	**0.0270**	**Model 3**	-0.4 (-0.8-0.1)	-0.4 (-0.9-0.1)	-0.9 (-1.4- -0.4)	**<0.0001**

Abbreviations: T, tertile, MSF_{sc}, midpoint of sleep corrected, SJL, social jetlag. Linear trends (P_{trend}) were obtained in linear regression models with MSF_{sc} and changes of SJL as continuous variable.

[a] Values are medians (Q1, Q3) of MSF_{sc} at baseline and changes of SJL (h:mm).

[b] Values are presented as adjusted least square means (95% Confidence Interval (CIs)) of MSF_{sc} and SJL. **Model 1** is unadjusted. **Model 2** adjusted for sex and age. **Model 3** adjusted the association between MSF_{sc} at baseline and changes in total eating jetlag additionally for changes in exercise at early daytimes (6:00 a.m.–14:00) on free days, and smoking (yes/no). **Model 3** of the regression between changes in SJL and total eating jetlag additionally adjusted for changes in exercise at late daytimes (≥14:00) on workdays, and changes in smoking (yes/no).

fewer students skipped breakfast on workdays during lockdown and timing of breakfast was comparable between work- and free days. This change might have been caused by a reduced SJL: the fact that students no longer needed to compensate for a SJL on free days (Roenneberg et al., 2019) enabled later chronotypes to synchronize their breakfast time between work- and free days. Our observation that SJL decreased most among late chronotypes is in line with the Global Chrono Corona Survey (GCCS) comparing sleep-wake rhythm in 11,431 adults from over 40 countries (Korman et al., 2020). In that study, participants of the youngest age group (18–22 years) experienced the largest reduction in amounting SJL to almost 1 h, i.e. similar to the change seen in our students in the latest chronotype tertile. Conversely, meal timing before and during the lockdown was, to the best of our knowledge, only examined in one Swedish survey including 191 individuals aged 47 years, which reported that EJL remained stable (Benedict et al., 2021). This contrasting finding is most likely attributable to the age of the investigated populations underlining that young students are more vulnerable for a high EJL because of their late chronotype accompanied by a risk for a larger SJL.

In terms of breakfast skipping, Yokoro et al. reported that more female Japanese students skipped breakfast during the absolute stay-at-home period (Yokoro et al., 2021). This was in fact associated with weight loss among those who used to consume breakfast before the COVID-19 pandemic (Yokoro et al., 2021). Yet similar to our study the group of breakfast skippers was small (n=29) compared to those continuing to eat breakfast (n=117). No data on chronotype were assessed in that study. Moreover, several studies but not all (Dragun et al., 2020) reported an increased snacking frequency during the lockdown (Bhutani et al., 2021; Gallo et al., 2020; Robinson et al., 2021) whilst in our study we observed a decrease in snacking frequency, especially among later chronotypes. These differences might be explained by the time when the surveys were conducted: most studies were conducted during the early phase of pandemic restrictions (March–May), when persons may have been particularly vulnerable to stress, food cravings (Bhutani et al., 2021), and emotional eating (Cecchetto et al., 2021), while we collected data when social restrictions were already eased locally (Mitteldeutscher Rundfunk, 2020). Nonetheless, the fact that we did not assess the emotional impact of COVID-19 and the resulting lockdown is a limitation, since they resulted in higher stress, anxiety, and more depressive symptoms among students (Matos Fialho et al., 2021; Sabrina et al., 2021). Hence, further studies should extrapolate whether maintaining flexibility in external obligations (e.g., flexible school/work schedules) after the lockdown may enable young students to better align their meal pattern with their chronotype. Yet, our data do not support that any COVID-19/lockdown associated emotional stress resulted in more erratic eating pattern, in fact, our study population aligned their meal timing with their inner clock throughout the week, which in turn might have reduced metabolic stress (Challet, 2019).

Our study has limitations that need to be considered: Whilst our study supports the relevance to consider evening snacking when relating chronotype to total EJL, we had to rely on an extrapolation for the individual timing of snacking. Moreover, we did not define snacks and this may have resulted in a heterogeneous interpretation of snacking by the students, depending on social and cultural aspects (Hess et al., 2016). Hence, snacking needs to be studied in more detail when investigating potential differences between chronotypes in timing and food selection in the evening. In addition, defining work- and free days is problematic: previous studies often defined free days as the weekend (Makarem et al., 2021; Zerón-Rugerio et al., 2019), while others refer to days without work (Benedict et al., 2021; Roenneberg et al., 2019; Staller & Randler, 2020). Based on the definition in this study (free of work/lectures), students were found to attend university courses on three days only during lockdown as compared to four days before lockdown (data not shown). Whilst this is in line with our finding of a higher flexibility suggested by a reduced SJL, students may generally have spent more time studying, due to the partial replacement of lectures by self-studying (Matos Fialho et al., 2021). Yet, for the present study "free days" should best reflect days on which students were free to choose their meal timing – even if they needed to study. In this context, it is perhaps more relevant that we did not assess social aspects, which may have a crucial impact on meal timing even on free days (e.g. breakfast with friends, later dinner/snacking due to special occasions) (Veronda & Irish, 2021) and could contribute to meal consumption against the inner clock. Moreover, we recruited a sample of academic students, hence our results may not extend to the general population. Another limitation concerns the follow-up examination, in which attrition amounted to 50% and the participation rate was higher in women than in men. Furthermore, recall bias may have been a problem since the questionnaires referred to the past four weeks. Finally, baseline and follow-up examinations were performed in different seasons. This might have caused a temporal shift in the midpoint of sleep to earlier daytimes as has been observed more notably for those with a later midpoint of sleep (Allebrandt et al., 2014).

Yet, this is, to the best of our knowledge, the first prospective study which compared meal timing before and during the first lockdown in young students in Germany. Rather than inquiring self-perceived changes in eating pattern – as done in retrospective studies (Keel et al., 2020; Robinson et al., 2021) – we prospectively collected detailed data on the timing of daily routines such as studying, meals/snacks physical activity, and sleeping pattern separately for work- and free days. The same questionnaires were repeated in the follow-up allowing precise comparison of the data before and during the lockdown.

5. Conclusion

In conclusion, young students with a later chronotype are more

vulnerable to a more erratic meal pattern which also related to a more pronounced SJL. During lockdown, flexible daily schedules allowed students to align their eating pattern with their inner clock. Hence, our study suggests that maintaining flexibility in external obligations (e.g., flexible school/work schedules) after the lockdown may enable young students to better align their meal pattern with their chronotype and thus maintain metabolic health.

Ethics approval and consent to participate

Approved by the Ethics Committee at the Paderborn University. Informed consent was obtained from all participants prior to participation.

Funding

The ChroNu Study is financially supported by the German Research Foundation (DFG) (BU 1807/3-2).

Authors' contributions

The study was conceived and supervised by Anette E. Buyken. Data assessment was performed by Bettina Krueger and Bianca Stutz. Bianca Stutz carried out the statistical analysis and wrote the original draft supervised by Anette E. Buyken. All authors contributed to the interpretation and discussion of the results and approved the final version of the submitted manuscript.

Availability of data and materials

Data are made available via a request to the authors based on a formal data sharing agreement.

Ethical statement

The study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Paderborn University and registered at clinicaltrials.gov (NCT04302922).

Declaration of competing interest

The authors declare no conflict of interest.

Data availability

Data will be made available on request.

Acknowledgements

The participation of all students in the ChroNu Study is gratefully acknowledged. We thank the staff of the ChroNu Study for administering of participants' visits.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.appet.2022.106333.

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Supplemental Table 1: Baseline characteristics among participants and non-participants in the online survey.

	Participants (*n=156*)	Non-participants (*n=161*)
Sex (females, n (%))	104 (67)	79 (49)
Age (years)	21.0 (20.0; 23.0)	22.0 (20.0; 23.0)
Smoking (n (%))[a]	11 (7)	20 (12)
Days of classes at university (n)	4 (3; 5)	4 (3; 5)
Start at university (h:mm)	10:12 (9:12; 11:00)	10:10 (9:15; 11:12)
End at university (h:mm)	15:36 (15:00; 16:40)	15:48 (14:45; 16:40)
Average travel time to university and back during week (h:mm)	0:32 (0:16; 1:00)	0:29 (0:15; 0:48)
Job (n (%))[b]	95 (61)	103 (64)
Living form (n (%))		
Shared apartment	74 (47)	76 (47)
Single apartment	25 (16)	32 (20)
Other (with parents/partner/own family)	57 (37)	53 (33)
Screen time >4 hours/day (h:mm)		
Workdays	84 (54)	81 (50)
Free days	56 (36)	74 (46)
Physical activity (n (%))[c]		
High (≥ 5 days/week)	29 (19)	39 (24)
Low (≤ 2 days/week)	62 (40)	50 (31)
Exercise intensity (n (%))[d]		
High (≥2 hours/week)	103 (66)	90 (56)
Low (<1 hours/week)	19 (12)	30 (19)
Exercise on workdays (n (%))		
Early (6:00–14:00)	46 (30)	49 (30)
Late (≥14:00)	126 (81)	139 (86)
Exercise on free days (n (%))		
Early (6:00–14:00)	70 (45)	71 (44)
Late (≥14:00)	110 (71)	116 (72)
Chronotype MSF_{sc} (h:mm)	4:37 (4:02; 5:15)	4:30 (3:42; 5:21)
Sleeping time (h:mm)		
Workdays	23:30 (22:51; 24:00)	23:15 (22:30; 24:00)
Free days	0:30 (23:59; 1:10)	0:15 (23:15; 1:15)
Wake-up time (h:mm)		
Workdays	7:30 (7:00; 8:00)	7:30 (7:00; 8:00)
Free days	9:00 (8:30; 10:00)	9:00 (8:10; 10:00)
Social jetlag (h:mm)	1:05 (0:46; 1:45)	1:07 (0:35; 1:45)
Breakfast (h:mm)		
Workdays	8:15 (8:00; 9:00)	8:15 (8:00; 8:30)
Free days	10:00 (9:00; 10:30)	10:00 (9:00; 10:30)
Lunch		
Workdays	13:00 (12:30; 13:30)	13:00 (12:30; 13:10)
Free days	13:30 (13:00; 14:00)	13:00 (13:00; 14:00)
Dinner		
Workdays	19:00 (18:30; 20:00)	19:00 (19:00; 20:00)
Free days	19:15 (19:00; 20:00)	19:00 (18:30; 20:00)
Breakfast jetlag (h:mm)	1:30 (1:00; 2:00)	1:30 (1:00; 2:00)
Lunch jetlag (h:mm)	0:45 (0:00; 1:00)	0:30 (0:00; 1:00)
Dinner jetlag (h:mm)	0:00 (-0:30; 0:30)	0:00 (-0:30; 0:30)
Eating midpoint (h:mm)		
Workdays	14:30 (13:30; 15:22)	14:13 (13:30; 15:15)
Free days	15:07 (14:30; 16:00)	15:00 (14:15; 16:03)
Total eating jetlag (h:mm)	0:45 (0:07; 1:15)	0:43 (0:00; 1:15)
Main meal eating jetlag (h:mm)[d]	0:37 (-0:07; 1:15)	0:30 (0:00; 1:00)
Breakfast skipping (n (%))		
Workdays	43 (28)	40 (25)
Free days	31 (20)	32 (20)
Lunch skipping (n (%))		
Workdays	11 (7)	10 (6)
Free days	33 (21)	36 (22)
Snacking in the morning (n (%))	65 (42)	47 (29)
Snacking in the evening (n (%))	68 (44)	68 (42)
Duration of nightly fasting (h:mm)		
Workdays	13:00 (11:45; 14:20)	13:00 (12:00; 14:42)
Free days	14:00 (12:45; 15:00)	14:00 (12:57; 15:00)

Abbreviations: MSFsc, midpoint of sleep corrected. [a] Smoking (yes/no), [b] job (yes/no), [c] physical activity: every activity resulting in sweating or heavily breathing, [d] Main meal eating jetlag (Zerón-Rugerio et al., 2019). Data are frequencies, or medians (Q1, Q3). Dinner skipping was minimal (i.e. <5%).

Supplemental Table 2: Adjusted mean total eating jetlag in tertiles of social jetlag at baseline for men and women.

	SJL			
	T1	**T2**	**T3**	**P_{trend}**
Men (n=134)				
SJL (h:mm)[a]	0:36 (0:22; 0:46)	1:07 (1:00; 1:17)	2:00 (1:50; 2:30)	
Model 1[b]	0.5 (0.2 – 0.8)	0.8 (0.4 – 1.1)	0.9 (0.6 – 1.3)	**0.0885**
Model 2	0.5 (0.2 – 0.8)	0.8 (0.4 – 1.1)	0.9 (0.6 – 1.3)	**0.0402**
Model 3	0.5 (0.2 – 0.8)	0.7 (0.3 – 1.0)	0.9 (0.6 – 1.3)	**0.0231**
Women (n=184)				
SJL (h:mm)	0:28 (0:15; 0:46)	1:00 (0:55; 1:15)	1:54 (1:40; 2:25)	
Model 1	0.3 (0.0 – 0.5)	0.5 (0.2 – 0.8)	1.1 (0.8 – 1.4)	**<0.0001**
Model 2	0.2 (0.0 – 0.5)	0.5 (0.2 – 0.8)	1.1 (0.8 – 1.4)	**<0.0001**
Model 3	0.6 (0.2 – 1.0)	0.7 (0.3 – 0.1)	1.2 (0.8 – 1.6)	**<0.0001**

Abbreviations: T, tertile, SJL, social jetlag. Linear trends (P_{trend}) were obtained in linear regression models with SJL as continuous variable. [a] Values are medians (Q1, Q3) of SJL (h:mm). [b]Values are presented as adjusted least square means (95% Confidence Interval (CIs)) of SJL. **Model 1** unadjusted. **Model 2** adjusted for age. **Model 3** additionally adjusted for transport time to university and back, and exercise at early daytimes (6:00–14:00) on free days in men and for age, days of lectures at university, transport time to university and back, high physical activity (≥5 days/week), and smoking (yes/no) in women.

Supplemental Table 3: Mean main meal EJL (Zerón-Rugerio et al., 2019) in sex-stratified tertiles of chronotype and SJL at baseline (n=317).

	Chronotype					SJL			
	T1	**T2**	**T3**	**P_{trend}**		**T1**	**T2**	**T3**	**P_{trend}**
Chronotype MSFsc (h:mm)[a]	3:35 (3:10; 3:50)	4:35 (4:22; 4:50)	5:35 (5:20; 6:00)		**SJL (h:mm)**	0:30 (0:17; 0:42)	1:07 (1:00; 1:15)	2:00 (1:45; 2:30)	
Model 1[b]	0.4 (0.1 – 0.6)	0.3 (0.1 – 0.6)	0.5 (0.3 – 0.8)	**0.2427**	**Model 1**	0.2 (0.0 − 0.5)	0.4 (0.1 − 0.7)	0.6 (0.4 − 0.9)	**0.0012**
Model 2	0.4 (0.1 − 0.6)	0.3 (0.1 − 0.6)	0.5 (0.3 − 0.8)	**0.4464**	**Model 2**	0.2 (0.0 − 0.5)	0.4 (0.1 − 0.7)	0.6 (0.4 − 0.9)	**0.0022**
Model 3a	0.4 (0.2 − 0.7)	0.3 (0.1 − 0.6)	0.5 (0.2 − 0.8)	**0.6160**	**Model 3b**	0.2 (0.0 − 0.5)	0.4 (0.1 − 0.7)	0.6 (0.4 − 0.9)	**0.0027**

Abbreviations: T, tertile, MSFsc, midpoint of sleep corrected; SJL, social jetlag. Linear trends (P_{trend}) were obtained in linear regression models with MSFsc and changes of SJL as continuous variable. [a] Values are medians (Q1, Q3) of MSFsc at baseline and changes of SJL (h:mm). [b] Values are presented as adjusted least square means (95% Confidence Interval (CIs)) of MSFsc and SJL. **Model 1** is unadjusted. **Model 2** adjusted for sex and age. **Model 3a** additionally adjusted for low exercise intensity (<1 hour/week), exercise at early daytimes (6:00–14:00) on free days, screen time (≥4 hours) on workdays, and smoking (yes/no). **Model 3b** of SJL and main meal EJL additionally adjusted for screen time (≥4 hours) on workdays.

APPENDIX C

OA2

Accepted for publication, currently under production

Glycemic response to meals with a high glycemic index differs between morning and evening - a randomized cross-over controlled trial among students with early or late chronotype

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Acknowledgements

We kindly thank Katja Bolzenius for her advice and great support in preparatory statistical analyses, and we thank Sandra Trenkamp (German Diabetes Center (DDZ)) for supervision of laboratory analyses. The participation of all students in the ChroNu Study is gratefully acknowledged. Moreover, we thank the staff of the ChroNu Study for administering participants during their visits.

Funding: The study was supported by the German Research Foundation (DFG) through grants BU1807/3-2, HE4510/5-2, and AL 1794/1-2.

PURPOSE

Glycemic response to the same meal depends on daytime and alignment of consumption with the inner clock, which has not been examined by individual chronotype yet. This study examined whether the 2-h postprandial and 24-h glycemic response to a meal with high glycemic index (GI) differ when consumed early or late in the day among students with early or late chronotype.

METHODS

From a screening of 327 students aged 18–25 years, those with early (n=22) or late (n=23) chronotype participated in a 7-day randomized controlled cross-over intervention study. After a 3-day observational phase, standardized meals were provided on run-in/washout (days 4 and 6) and intervention (days 5 and 7), on which participants received a high GI meal (GI=72) in the morning (7 a.m.) or in the evening (8 p.m.). All other meals had a medium GI. Continuous glucose monitoring was used to measure 2-h postprandial and 24-h glycemic responses and their variability.

RESULTS

Among students with early chronotype 2-h postprandial glucose responses to the high GI meal were higher in the evening than in the morning (iAUC: 234 (±92) vs. 195 (±91) (mmol/L) x min, p=0.042). Likewise, mean and lowest 2-h postprandial glucose values were higher when the high GI meal was consumed in the evening (p<0.001; p=0.017). 24-h glycemic responses were similar irrespective of meal time. Participants with late chronotype consuming a high GI meal in the morning or evening showed similar 2-h postprandial (iAUC: 211 (±110) vs. 207 (±95) (mmol/L) x min, p=0.9) and 24-h glycemic responses at both daytimes.

CONCLUSIONS

Diurnal differences in response to a high GI meal are confined to those young adults with early chronotype, whilst those with a late chronotype seem vulnerable to both very early and late high GI meals. Registered at clinicaltrials.gov (NCT04298645; 22/01/2020).

Keywords: chronotype, circadian misalignment, glucose homeostasis, glycemic index, meal time

INTRODUCTION

Accumulating evidence suggests that eating meals late in the evening affects postprandial (pp) glucose and insulin responses more adversely than consuming identical meals at early daytimes [1]. This is particularly pronounced for evening consumption of carbohydrate-rich meals with a high glycemic index (GI) among both

healthy individuals [2, 3] and persons with impaired fasting glucose and/or impaired glucose tolerance [4]. Mechanistically, this phenomenon is likely attributable to the diurnal rhythm of glucose homeostasis characterized by a decrease in insulin secretion and/or sensitivity over the day resulting in lower glucose tolerance in the evening [5, 6]. Hence, the recent trend to shift main daily energy intake to later daytimes [7] is a public health concern and may contribute to the worldwide burden of type 2 diabetes [8].

Individuals with a late circadian phenotype, i.e. late chronotype, who habitually consume their main meals in the evening [9], may be particularly at risk for type 2 diabetes. A recent meta-analysis reported higher fasting blood glucose and HbA1c levels as well as a higher risk for type 2 diabetes among healthy individuals with a late chronotype compared to individuals with an early chronotype [10]. Persons with a late chronotype are also more likely to experience discrepancies between their circadian rhythm and socially determined schedules such as early starting time of university/school [11]. Hence, for individuals with a late chronotype consumption of an early breakfast – due to social routines – could entail circadian misalignment (which characterizes a de-synchronized biological and behavioral cycle [5]). Meanwhile, persons with an early chronotype may be vulnerable to a late high GI meal due to both circadian misalignment and the above described circadian rhythmicity of glucose tolerance. Since the concurrence of elevated melatonin concentrations and food consumption may adversely affect glucose tolerance [12] it is of interest to investigate melatonin concentration in persons with different chronotypes (e.g. in routinely measured fasting samples).

To date, the diurnal glycemic response has not been investigated by chronotype yet. Therefore, this study addresses the hypothesis that a diurnal rhythm – with higher 2-h pp and 24-h glycemic response to a meal rich in carbohydrates from higher GI sources when consumed early in the morning (7 a.m.) or late in the evening (8 p.m.) may be discernible in persons with early chronotype, in whom late consumption may represent circadian misalignment. By contrast, we hypothesize that early consumption may entail circadian misalignment for persons with a late chronotype. Hence, we compared 2-h pp and 24-h glycemic responses in a cross-over trial conducted in two samples of students with either early or late chronotype.

RESEARCH DESIGN AND METHODS

Study population

For the Chronotype and Nutrition (ChroNu) study a screening of 327 students was conducted during September 2019 to January 2020, as described previously [11]. In brief, students aged 18–25 years at Paderborn University were answered questionnaires on their chronotype and the timing of daily routines; body composition was measured. Exclusion criteria are listed in figure 1. Among the 231 students eligible for inclusion in the controlled nutritional trial (Figure 1), those with the earliest (n=40) and the latest (n=40) chronotype were invited. Of these, 20 persons declined the invitation before and 11 individuals after randomization, i.e. they did not participate in the trial. During the trial, 3 further persons were excluded due to illness/non-compliance and technical issues with the continuous glucose monitoring device. Hence, 46 students completed the nutrition trial. Data from one participant were excluded for the analysis due to non-physiological glucose readings, resulting in a final sample of n=45 for analysis. The trial was conducted at Paderborn University during September 2020 to December 2020. Informed consent was obtained from all participants prior to the trial. The study protocol was approved by the Ethics Committee of Paderborn University (16.05.2019) and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments [13]. The trial was registered at clinicaltrials.gov (NCT04298645).

Chronotype assessment

Chronotype was assessed both at screening and prior to the nutrition trial using the Munich ChronoType Questionnaire, which enquires about sleep time separately for work- and work-free days [14]. The individual chronotype was the midpoint of sleep between sleep-onset and sleep-offset and corrected for accumulated sleep debt (temporal difference in sleep duration between work and work-free day) during workdays (MSFsc).

Design of the nutrition trial

On day 1, participants were asked to fill in online questionnaires via REDCap [15]. On day 4, i.e. after a 3-day observational phase, participants were randomized to the order of high GI (GI≥70) meal consumption in the morning/evening (arm 1) or evening/morning (arm 2) on the intervention days (days 5 and 7), preceded by a run-in/wash-out day (days 4 and 6), respectively (Figure 1). Participants were instructed to avoid consumption of legumes on day 3 to prevent any potential influences on the fasting glycemia values obtained in the morning of the run-in day [16]. In the morning of the run-in day, fasting blood sample was taken, and participants consumed breakfast and received their morning snack. Participants returned for a freshly prepared warm lunch and received

consecutive study afternoon snack, dinner, breakfast, morning snack in labelled boxes for consumption at home until lunch on the next day, which was again provided at the study center. This schedule was maintained until day 7, when only afternoon snack and dinner were handed out after lunch. Participants were instructed to consume meals/snacks without a break at predefined times (Supplemental Table 1&2). On run-in/wash-out days, participants were instructed to consume their dinner before 9 p.m. to ensure a 10 h fasting period before the intervention day. Participants were asked to record the timing of meal/snack consumption, their activities, and sleep timing in a diary to corroborate compliance.

Intervention

An identical high GI meal was provided in the morning (7 a.m.) or evening (8 p.m.), i.e. at times commonly imposed by social schedules, yet potentially causing circadian misalignment for late/early chronotypes [14]. The meal consisted of a Mars® bar, Cornflakes (Kellog´s®), low-fat milk (1,5%), and a soft pretzel (Ditsch®) resulting in an estimated meal GI of 72 (Supplemental Table 1). On the intervention days, this high-GI meal provided 35% of the daily amount of available carbohydrates (grams). All other meals/snacks on the intervention and run-in/wash-out days were designed to have an estimated medium GI between 46 and 59 (Supplemental Table 1&2), to avoid second meal effects [16]. On the run-in/wash-out days, lunch provided the largest proportion of available carbohydrates. Meal GI estimation was conducted according to a previously published procedure [17]. Food items with a published GI [18] were given preference to allow for a valid estimation of the meal GI particularly of the intervention meal. Hence, pretzels were used, i.e. the only tested German bread with a value GI >70 [19]. If more than one published GI value was available, the mean of these values was assigned. The dietary GI of each meal/snack was calculated as the sum of glycemic load (GL) values of each food divided by the sum of their available carbohydrates (g)*100 [17].

Participants followed an isocaloric diet to maintain body weight. To this end, total energy expenditure was estimated individually based on resting energy expenditure using the formula by Harris & Benedict [20] multiplied by a physical activity level of 1.4 since participants were instructed to avoid (vigorous) physical activity. Participants were grouped into categories based on the total energy expenditure distribution of the study population: 1900 kcal, 2100 kcal, 2300 kcal, 2500 kcal, 2700 kcal, 2900 kcal. During the trial, participants were allowed to switch the TEE category once. The energy content of the provided meals was calculated using the nutrition programme DGExpert designed

by the German Nutrition Society, which is based on the German food table (Bundeslebensmittelschlüssel) [21]. The diets of the intervention and the run-in/wash-out days were designed to comply with the recommendations of the German Nutrition Society to consume a diet rich in carbohydrates [22] and contained 14En% from protein, 30En% from fat, 53En% from available carbohydrates, and 3En% from dietary fiber. Noteworthy, the macronutrient distribution (En%) was similar on all study days. During the trial, participants were asked to consume the provided foods only and to abstain from consuming alcohol/alcohol-free drinks, caffeinated/decaffeinated beverages, and carbohydrate containing beverages. Participants were provided with a selection of teas containing <0.3g carbohydrates/serving (200 mL).

Outcomes

The primary outcome, on which the power calculation was based, was the 2-h difference in the incremental area under the curve (iAUC) while the further outcomes were the difference of iAUC and mean amplitude of glucose excursions (MAGE) over a time span of 24 h following the consumption of the high GI meal between morning and evening. Additionally, parameters describing glycemic variability (mean, standard deviation, highest, and lowest glucose value) were analyzed. During the study, glycemic responses were recorded using continuous glucose monitoring (G6, Dexcom, San Diego, CA, USA), which measures subcutaneous interstitial glucose concentrations resulting in mean glucose value every 5 min. The device was blinded during the trial (days 4-8).

Corroboration of chronotype

During the trial, participants were asked to wear an accelerometer (E4 wristband, Empatica SRI, Italy) day and night to objectively monitor their activity and resting phases. Sleep and awake times during the trial were estimated based on movement recordings of the accelerometer and bedtimes entered in the diary, which the participants used to record their daily routines/activities during the study. Time of sleep onset and wake-up during the nutrition trial was averaged for days 4 to 7.

Anthropometric and laboratory measurements

To monitor changes in anthropometry, body composition, i.e. visceral fat mass and skeletal muscle mass, was measured by using Bioimpedance Analysis (mBCA 515, SECA, Hamburg, Germany) on day 1 (in the afternoon) and day 8 (in the morning) (Supplemental Table 3). Waist circumference (cm) was measured midway between the lowest rib and the iliac crest. Body size was measured using an ultrasonic measuring

station (seca 287 dp, Hamburg, Germany) from SECA. BMI was calculated by weight (kg)/height (m)².

On day 4, venous blood samples were collected at 7 a.m. after ≥10 h overnight fast for measurement of glucose, insulin, lipids, and high-sensitivity C-reactive protein (hsCRP). Blood samples were centrifuged after 10 and 30 min. EDTA-plasma and serum samples were stored at -20 °C and shipped to the German Diabetes Center in Düsseldorf for analyses. Fasting plasma insulin was measured with a chemiluminescence immunoassay (Immulite 2000 xPi; Siemens, Erlangen, Germany). A clinical chemistry autoanalyzer (Cobas c-311; Roche, Mannheim, Germany) was used to measure fasting blood glucose (hexokinase reference method), triglycerides (TGs), i.e., lipoproteins, low-density cholesterol (LDLc), high-density cholesterol (HDLc), as well as plasma nonesterified fatty acids using enzymatic colorimetric assay, and hsCRP with the use of an immunoturbidimetric assay [23, 24]. Melatonin was subsequently measured by ELISA (sunrise, TECAN IBL International, Hamburg, Germany) for the 44 participants with sufficient serum material at Medizinische Laboratorien, Düsseldorf. HOMA-IR was calculated as (fasting blood insulin in µU/mL*fasting blood glucose in mmol/L)/22.5 [25].

Characteristics on eating pattern

Habitual consumption (yes/no) and timing of meals/snacks were inquired separately for work- and work-free days. Non-consumption of breakfast/lunch/dinner was defined as skipping the corresponding meal.

Sample size

Sample size estimation of expected difference in the 2-h pp difference in morning vs. evening iAUC (primary outcome) following the consumption of the high-GI intervention meal was based on data from Morris et al. [5]. They observed that the 2-h pp iAUC to a carbohydrate-rich meal was 913 ± 26 (SEM) (mmol/L) x min in the morning and 1,096 ± 17 (mmol/L) x min in the evening (values conservatively estimated from Figure 4 [5]) , i.e. differed by approx. 180 (mmol/L) x min. Hence, including a total of n=8 participants would accordingly allow to detect a difference of <180 (mmol/L) x min between the morning and evening meal with a power of 80% (PROC POWER, SAS University Edition) – using a standard deviation of 98 (mmol/L) x min (i.e. estimated from the more conservative SEM reported for morning consumption [5]). Based on previous experiences [26] we assumed a 15% drop-out rate, hence the estimated sample size per arm was n=10 (n=20 in total). Since we planned to perform this study in two separate

samples with early and late chronotypes we aimed to include 40 persons in total. With an expected participation rate of 66%, our aim was to recruit 60 eligible participants. We estimated that a total of 300 students needed to be screened to identify the participants with the latest and earliest chronotype (10% each) identified as 20% of the participants with each the earliest and latest MSFsc among the cohort.

Randomization and masking

Due to the COVID19 pandemic fewer students were willing to participate. Hence n=80 persons had to be invited in total. Of these, 60 participants initially accepted the invitation and were randomly assigned to arm 1 or arm 2 stratified by sex and chronotype with a block size=4 considering 20 participants per strata [27] by JD (University of Bergen), Figure 1. While the participants and researchers were not blinded to the study arm due to the nature of the study involving provision of meals, researchers were blinded to the participants´ chronotype.

Calculations

For analysis of 2-h pp and 24-h iAUC trapezoidal rule ignoring areas below baseline was applied [28]. Baseline was calculated as the mean of glucose readings 5 min. before and i) at time point of meal consumption (2-h-pp iAUC) and ii) at 7 a.m. (24-h-pp iAUC) in accordance with GI testing guidelines [28]. MAGE was calculated by use of the validated EasyGV program [29]. 24-h glycemic response and variability covers a timespan from the intervention day (7 a.m.) until 7 a.m. of the following day.

Statistical analyses

Descriptive data are reported as mean ± SD if normally distributed, otherwise as median (Q1, Q3). Categorical variables are shown as percentages. As this study aimed to compare effects on 2-h pp and 24-h glycemic response following high-GI meal consumption in the morning vs. evening within both a group of early and a group of late chronotypes, multilevel linear regression was applied including chronotype and time of consumption (morning or evening) as fixed effects and participant as a random effect. By nature, these models consider the dependence between repeated measures within a person (PROC MIXED in SAS). Beta-coefficients (and 95% confidence limits) for the time variable are presented as estimates of the mean differences between morning and evening consumption. To facilitate interpretation differences are presented as evening minus morning consumption. The variable 24-h standard deviation was log-transformed

to achieve normal distribution of the model residuals. The beta-coefficient for this variable was retransformed and differences represent percent differences between evening and morning consumption [31].
Only few participants exhibited >1 standard deviation during 2-h pp interval (n=6 early; n=8 late chronotypes) allowing for a calculation of 2-h MAGE, hence, only 24-h MAGE was analysed.

To examine whether melatonin concentrations (available from routinely measure fasting levels only) may be related to glucose tolerance in this study correlation and linear regression were performed relating melatonin concentrations to the primary outcome 2-h pp glucose iAUC following the high-GI intervention meal. Since melatonin measurements were only available from fasting (i.e. morning) blood samples this analysis was confined to 2-h pp glucose iAUC after morning high-GI meal consumption. Statistical analyses were performed using SAS procedures (SAS version 9.4; SAS Institute, Cary, NC, USA) considering p-values <0.05 as statistically significant except for analyses of interactions where p-values <0.1 were considered significant [32].

RESULTS

All results are presented stratified by chronotype in accordance with the study design. This was underpinned by interactions of chronotype with the effects of the intervention (morning vs. evening) on 2-h pp (mean (p=0.09) and highest glucose values (p=0.06)) and 24-h (highest glucose values (p=0.04), standard deviation (p=0.02), and MAGE (p=0.098)) glucose response variables (all p<0.1, which is regarded significant for interactions [32]).

Characteristics of the study population

Participants were on average 22 years old and healthy as indicated by their body composition and physiological data (Table 1). Persons with early and late chronotypes differed in their mean morning melatonin levels (27.4 vs. 36.0 ng/L) measured from blood samples withdrawn at 7 a.m. MSFsc differed by approximately 1:54 h:min between early and late chronotypes. Similarly, time when falling asleep and waking up were notably different between the two chronotype groups. Both chronotypes had to wake up earlier than normal during the nutrition trial.

Glycemic response of participants with early chronotype

For persons with an early chronotype, the 2-h pp glycemic response was lower when the intervention high-GI meal was consumed early in the morning compared to late in the evening (195 (± 91) vs. 234 (± 92) (mmol/L) x min, p=0.042) (Table 2). Similarly, the mean (p≤0.001) and the lowest 2-h pp glucose values (p=0.017) were lower in the morning. Figure 2A illustrates that glucose levels increased similarly within the first 50 min. pp, but remained elevated for a longer period when the intervention meal was consumed in the evening. Additionally, high GI meal consumption in the evening resulted in a higher standard deviation of the 24-h responses (p=0.001). Figure 2C shows that evening glycemic responses to the high GI meal remained elevated for longer (until 1 a.m.) than evening responses to the medium GI meal.

Glycemic response of participants with late chronotype

Participants with a late chronotype showed comparable 2-h pp glycemic responses and variability after consumption of the high GI meal early in the morning and late in the evening; only the lowest 2-h glucose value was higher in the evening (5.00 (± 0.61) vs. 5.33 (± 0.53) (mmol/L) x min; p=0.024) (Table 2, Figure 2 B). Similarly, with respect to 24-h glycemic responses no significant differences were seen (Table 2, (Figure 2D). As with early chronotypes, evening glucose levels remained elevated for ~5 h after the high GI evening meal.

Analysis of melatonin

Analysis for the sample revealed that the morning melatonin level was associated with the 2-h pp glycemic response to the high GI meal consumed in the morning (r=0.33; p=0.03) (Supplemental Figure 1).

Anthropometric analysis

Among both groups, BMI and waist circumference were somewhat lower when measured after the intervention in the morning of day 8 in comparison to measurements on day 1 in the afternoon (Supplemental Table 3).

DISCUSSION

This is the first study examining the 2-h and 24-h glycemic responses to high GI meals consumed early in the morning (7 a.m.) and late in the evening (8 p.m.) in two selected samples of young adults with early and late chronotype, confirmed with two different methods - the MCTQ (questionnaire) and accelerometers. Importantly, our study

suggests that diurnal differences in 2-h pp glycemia – whilst seen among students with early chronotype – may not hold true for young adults with a late chronotype.

Findings among students with late chronotype

Of note, individuals with late chronotype showed no difference in 2-h and 24-h glycemic response to morning and evening high GI meals. It could be argued that our observation for students with late chronotype may be due to an emerging insulin resistance, which may subsequently have contributed to some loss in circadian rhythmicity. In fact, among persons with prediabetes, higher HOMA-IR levels were associated with a reduced circadian rhythmicity [35], yet the authors speculate that this was largely a consequence of a loss in circadian rhythmicity caused by higher BMI levels. Whilst in our study, pp insulin concentrations were not investigated, fasting HOMA-IR was similar among adults with late or early chronotype and both groups were on average of normal weight (Table 1). Hence, this argues against the idea that metabolic abnormalities may have contributed to a loss in circadian rhythmicity.

By contrast, the timing of the high GI meal at 7 a.m. in this controlled trial was designed to interfere with circadian rhythmicity among persons with a late chronotype (MSFsc =5:50 a.m.), who habitually consume breakfast at 11 a.m. on work-free days (Table 1). Meal consumption against the inner clock results in a conflict between the rhythm of peripheral clocks and the central pacemaker of the diurnal rhythm located in the suprachiasmatic nucleus [36]. Consequently, meal consumption induces peripheral signals that activate organs and tissues, while the central pacemaker still signals the biological night [36]. Of note, higher morning melatonin levels among persons with late chronotype underpins our assumption of circadian misalignment, since melatonin concentrations are regulated by the suprachiasmatic nucleus and follow a circadian rhythm (i.e. increasing ~2 h before biological sleep, peaking in the first half of sleep phase, and declining continuously over ~2-3 h after habitual wake-up [12, 37, 38]). Higher melatonin levels have been shown to inhibit glucose-stimulated insulin secretion through binding to melatonin-receptors in the pancreatic beta cells and/or decrease insulin sensitivity, i.e. affecting glucose tolerance [12]. Hence, this may have contributed to the absence of lower glycemic response in the morning among persons with a late chronotype. Of note, our subsequent analysis confirmed that higher melatonin levels drawn at ~7 a.m. at day 1 of the intervention were associated with higher pp glycemic responses at 7 a.m. on the intervention days 5 or 7. In line with our results, another study

among healthy individuals reported higher morning melatonin levels in response to sleep-restriction by ~2.5 h compared to a habitual sleep phase (wake-up time 5:30 a.m. vs. 8 a.m.) [37]. In that study, sleep restriction resulted in increased pp glucose response following breakfast at 6:15 a.m. when compared to 8:45 a.m. after habitual sleep duration [37]. Taken together, our data indicate that a high GI meal consumed early in the morning may be similarly detrimental to its consumption in the evening among persons with a late chronotype, hence supporting our hypothesis of a circadian misalignment.

Findings among students with early chronotype

In line with the diurnal decline in glucose homeostasis [5, 1], the hypothesized differences in 2-h glycemic response to the high GI meal consumed in the morning and evening were observed among adults with early chronotype. Noteworthy, differences emerged after 50 min (Figure 2A), suggesting that a higher early-phase insulin response in the morning may have led to a faster decrease of glucose concentrations than in the evening when beta cell responsiveness is reduced [6]. Of note, higher mean and 24-h glucose values emphasize the lasting effect of a high GI meal late in the evening on glucose homeostasis. Similarly, a study reported sustained adverse influences of a late evening meal consumption (9 p.m.) compared to early evening meal time (6 p.m.) among healthy adults on mean diurnal glucose responses [39]. In our study, evening meal timing (8 p.m.) was later than self-reported habitual dinner time (median 7 p.m.) among early chronotypes and only ~3 h apart from their habitual time of falling asleep. Hence, timing of the evening meal may additionally represent some degree of circadian misalignment, which has been shown to lower glucose tolerance mainly by reduced insulin sensitivity [40] independently of diurnal rhythms [5]. Another study also reported higher glucose levels after late evening meal consumption (10 p.m.) compared to the early evening meal time (6 p.m.) among young healthy adults accustomed to a bedtime between 10 p.m. and 1 a.m. [41]. The authors attributed this difference to circadian misalignment acting primarily among participants who habitually sleep at early daytime [41].

We speculate that previous studies – often entailing study visits early in the morning – were predominantly performed among persons with early chronotype. Further studies are needed to examine whether a diurnal difference between morning and evening consumption may also be discernible among adults with late chronotypes when comparing glycemic response to a high GI meal consumed late in the morning (e.g. 11 a.m.) compared to its consumption in the evening.

Of note, for both adults with early and late chronotype glucose levels remained elevated for ~5 h after the high GI meal consumed at 8 p.m. (Figure 2 C+D). Previous studies reported higher glucose levels after earlier (7 p.m.) vs. later (10:30 p.m.) dinner consumption that were maintained up to 5 h until night and thus interfered with the participants´ sleep phase [41, 42].

The public health implications of our study results are thus twofold: First, carbohydrate-rich meals with a high GI should best be avoided particularly at later daytimes [5, 2] regardless of chronotype. Second, socially determined schedules in institutions such as school/university need to enable more flexibility in the timing of breakfast particularly for persons with late chronotype. This group presently either skips breakfast (with potential adverse consequences [43]) or consumes breakfast very early (as in our study), hence increasing the risk of circadian misalignment. Since an early breakfast may only be beneficial for adults with early chronotype, social schedules at institutions should allow breaks for a breakfast later in the morning.

Strengths and limitations

The main strength of this study is the study population with selected early and late chronotypes based on an initial screening using a validated questionnaire [34]. This resulted in a notable difference in MSFsc by almost 2 h. In addition, both wake-up time estimated from the data recorded by the accelerometer and mean melatonin levels confirm our distinction between the early and late chronotype group.

There are some limitations to this study. First, this study was a priori designed to compare effects on glycemic response following high GI meal consumption in the morning vs. evening within two chronotype strata. This was based on the rather explorative purpose of this study to examine whether either early or late chronotypes are vulnerable to eating meals against their inner clock and secondly on pragmatic considerations since conduction of a study powered for analysis of an interaction would have quadrupled the sample sizes in each group, and hence required a screening of an unfeasibly large sample (approximately 1200 students) [44]. Indeed, morning or evening iAUC did not differ significantly between early and late chronotypes (data not shown), yet this was not the aim of this study and may largely reflect the lack of power for this comparison. Nonetheless interaction tests confirm differences between early and late chronotypes for the difference between morning and evening consumption for selected outcomes (see methods). Despite the fact that we aimed to include persons with extreme early and late MSFsc [34], the study population comprises individuals with merely moderately early or

moderately late chronotype. Hence, this potentially limited our possibility to detect more extreme glycemic responses. Another limitation concerns the absence of measured glucose homoeostasis associated hormones such as insulin and those that display circadian rhythmicity, e.g. cortisol and ghrelin, or those involved in the synchronization of the central circadian rhythm with the peripheral tissues such as leptin, adipokines, and incretins [36]. Also, data on the individual circadian rhythm at the time of the intervention are lacking. Moreover, we were not able to perform an intention-to-treat analysis because the persons who declined participation did not participate in any of the study visits after randomization. However, since dropout occurred in all groups, selection bias towards a null effect is improbable, as it would only be possible if dropout individuals were expected to show an opposite effect. Finally, this study was conducted among young and healthy university students, thus our results may not be generalizable to older or less healthy people.

CONCLUSIONS

Glycemic responses to a high GI meal were higher in the evening than in the morning among adults with early chronotype, in agreement with the concurrence of circadian deterioration of glucose homeostasis and late evening meal consumption. Conversely, individuals with late chronotype showed no diurnal differences suggesting vulnerability to high GI meal consumption both in the very early morning and late in the evening. Further studies are needed to replicate our findings and to examine the physiological relevance of the observed differences.

Ethical standards

Informed consent was obtained from all participants prior to the trial. The study protocol was approved by the Ethics Committee of Paderborn University and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its late amendments.

Author Contributions:

AEB conceptualized the research and supervised the project: JD performed randomization; BS, BK, JG, CH, CR, RJ conducted research; BS analysed data and performed statistical analysis under the guidance of AEB and GBB; JG supported dietary intervention and statistical analysis; BS wrote the paper supervised by AEB; BK, JG, CH, CR, RJ, JD, UA, NJ, GBB reviewed and edited the manuscript; all authors contributed to

the interpretation and discussion of the results and approved the final manuscript. AEB had primary responsibility for the final content.

Competing Interests: BS, BK, JG, NJ, JD, GBB, RJ, RC declare that they have no conflict of interest. AEB is a member of the International Carbohydrate Quality Consortium (ICQC), and a co-author of the popular cookbook “Nordisch abnehmen”.

The German Diabetes Center is funded by the German Federal Ministry of Health (Berlin, Germany) and the Ministry of Culture and Science of the state North Rhine-Westphalia (Düsseldorf, Germany) and receives additional funding by the German Federal Ministry of Education and Research (BMBF) through the German Center for Diabetes Research (DZD e.V.).

Data Sharing:

Data described in the manuscript, code book, and analytic code will be made available upon request pending [formal data sharing agreement].

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TABLE 1: Characteristics of the two study populations (early and late chronotypes).

	Early chronotypes (n=22)	Late chronotypes (n=23)
Anthropometric and laboratory characteristics		
Female sex, n (%)	14 (64)	12 (52)
Age, years	22 (21; 23)	22 (21; 24)
BMI, kg/m²	22.4 (± 2.2)	22.5 (± 2.6)
Waist circumference, m	0.7 (0.7; 0.8)	0.8 (0.8; 0.9)
Visceral fat mass, L	0.4 (0.3; 0.6)	0.7 (0.4; 1.3)
Skeletal muscle mass, kg	23.2 (20.1; 28.4)	24.9 (21.2; 31.3)
Fasting blood glucose, mmol/L	5.1 (± 0.4)	5.2 (± 0.3)
Fasting insulin, µU/mL	6.9 (± 2.7)	7.3 (± 3.9)
HOMA-IR	1.6 (± 0.6)	1.7 (± 0.9)
Melatonin, ng/L	27.4 (22.7; 38.1)	36.0 (29.4; 57.1)
hsCRP, mg/dL	0.1 (0.0; 0.1)	0.0 (0.0; 0.1)
Non-esterified fatty acids, µmoL/L	359 (231; 589)	409 (309; 524)
Triglycerides, mg/dL	98 (± 42)	99 (± 45)
HDLc, mg/dL	61 (± 13)	64 (± 15)
LDLc, mg/dL	104 (± 25)	97 (± 25)
Circadian characteristics and habitual meal/snack consumption		
Chronotype MSFsc (o'clock)		
At screening	3:26 (2:55; 3:38)	6:00 (5:35; 6:23)
At intervention[1]	3:54 (3:15; 4:18)	5:50 (5:10; 6:25)
Time when falling asleep (o'clock)		
Workdays[1]	22:50 (22:25; 23:11)	1:00 (00:15; 1:10)
Work-ree days[1]	23:32 (23:10; 00:00)	2:00 (1:20; 2:10)
During nutrition trial[2]	22:46 (22:21; 23:12)	23:48 (23:31; 00:47)
Wake-up time (o'clock)		
Workdays[1]	7:00 (6:30; 7:30)	9:00 (8:00; 9:05)
Work-free days[1]	8:00 (7:15; 8:30)	10:00 (9:00; 10:45)
During nutrition trial[2]	6:36 (6:16; 6:44)	7:07 (6:41; 7:26)
Breakfast timing (o'clock)[1]		
Workdays	7:52 (7:00; 8:15)	10:00 (9:00; 10:00)
Work-free days	9:00 (8:37; 9:30)	11:00 (10:00; 12:00)
Lunch timing (o'clock)[1]		
Workdays	13:00 (12:30; 13:30)	14:00 (13:00; 14:00)
Work-free days	13:30 (12:30; 14:00)	14:00 (13:30; 15:00)
Dinner timing (o'clock)[1]		
Workdays	19:00 (18:30; 19:00)	19:30 (19:00; 20:00)
Work-free days	19:00 (18:00; 19:00)	19:30 (18:30; 20:46)

Breakfast skipping (n (%))[1]		
Workdays	4 (18)	5 (22)
Work-free days	2 (9)	4 (17)
Lunch skipping (n (%))[1]		
Workdays	1 (5)	4 (17)
Work-free days	7 (37)	7 (30)
Snacking in the morning (n (%))[1]		
Workdays	8 (36)	5 (22)
Work-free days	5 (23)	4 (17)
Snacking in the evening (n (%))[1]		
Workdays	2 (9)	6 (26)
Work-free days	6 (27)	10 (43)

Abbreviations: hsCRP, high-sensitivity C-reactive protein; HDLc, high-density cholesterol; LDLc, low-density cholesterol; MSFsc, midpoint of sleep corrected. 1 estimated time of the past 4 weeks before intervention [34]. Note that lectures were still held online at university. 2 days 4 to 7. *Dinner skipping was minimal (i.e. <5%). Data are frequencies, means ± standard deviation, or medians (Q1, Q3).

TABLE 2: Glycemic response parameters to a high GI meal consumed in the morning and in the evening by chronotype group.

Glycemic response parameters	**Early chronotype (n=22)**				**Late chronotype (n=23)**			
2 h pp response after high GI meal consumed	**Morning (7 a.m.)**	**Evening (8 p.m.)**	**Difference (95% CI) evening versus morning[1]**	**p**	**Morning (7 a.m.)**	**Evening (8 p.m.)**	**Difference (95% CI) evening versus morning[1]**	**p**
iAUC((mmol/L) x min)	195 (± 91)	234 (± 92)	40 (2; 77)	**0.042**	211 (± 110)	207 (± 95)	-4 (-55; 48)	0.888
Mean glucose value (mmol/L)	6.75 (± 0.91)	7.32 (± 0.83)	0.57 (0.29; 0.86)	**<0.001**	7.12 (± 1.04)	7.28 (± 0.68)	0.16 (-0.20; 0.53)	0.362
Highest glucose value (mmol/L)	9.04 (± 1.42)	9.57 (± 1.37)	0.52 (0.07; 1.11)	0.080	9.67 (± 1.58)	9.39 (± 1.17)	-0.28 (-0.92; 0.35)	0.365
Lowest glucose value (mmol/L)	4.80 (± 0.71)	5.19 (± 0.54)	0.38 (0.08; 0.69)	**0.017**	5.00 (± 0.61)	5.33 (± 0.53)	0.32 (0.05; 0.59)	**0.024**
Standard deviation (mmol/L)	1.34 (± 0.44)	1.42 (± 0.50)	0.07 (-0.18; 0.33)	0.551	1.52 (± 0.51)	1.30 (± 0.41)	-0.21 (-0.47; 0.04)	0.098
24-hour glycemic response on days with high GI meal consumed	**Morning (7 a.m.–7 a.m.)**	**Evening (7 a.m.–7 a.m.)**	**Difference (95% CI) evening versus morning[1]**		**Morning (7 a.m.–7 a.m.)**	**Evening (7 a.m.–7 a.m.)**	**Difference (95% CI) evening versus morning[1]**	
iAUC ((mmol/L) x min)	1004 (± 399)	1071 (± 289)	67 (-114; 248)	0.452	962 (± 368)	987 (± 352)	26 (-138, 190)	0.748
Mean glucose value (mmol/L)	5.87(± 0.59)	5.97 (± 0.58)	0.11 (0.00; 0.21)	0.052	6.06 (± 0.38)	6.05 (± 0.43)	-0.01 (-0.12; 0.11)	0.876
Highest glucose value (mmol/L)	9.19 (± 1.20)	9.68 (± 1.26)	0.48 (-0.04; 1.00)	0.069	9.74 (± 1.46)	9.42 (± 1.17)	-0.32 (-0.89; 0.24)	0.251

Lowest glucose value (mmol/L)	4.15 (± 0.67)	4.44 (± 0.65)	0.29 (-0.06; 0.63)	0.098	4.46 (± 0.65)	4.51 (± 0.46)	0.05 (-0.24; 0.34)	0.719
Standard deviation (mmol/L)	0.79 (± 0.15)	0.92 (± 0.21)	16% (7%; 24%)[2]	**0.001**	0.87 (± 0.24)	0.86 (± 0.20)	0.2% (-10 %; 11%)[2]	0.972
MAGE (mmol/L)	2.25 (1.74; 2.46)	2.17 (1.88; 2.65)	0.17 (-0.12; 0.45)	0.233	2.31 (1.87; 2.77)	2.23 (1.77; 2.59)	-0.07 (-0.42; 0.27)	0.661

Abbreviations: n, sample size; iAUC, incremental area under the curve; MAGE, mean amplitude of glucose excursions; CI, confidence interval. Data are means ± standard deviation or medians (Q1, Q3) calculated from the individual iAUC, mean, highest and lowest value as well as the intra-individual standard deviation obtained during 2-h pp or 24-h pp each individual. MAGE was analyzed for 24 h-period only due to low number of participants with >1 standard deviation during 2-h pp interval. [1] Difference estimated from multilevel linear regression (ß coefficients) [2] Percentage difference evening vs morning as estimated from log-transformed variable. Significant P-values (<0.05) are marked in bold.

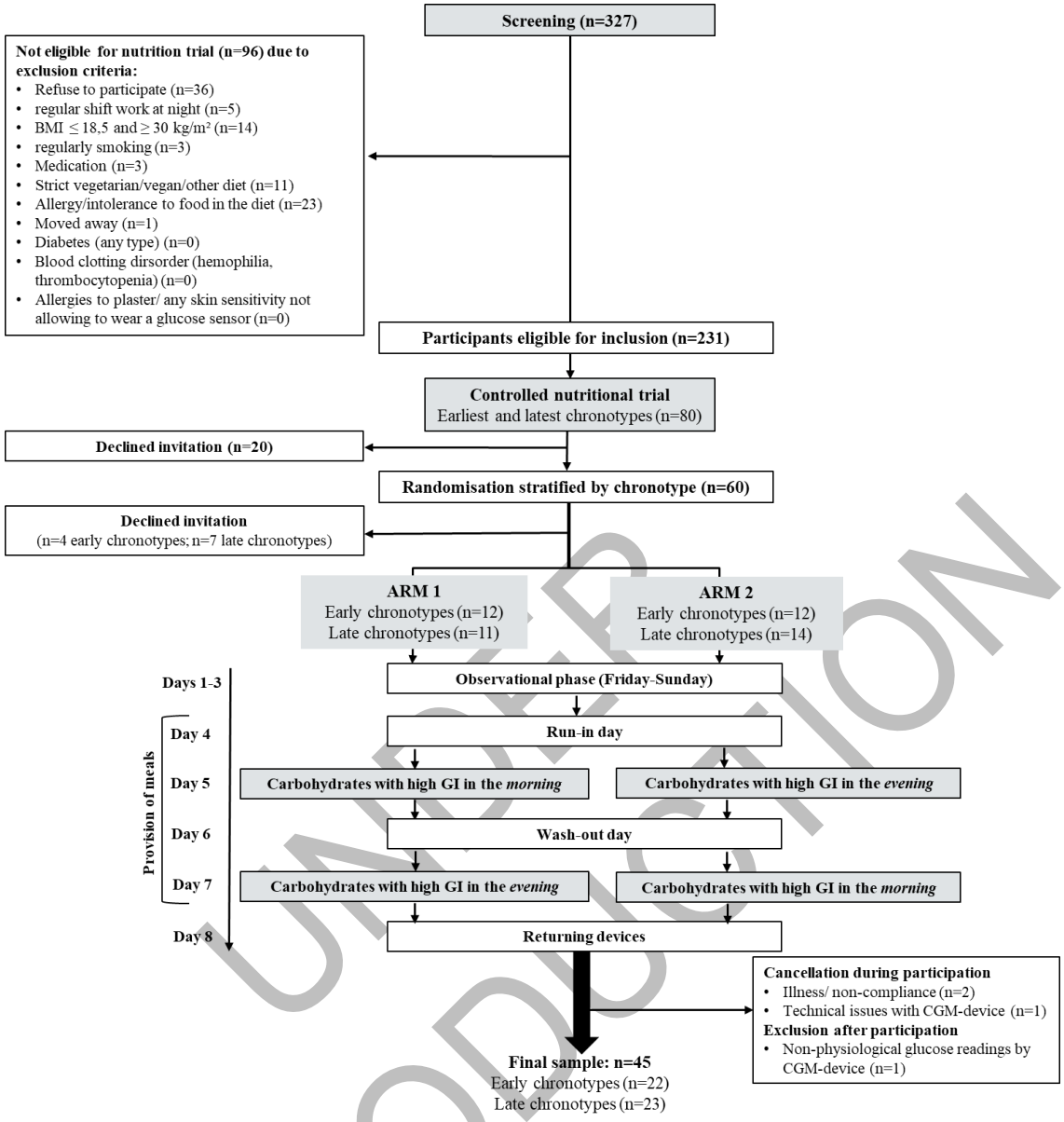
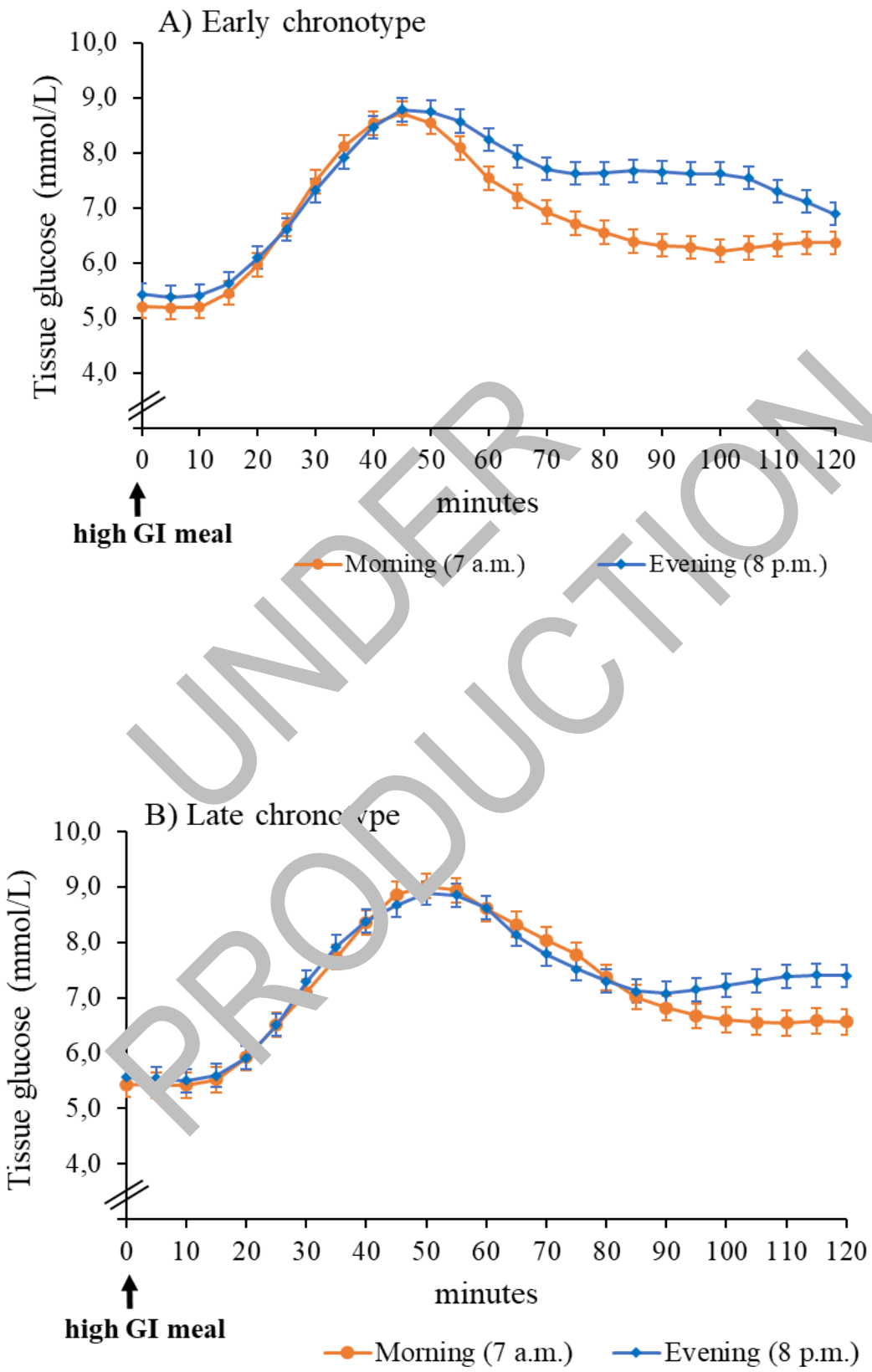


Figure 1: Flow chart of study participants and the procedure of the controlled nutrition trial. Of n=327 screened students, n=80 were invited to participate of which n=46 completed the intervention while one participant was excluded due to non-physiological glucose recordings.



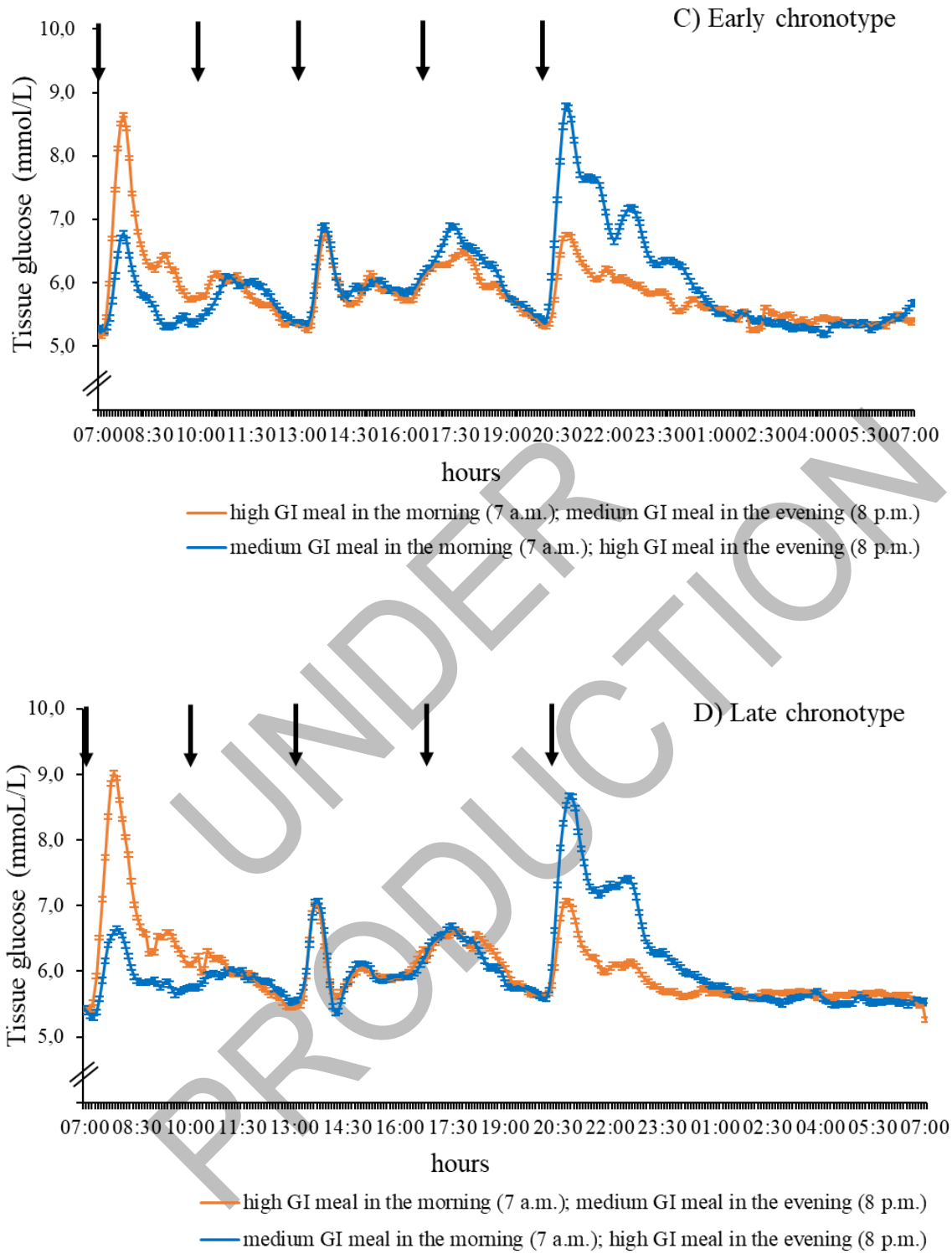


Figure 2: Mean glucose levels (± standard error) 2-h pp following a high GI meal in the morning (blue) and in the evening (orange) (panel A-B) and 24-h distribution (7-7 a.m.; panel C-D) among participants with early and late chronotype (n= 22; n=23, respectively). 2-h pp mean glucose values were significantly higher after high GI meal in the evening than in the morning among early chronotypes only ($p<0.001$). Black arrows indicate meal/snack consumption.

SUPPLEMENTAL TABLE 1: Meal plan for the high GI intervention days 5+7 – example for the 2100 kcal group.

Meals and instructed times of consumption	GI	GL[1]	Amount [g]	Kcal	Protein [g]	Fat [g]	Av. carbohydrates [g]	Fiber [g]	References
Breakfast (7:00 a.m.)/dinner (8:00 p.m.)									
Cornflakes (Kellog´s)	81	29	42	161	3	0	35	1	Mean of five studies (16)
Milk, 1,5 % fat content	30	2	170	81	6	3	8	0	Mean of milk, reduced fat (three studies) and milk, skim/low-fat (16)
Soft pretzel (Ditsch)	80	23	60	165	5	2	29	2	(17)
Mars® bar	65	16	35	158	1	6	25	0	Mean of 2 studies (16)
Meal GI[2]/GL[3]	***72***	***70***							
Morning snack (9:30-10:30 a.m.)									
Walkers Highland Oatcakes	57	12	36	168	4	7	21	2	(39)
Apple slices	39	5	95	61	0	0	14	2	(16)
Meal GI[2]/GL[3]	***50***	***17***							
Lunch[4] (1:00 p.m.)									
Spaghetti (Transgourmet)	48	24	72	263	9	2	50	2	(40)
Chicken breast	0	0	90	93	21	1	0	0	
Red pepper / Capsicum	52	1	45	11	0	0	1	1	Mean of green peas, sweet corn, carrots, pumpkin (16)
Carrots, diced	41	1	45	18	0	0	3	1	mean of two studies (16)
Tomato sauce[5]	32	1	146	54	3	0	8	2	(16)
Olive oil	0	0	15	133	0	15	0	0	
Meal GI[2]/GL[3]	***48***	***31***							
Afternoon snack (4:00-5:00 p.m)									
Belvita biscuits, milk&cereals	45	9	31	139	2	4	21	2	(25)
Kiwi slices	58	7	125	70	1	1	11	5	(16)
Meal GI[2]/GL[3]	***50***	***16***							
Dinner (8:00 p.m.)/Breakfast (7:00 a.m.)									
Bread (Lieken Urkorn, Paderborner)	62	21	80	174	5	1	34	5	(17)
Gouda cheese, 50% fat content	0	0	48	172	12	14	0	0	Mean of five studies (16)
Butter	0	0	16	117	0	13	0	0	

Cucumber slices	52	0	55	5	0	0	1	0	Mean of green peas, sweet corn, carrots, pumpkin (16)
Carrot sticks	37	1	45	18	0	0	3	1	mean of two studies (16)
Apple slices	39	4	70	41	0	0	9	1	(16)
Meal GI[2]/GL[3]	***56***	***16***							
Estimated GI/GL on intervention day	**58**	**160**							
Total[6]				**2100**	**74**	**70**	**274**	**29[7]**	
Total % energy					**14**	**30**	**53**	**3**	

Abbreviations: g, grams; kcal, kilocalorie; G, glycaemic index; GL, glycemic load. [1]Glycemic load= (g available carbohydrates*GI)/100; [2]dietary GI= (sum of GL/ g available carbohydrates)*100; [3]dietary GL= sum of GL; [4] Lunch was freshly cooked. Nutritional and GI values refer to the uncooked condition; [5]Tomato sauce was self-made: canned tomatoes (mashed) (GI=52, GL= 2; mean of green peas, sweet corn, carrots, pumpkin (16), tomato puree (GI=52, GL=1; mean of green peas, sweet corn, carrots, pumpkin (16), sucrose (GI=56, GL=1; mean of six studies (16), vegetable broth, Italian herb mix (dry), salt, and pepper (all GI=0, GL=0); [6] total sum deviates from individual data listed due to rounding of decimals. [7] 2 kcal account for 1g fiber to achieve 100% total energy.

SUPPLEMENTAL TABLE 2: Meal plan for the run-in/wash-out day – example for the 2100 kcal group.

Meals and instructed times of consumption	GI	GL[1]	Amount [g]	Kcal	Protein [g]	Fat [g]	Av. carbohydrates [g]	Fiber [g]	References
Breakfast (until 12:30 a.m.)									
Alpen Original Müsli	55	32	88	332	10	5	58	7	(16)
Milk, 3,8% fat content	31	2	165	109	5	6	8	0	mean of seven studies milk, full-fat (16)
Orange	37	4	115	65	1	0	12	3	Mean of two studies (16)
Meal GI[2]/GL[3]	***50***	***39***							
Morning snack (until 12:30 a.m.)									
Walkers Highland Oatcakes	57	8	24	112	3	5	14	1	(39)
Grapes	59	10	120	83	1	0	18	2	(16)
Meal GI/GL	***58***	***18***							
Lunch[4] (1:00 p.m.)									
Basmati rice, Oryza Himalaya	62	37	80	285	7	1	60	3	(40)
Zucchini	52	1	80	18	2	0	2	1	mean of green peas, sweet corn, carrots, pumpkin (16)
Sweet corn, canned	52	2	40	35	1	1	5	1	mean of 5 studies (16)
Tomato sauce[5]	52	1	158	48	3	0	6	2	(16)
Feta cheese	0	0	40	115	7	10	0	0	
Olive oil	0	0	10	10	0	10	0	0	
Dessert									
Plain yoghurt, 3,8 % fat content	19	1	110	80	5	4	6	0	mean of four studies, natural yoghurt (16)
Raspberries	51	2	90	40	1	0	4	4	mean of blueberries wild; grapes, black, strawberries (16)
Honey	61	5	11	34	0	0	8	0	mean of 17 studies (16)
Meal GI/GL	***57***	***52***							
Afternoon snack (until 9:00 p.m.)									
Belvita biscuits, milk & cereals	45	8	25	112	2	4	17	2	(25)
Banana	59, 6	10	130	81	1	0	17	2	mean of three studies (16)

Meal GI/GL	***52***	***18***							(16)
Dinner (until 9:00 p.m.)									
Couscous, cooked	65	21	50	170	6	1	32	3	mean of 3 studies with identical preparation method (39)
Red pepper / capsicum	52	1	45	10	0	0	1	1	mean of green peas, sweet corn, carrots, pumpkin (16)
Tomato	52	1	45	9	0	0	1	1	mean of green peas, sweet corn, carrots, pumpkin (16)
Eggs, boiled	0	0	80	109	9	7	1	0	
Cucumber	52	0	35	4	0	0	0	0	mean of green peas, sweet corn, carrots, pumpkin (16)
Avocado	0	0	70	97	1	9	2	3	
Dressing[6]	0	0	14	62	0	7	0	0	
Meal GI/GL	***58***	***22***							
Estimated GI/GL on run-in/wash-out day	**55**	**150**							
Total[7]				**2100**	**65**	**72**	**274**	**36[9]**	
Total % energy[8]					**13**	**30**	**53**	**3**	

Abbreviations: g, grams; kcal, kilocalorie; GI, glycaemic index; GL, glycemic load. [1]Glycemic load= (g available carbohydrates*GI)/100; [2]dietary GI= (sum of GL/ g available carbohydrates)*100; [3]dietary GL= sum of GL [4] Lunch was freshly cooked. Nutritional and GI values refer to raw ingredients; [5]Tomato sauce was self-made: canned tomatoes (mashed) (GI=52, GL= 2; mean of green peas, sweet corn, carrots, pumpkin (16)), tomato puree (GI=52, GL=1; mean of green peas, sweet corn, carrots, pumpkin (16)), vegetable broth, dried herbs, salt, and pepper (all GI=0, GL=0); [6] dressing: olive oil, herbs, salt (all GI=0, GL=0); [7] total sum deviates from individual data listed due to rounding of decimals; [8] 1% accounts for organic acids. [9] 2 kcal account for 1g fiber to achieve 100% total energy.

APPENDIX D

OA3

Association between glucose dips and the feeling of hunger in a dietary intervention study among students with early and late chronotype- secondary analysis of a randomized cross-over nutrition trial

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Abstract

Consumption of foods with high glycaemic index (GI) can cause hyperglycemia, thus increasing postprandial hunger. Since circadian rhythm differs intra-individually, we describe glucose dips after breakfast/dinner with high/medium estimated meal GI among students with early (n=22) and late chronotype (n=23) and examine their relation to the feeling of hunger in a secondary analysis of a randomized cross-over nutrition trial. Glucose dips reflect the difference between the lowest glucose value recorded 2-3 hours postprandially and baseline, presented as percentage of average baseline level. Associations between glucose dips and the feeling of hunger were analyzed using multilevel linear models.

Glucose dips were lower after medium GI meals than after high GI meals among both chronotype groups (p=0.03). Among early chronotypes, but not among late chronotypes, glucose dip values were lower after breakfast than after dinner (-4.9 % vs. 5.5 %, p=0.001). Hunger increased throughout the day among both chronotypes but glucose dips were not related to the feeling of hunger at the meal following breakfast. Interestingly, lower glucose dip values 2-3 hours postprandially occurred particularly after medium GI meals and were seen after breakfast among early chronotypes. These glucose dips did not predict hunger at meals after breakfast.

Keywords: *chronotype, circadian misalignment, glycemic index, glucose dips, hunger, fullness*

1. Introduction

The control of hunger and the impact of meal timing have regained much interest for personalized nutrition in the context of different circadian phenotypes, i.e. chronotype (Franzago et al., 2023). Hunger reflects a lack of energy signaled by an empty stomach, hormones such as high ghrelin concentrations, and metabolic signals, e.g. low blood glucose levels, to initiate food consumption (Amin & Mercer, 2016; Blundell et al., 2020). The impact of blood glucose levels on hunger was first described by Mayer´s 'glucostatic hypothesis' stating that a decline in blood glucose concentration increases hunger whereas high blood glucose levels increase the feeling of satiety (Mayer, 1952). However, results from subsequent studies did not consistently support this hypothesis (Kim et al., 2019; Woods & D'Alessio, 2008). Recently, researchers around Wyatt revived Mayer's hypothesis and examined in their study the role of glucose in hunger control among 1070 healthy adults participating in the PREDICT study (Wyatt et al., 2021).

According to their study investigating different glucose homeostasis parameters, the key postprandial glycemic measure associated with hunger and subsequent food intake was the dip in glucose levels 2-3 hours after meal consumption. Noteworthy, glucose dips were most pronounced following an oral glucose tolerance test (OGTT), which has a glycemic index (GI) of 100, out of five standardized breakfasts served in the PREDICT study (Wyatt et al., 2021).

Indeed, after consumption of a high-glycemic index (GI) food item (GI>70), blood glucose levels increase rapidly, but generally decrease steeply subsequently to levels below baseline within the 2-hour postprandial period, a condition termed 'reactive hypoglycemia'. This hypoglycemic state is characterized by both the persistence of hyperinsulinemia and the suppression of glucagon (Ludwig, 2002). Furthermore, the suppression of gluconeogenesis and lipolysis signals a low energy status, hence stimulating hunger and food consumption to restore energy homeostasis. However, while low-GI meals have been associated with increased satiety and delayed return of hunger (Ludwig et al., 1999), the impact of the GI as a predictor for occurring hunger still remains controversial (Tremblay & Bellisle, 2015; Wu et al., 2014).

Additionally, both glucose and hunger homeostasis underlie a circadian rhythm: hunger increases throughout the day and peaks in the evening (Sargent et al., 2016; Scheer et al., 2013), while glucose homeostasis deteriorates in later daytime, resulting in higher postprandial glucose responses to the same meal consumed in the evening compared to the morning (Morgan et al., 2012; Morris et al., 2015). These circadian rhythms likely differ between persons with early and late chronotypes, hence the feeling of hunger before a meal at early and late daytimes may differ depending on their chronotype.

This secondary analysis draws on the Chronotype and Nutrition (ChroNu) Study, which aimed to investigate differences in the short-term glucose response to morning and evening meals among students with early and late chronotype. In this nutrition trial, participants also rated their feeling of hunger and fullness before consuming meals/snacks. Hence, this secondary analysis aims to (i) describe the diurnal profile of hunger and glycemia when a high or medium GI meal was served as breakfast and on a day when the identical high or medium GI meal was served as dinner among persons with either an early or late chronotype. It further aims to examine whether glucose parameters including glucose dips differ (ii) following a high GI vs. medium GI meal, and (iii) between breakfast vs. dinner among persons with either an early or late chronotype. Lastly (aim iv), we wanted to assess the association between glucose parameters and

the feeling of hunger following breakfast only, since hunger/fullness was not inquired after dinner.

2. MATERIALS AND METHODS

2.1 Study population

The ChroNu study aimed to compare the 2-hours postprandial and 24-hour glycemic response to a meal rich in carbohydrates from higher GI sources when consumed early in the morning (7 a.m.) or late in the evening (8 p.m.). This was performed in a cross-over trial in two samples of students with early or late chronotype. Based on a screening of 327 students aged 18-25 years from Paderborn University, 49 students participated in the controlled nutrition trial, of whom 45 participants were included in the original and present analysis (supplemental figure 1). Prior to the start of the study, informed consent was obtained from all participants. The study protocol was approved by the Ethics Committee of Paderborn University. The controlled nutrition trial was registered at clinicaltrials.gov (NCT04298645).

2.2 Study design

Participants were randomized by sex and chronotype to the order of a high GI (GI=72) meal consumed either in the morning/evening (arm 1) or in the evening/morning (arm 2) at two intervention days, preceded by a run-in/wash-out day, Figure 1. In the morning of the run-in day, participants received a breakfast and a midmorning snack after fasting blood samples were collected. On each day, participants returned for lunch to the study center and received further meals and snacks, which had to be consumed at predefined times. On the intervention days, an identical high GI meal (Mars®bar, Cornflakes (Kellog´s®), low-fat milk (1.5%), soft pretzel) with an estimated GI of 72 was provided in the morning (7 a.m.) or evening (8 p.m.) to potentially cause circadian misalignment for late/early chronotypes (Roenneberg et al., 2019). All other meals/snacks on the intervention and run-in/wash-out days had a medium GI (46-59) to avoid second meal effects (Wolever et al., 1988). Researchers were only blinded to the participants´ chronotype due to the provision of meals/snacks. For this secondary analysis, data of hunger ratings recorded before participants consumed their meals/snack on the intervention days (days 5+7) and 2-3-hours postprandial glucose data following the consumption of high/medium GI breakfast and dinner were used.

2.3 Assessment of hunger and fullness

Participants were asked to mark their feeling of hunger or fullness on a 19 cm labelled magnitude satiety scale (LMS) (Zalifah et al., 2008) in a diary before every meal and snack they consumed, i.e. at 7 a.m. before breakfast, between 9:30 and 10:30 a.m. before midmorning snack, at 1 p.m. before lunch, between 4 and 5 p.m. before afternoon snack, and at 8 p.m. before dinner. The LMS is subdivided by the feeling of *„Neither hunger nor full“*= (0 cm, i.e. center of the scale) and stages describing an increased or decreased feeling of hunger/fullness. The ends of the scale describe *„Greatest imaginable hunger“* =(-9,5 cm) and *„Greatest Imaginable Fullness“* =(9,5 cm). The LMS was freely translated by the study team (BS) into German for this study purpose.

2.4 Assessment of chronotype

Both at screening and prior to the nutrition trial, we assessed the chronotype with the Munich ChronoType Questionnaire, which inquires sleep time separately for workdays and free days (Roenneberg et al., 2019). The chronotype was calculated as the midpoint of sleep between sleep onset and sleep offset and corrected for accumulated sleep debt during workdays (MSFsc). During the trial, sleep and awake times were estimated based on the participant´s movements recorded by an accelerometer (E4 wristband, Empatica SRI, Italy) and the bedtimes recorded in a diary. Chronotypes were selected for the trial based on their chronotype assessed at screening.

2.5 Continuous glucose measurement

During the study, glycemic responses were recorded using continuous glucose monitoring (G6, Dexcom), which measures subcutaneous interstitial glucose levels resulting in mean glucose value every 5 min. During the trial, the device was blinded.
Glucose dips were calculated as the difference between the lowest glucose reading in the 2-3 hours postprandially after (i) high/medium GI breakfast or directly before midmorning snack consumption (whichever came first) and (ii) high/medium GI dinner minus the average baseline glucose level (glucose readings -5 min and min 0, i.e. directly before and at meal consumption), presented as a percentage of average baseline level. The glucose $dip_{2\text{-}3hr}$ is expressed as a percentage to adjust for differences in participants' baseline glucose levels. Negative glucose dip values indicate states of mild hypoglycemia while positive glucose dip values indicate that blood glucose levels remain

elevated above baseline level. Glucose rise was calculated as the maximum level above baseline 2 hours postprandially and is also presented as a percentage of the average baseline glucose level (Wyatt et al., 2021). Since the participants were allowed to consume their midmorning snack 2:30 hours after breakfast within a one-hour time window, some of the participants have an incomplete 3-hour postprandial time period after breakfast. For the respective variables (glucose $dip_{2\text{-}3hr}$, lowest $glucose_{0\text{-}3hr}$, highest $glucose_{0\text{-}3hr}$), all data available (i.e. also incomplete 3-hour time periods) were considered in the initial analyses.

2.6 Laboratory and anthropometric measurements

On the run-in day, venous blood samples were drawn at 7 a.m. after ≥10 h fasting period to analyze insulin, glucose, lipids, and high-sensitivity C-reactive protein (hsCRP) at the German Diabetes Center in Düsseldorf. Melatonin was subsequently measured at Medizinische Laboratorien, Düsseldorf. HOMA-IR was calculated as (fasting blood insulin (µU/mL)*fasting blood glucose (mmol/L))/22.5 (Wallace et al., 2004). Body composition was measured by using Bioimpedance Analysis (mBCA 515, SECA). Body Mass Index (BMI) was calculated by weight (kg)/height (m)².

2.7 Statistical analysis

Characteristics of the study participants are presented as means and standard deviations for normally distributed variables or as medians (25th, 75th percentile) for non-normally distributed continuous variables; total numbers (n) and percentages were presented for categorical variables. Statistical analyses were performed using SAS procedures (SAS version 9.4; SAS Institute, Cary, NC, USA) considering *p*-values <0.05 as statistically significant. The hypotheses underlying the following analyses (see introduction) were specified before carrying out the statistical analysis according to a pre-specified analytic plan: For research aim 1, in a descriptive approach, hunger (before each meal/ snack) was plotted against diurnal glycemia (6 a.m. to 11 p.m.) separately for the day when a high or medium GI meal was served as breakfast and when the identical high or medium GI meal was served as dinner for persons with an early and late chronotype. Research aims 2 and 3 were addressed in a combined model: To examine whether glucose parameters differ in the 2-3-hour postprandial window following a medium or high GI meal (aim 2) and/or at breakfast or dinner (aim 3) among persons with either early or late chronotype, multilevel linear regression models (PROC

MIXED in SAS) were applied with glucose parameters as the dependent variables. By using mixed models including both fixed and random effects, we account both for the repeated measurements occurring for each participant and for variation between measurements within an individual. Both the GI category of the meal (medium vs. high) and the timing of the meal (breakfast vs. dinner) were used as independent variables. Sex, age, BMI, fat mass, fat free mass, waist circumference, chronotype (early/late), fasting insulin levels, HOMA-IR, and melatonin levels were each separately considered as potential influencing factors. To keep the models minimally adjusted, only those variables that substantially modified the association with glucose parameters, significantly predicted the glucose parameters (Maldonado & Greenland, 1993), or improved the coefficient of determination (Kirkwood, 2010) were considered. All analyses are presented separately by chronotype since this study was performed in two samples of persons with either an early or late chronotype.

To examine the association between selected postprandial glucose response variables and the feeling of hunger/fullness after breakfast/before midmorning snack consumption (aim 4), again multilevel linear regression models were applied with hunger as the dependent and glucose parameters as independent variables. Of note, as information on the feeling of hunger was only collected before the respective meals/snacks, no information on the feeling of hunger 2-3 hours after dinner is available. Hence, only data for breakfast can be considered for this last research aim. Model adjustments were performed as described above.

As the participants had to fast at least 2:30 hours before consuming their midmorning snack, some of them had their snack before the 3-hour postprandial time period was completed. For those participants, only data until start of snack consumption was included in the analysis, resulting in less than 11 data points for glucose measurements. Hence, additional sensitivity analyses were conducted including only those participants with complete 180 min. postprandial glucose data (n=26).

3. RESULTS

The participants were young and healthy university students on average aged 22 years with a BMI of 22.5 kg/m^2, **Table 1**. Participants with early and late chronotypes differed in their MSFsc by approximately 1:54 h:min. Moreover, both chronotypes had breakfast earlier and dinner later than normal on the intervention days. Among both chronotype groups hunger increased throughout the day and was most pronounced

before dinner. Of note, participants with an early chronotype already showed an increased feeling of hunger before lunch, which was less pronounced among those with late chronotype (-4.1 (-5.4; -1.7) cm; -1.8 (-4.1; 0.1) cm, respectively.

Figure 2 illustrates the diurnal developments of glucose and hunger values after a high GI breakfast/medium GI dinner (panels a+b) or medium GI breakfast/high GI dinner (panels c+d) (**aim 1**). Glucose levels were higher following the consumption of a high GI breakfast and dinner, while medium GI meals/snacks caused a smaller glucose rise. Before breakfast, participants felt neither hungry nor full, but before the subsequent midmorning snack those with a late chronotype felt rather full, while those with an early chronotype again felt neither hungry nor full. After the midmorning snack, hunger increased throughout the day with a peak before dinner irrespective of breakfast GI. However, individuals with an early chronotype seemed to feel hungrier before their afternoon snack when they consumed a medium GI breakfast (panel c) than after consuming a high GI breakfast. In contrast, those with a late chronotype seemed to be hungrier before their afternoon snack after having a high GI breakfast and less hungry when consuming a breakfast with medium GI.

Table 2 presents the results of the analysis on the difference of examined glucose parameters by GI category (medium/high) and meal type (breakfast/dinner) (**aims 2+3**). In both chronotype groups, lower **glucose dips$_{2\text{-}3h}$**-values were observed after medium GI meals in comparison to high GI meals (both p=0.03). However, for early chronotypes only, glucose dip-values were below fasting state after breakfast and lower than after dinner (breakfast -4.89 (-7.61, -0.54) % vs. dinner 5.45 (-7.26, 11.6) %, difference between meal p=0.001)). Both **highest glucose levels$_{0\text{-}3h}$** and **glucose rise$_{0\text{-}2h}$** were significantly higher after a high GI meal in comparison to a medium GI meal in both early and late chronotypes (all p for GI <0.0001). There were no other differences between the meal type (breakfast vs. dinner) for any of the glucose parameters among those with late chronotype (all p for meal >=0.05).

Results on **aim 4**, i.e. examining the **association between glucose dips$_{2\text{-}3h}$ and the feeling of hunger** after breakfast consumption (**Table 3**), indicate no association between the glucose parameters and the feeling of hunger for both chronotype groups (all p ≥0.2).

Results from **sensitivity analyses** on the association between glucose parameters and the feeling of hunger after breakfast, including only those 26 of the 45 participants with complete 180 min. postprandial data, similarly revealed differences for

medium vs high GI, however for the highest glucose values only; also differences in glucose dips between breakfast and dinner continued to be seen for early chronotypes only. No associations were seen between glucose parameters and the feeling of hunger. (**Supplemental Tables 1 and 2**).

4. DISCUSSION

In this secondary analysis of a controlled nutrition trial we examined glucose dips and other glucose parameters and the feeling of hunger/fullness among two selected samples of young adults with early and late chronotype: Firstly, we observed that the previously reported diurnal rhythm of hunger occurred irrespective of chronotype and irrespective of a high GI of the preceding meal (**aim 1**). Secondly, glucose dips were more discernible after a medium GI meal compared to a high GI meal for both chronotypes (**aim 2**). Furthermore, consistent glucose dips were only seen after medium GI breakfasts among participants with an early chronotype (**aim 3**). Finally, glucose parameters were not related to the feeling of hunger following breakfast (**aim 4**).

4.1 Diurnal profile of hunger and glycemia (Aim 1)

Our observations underline the robust diurnal rhythm of hunger, which increases throughout the day (Scheer et al., 2013) irrespective of circadian misalignment, meal timing (McHill et al., 2022; McHill et al., 2018; Qian et al., 2019), and chronotype (Beaulieu et al., 2020). Although the diurnal rhythm of subjective hunger was similar among both chronotype groups, persons with late chronotype felt rather full before they consumed their midmorning snack ~3 hours after breakfast irrespective of its GI. This in contrast to Beaulieu who observed a greater perceived fullness in early compared to late chronotypes following meal consumption in the morning (8:00-10:00 a.m.) (Beaulieu et al., 2020). Such differences may arise from the fact that – in contrast to our study sample – Beaulieau characterized the chronotype by a median split of the morningness-eveningness score, potentially resulting in less extreme chronotypes. In our study, persons with late chronotype (MSF_{sc} of 5:50 a.m.) may have consumed the midmorning snack (~10 a.m.) close to the end of their biological night (mean wake-up time ~10 a.m. on work-free days), when circulating ghrelin levels are low, thus resulting in decreased feeling of hunger and increased fullness (Chaput et al., 2023).

4.2 Glucose parameters including glucose dips by meal GI and breakfast/dinner (Aims 2&3)

The use of the proc mixed model allowed for a separate appraisal of the relevance of GI (medium vs. high) and the relevance of meal (breakfast vs. dinner), independently of each other (see table 2). At first glance, the more pronounced glucose dips 2-3 hours after medium compared to high GI meals (independently of meal) seems contradictory to the concept of a '*reactive hypoglycemia*', proposed to occur especially after the consumption of high-GI foods (Brand-Miller et al., 2009). However, particularly studies on food structure (i.e. solid vs. liquid food items) and sugar components indicate that even some low GI foods induce glucose dips below baseline due to a higher as well as earlier insulin secretion (Brand-Miller, 2009): For instance, juices cause a rapid increase in glucose levels, hence leading to exaggerating counter regulatory responses, i.e. excessive insulin secretion, which consequently result in glucose dips (~60 min. postprandial) comparable to high-GI food items. However, the GI calculation according to the ISO standard (International Standards Organisation, 2010) ignores glucose values below baseline, hence, glucose dips may also occur after consumption of medium or even low GI foods like fruit juices. The test foods used in our study (rye wheat sourdough bread (medium GI) and pretzel (high GI)) did not induce glucose dips in the 120 min. testing period for GI determination (Goletzke et al., 2016), but since GI measurement considers only the 120 min response they might have led to glucose levels below baseline thereafter. Thus, from a methodological point of view in line with Wyatt´s study (Wyatt et al., 2021) the present study suggests the need for more attention to the entire glucose trajectories (i.e. the rise and potential fall below baseline levels) and the extension to the postprandial window to 180 min.

Moreover, the proc mixed analysis revealed that – independently of meal GI – more negative glucose dips-values were seen after breakfast compared to dinner among participants with an early chronotype only. This observation may be explained by the diurnal rhythm of glucose and insulin homeostasis: Insulin secretion and/or sensitivity decreases over the day, resulting in higher glucose levels and lower glucose tolerance to the same meal in the evening (Morris et al., 2015; Saad et al., 2012). As an excessive insulin secretion is one of the main hormonal pathways inducing postprandial hypoglycemia (Ludwig, 2002), this pathway might be attenuated in the evening compared to the morning, leading to less pronounced or no glucose dips below baseline 2-3 hours after dinner. Furthermore, the late dinner (8 p.m.) may have induced some degree of circadian misalignment, which also decreases insulin sensitivity/secretion

resulting in a lower glucose tolerance (Qian et al., 2019), thus presenting an additional challenge for glucose homeostasis among participants with early chronotype. Hence, it is not surprising that glucose dips did not differ between breakfast and dinner for persons with late chronotype because breakfast time (7 a.m.) might have interfered with the circadian rhythmicity reflected by a MSFsc at 5:50 a.m. In the evening, glucose dips may not occur due to the lower glucose tolerance in the evening (Qian et al., 2019), which may similarly affect persons with late chronotype despite their delayed endogenous rhythm (Roenneberg et al., 2019).

4.3 Association between glycemic response and hunger after breakfast (Aim 4)

As mentioned above, Wyatt et al. identified glucose dips 2-3 hours after breakfast consumption as the key postprandial glycemic measure associated with hunger and subsequent food consumption (Wyatt et al., 2021). In this study, they analyzed 1.070 healthy participants from the PREDICT cohort, who consumed in total 8.624 standardized breakfast meals followed by ad libitum meal consumption beginning 3 hours after breakfast (Wyatt et al., 2021). In our study, we used estimated GI values for each meal/snack. Our results did not confirm Wyatt's data in several ways: Firstly, while the GI of the study foods was not specifically considered in Wyatt's study, the greatest hypoglycemic state was observed after the OGTT (defined by a GI of 100) (Wyatt et al., 2021).

Secondly, we did not observe an association between glucose dips in response to a standardized breakfast and hunger irrespective of meal GI in the morning. One reason may be that glucose dips were smaller in our cohort than in the PREDICT study (mean glucose dip in our study after a medium GI meal: -2.70 (-7.61, 2.88) % vs. mean glucose dip in the PREDICT study after the UK average breakfast: 6% (SD: 10%)) and hence did not stimulate the feeling of hunger in a comparable way. It might be speculated that not only the percentage change to baseline levels but also the absolute level below baseline is important, indicating that glucose levels, although falling partly below baseline, never reached problematically low levels in our population (e.g. lowest glucose $value_{0\text{-}3h}$ 4.42 (±0.83) mmol/L compared to hypoglycemia defined ≤3.9 mmol/L in persons with diabetes (American Diabetes Association, 2019). Moreover, participants of the PREDCIT study were older (mean age: 41-45 years (UK and US cohort, respectively)) than our study sample. Our observations are also contradictory to an observational study reporting that glucose nadirs preceding a meal significantly predicted

hunger and subsequent energy intake among 31 obese and healthy individuals aged ~39 years old in free-living conditions (Kim et al. 2019). However, no information on meal composition or GI is provided in that study. Therefore, we can only speculate that glucose dips may be negligible for hunger sensations in young and healthy persons and hence do not bear the risk for increased energy intake (Ludwig et al., 1999; Roßbach et al., 2018; Wyatt et al., 2021).

Some limitations of this study need to be considered. First, this is a secondary analysis of a controlled nutrition study, which was designed to compare effects on glycemic responses following high GI meal consumption in the morning vs. evening within two chronotype groups. Consequently, the study may have lacked statistical power to detect an association between glucose dips and subjective hunger. Second, we did not measure hunger/fullness after dinner, thus we could not compare the entire diurnal effect of meal GI on hunger nor analyze all diurnal differences in the association between glucose dips and hunger. Considering the established lower glucose tolerance in the evening (Morris et al., 2015), a higher glucose rise in response to a high GI meal may have resulted in longer subjective fullness after dinner than breakfast. Third, the intervention schedule led to incomplete 2-3 hour windows for some of the participants. Sensitivity analysis in the notably smaller sample with complete 180 min data supported our main conclusions. Last, we did not measure appetite or satiety hormones, e.g. ghrelin, GLP-1, insulin, and leptin, which also display a circadian rhythm (Challet, 2019) and may have given further insight on the participants´ circadian rhythmicity at the time of intervention.

Despite the limitations, this study is the first combining data of glucose dips after medium and high GI with those of postprandial hunger after an extended time period up to 180 min. It has a controlled design for energy intake accounting for the individual BMI and sex. The high and medium GI meals consisted of food items with measured GI according to ISO guidelines (The University of Sydney). Moreover, this study has a well-defined population stratified by the earliest and latest chronotype determined by MSF of a cohort screened beforehand, which is in contrast to other studies that often use the median split only (Beaulieu et al., 2020).

5. CONCLUSION

Taken together, in our young and healthy study sample, a medium but not a high GI was associated with lower glucose dip values 2-3 hours postprandially, particularly in

the morning and among early chronotypes. These glucose dips did, however, not predict hunger after breakfast irrespective of meal GI and chronotype.

FUNDING

The ChroNu Study is financially supported by the German Research Foundation (DFG) (BU 1807/3-2).

AUTHOR CONTRIBUTIONS

B. Stutz, J. Goletzke, B. Krueger, N. Jankovic, U. Alexy, C. Herder, R. Jakobsmeyer, C. Reinsberger, A.E. Buyken

AEB conceptualized the research and supervised the project: BS and JG analyzed data and performed statistical analysis under the guidance of AEB; BS and JG wrote the paper supervised by AEB; BK, NJ, UA, CH, RJ, CR reviewed and edited the manuscript; all authors contributed to the interpretation and discussion of the results and approved the final manuscript. AEB had primary responsibility for the final content.

CONFLICTS OF INTEREST

BS, JG, BK, NJ, UA, RJ, RC declare that they have no conflict of interest. AEB is a member of the International Carbohydrate Quality Consortium (ICQC), and a co-author of the popular cookbook “Nordisch abnehmen”.

The German Diabetes Center is funded by the German Federal Ministry of Health (Berlin, Germany) and the Ministry of Culture and Science of the state North Rhine-Westphalia (Düsseldorf, Germany) and receives additional funding by the German Federal Ministry of Education and Research (BMBF) through the German Center for Diabetes Research (DZD e.V.).

ACKNOWLEDGEMENTS

The participation of all students in the ChroNu Study is gratefully acknowledged. Moreover, we thank the staff of the ChroNu Study for administering participants during their visits.

AVAILABILITY OF DATA AND MATERIALS

Data are made available via a request to the authors based on a formal data sharing agreement.

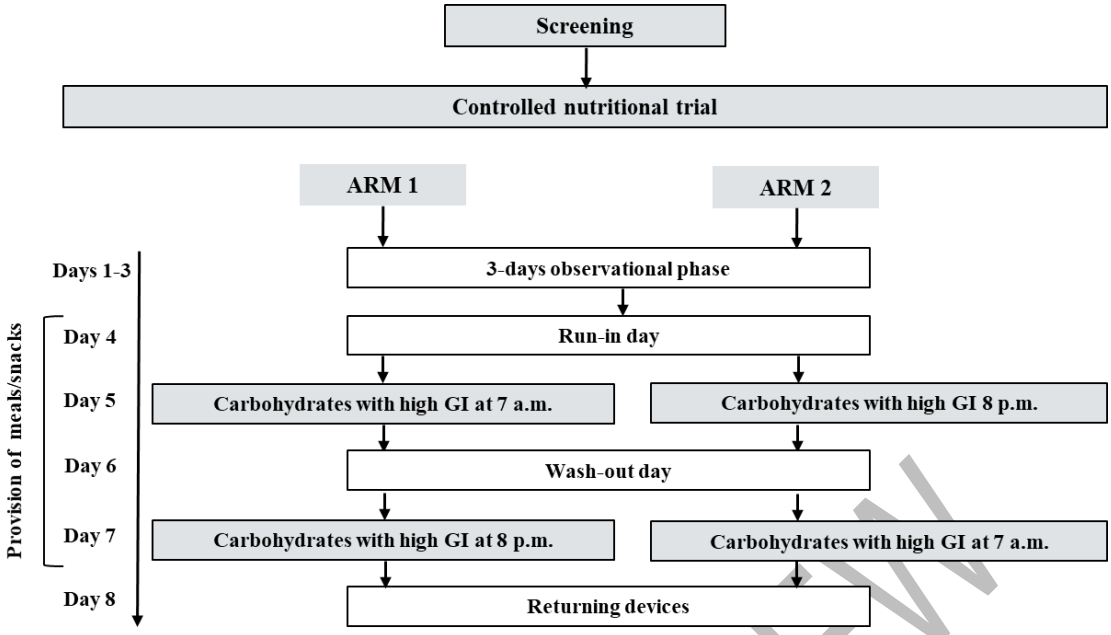


Figure 1: Overview of the controlled nutrition trial.

TABLE 1: Characteristics of the study population (n=45).

	Early chronotype (n=22)	Late chrontoype (n=23)
Anthropometric and laboratory characteristics		
Female sex, n (%)	14 (64)	12 (52)
Age, years	22 (21; 23)	22 (21; 24)
BMI, kg/m²	22.4 (± 2.2)	22.5 (± 2.6)
Waist circumference, m	0.74 (0.71; 0.80)	0.78 (0.75; 0.87)
Visceral fat mass, L	0.40 (0.31; 0.56)	0.66 (0.38; 1.25)
Skeletal muscle mass, kg	23.2 (20.1; 28.4)	24.9 (21.2; 31.3)
Fasting blood glucose, mmol/L	5.1 (± 0.4)	5.2 (± 0.3)
Fasting insulin, µU/mL	6.9 (± 2.7)	7.3 (± 3.9)
HOMA-IR	1.6 (± 0.6)	1.7 (± 0.9)
Melatonin[1], ng/L	27.4 (22.7; 38.1)	36.0 (29.4; 57.1)
hsCRP, mg/dL	0.1 (0.0; 0.1)	0.0 (0.0; 0.1)
Non-esterified fatty acids, µmoL/L	359 (231; 589)	409 (309; 524)
Triglycerides, mg/dL	98.0 (± 41.8)	98.9 (± 44.8)
HDL-cholesterol, mg/dL	61.2 (± 13.4)	63.6 (± 15.1)
LDL-cholesterol, mg/dL	103.6 (± 24.8)	97.0 (± 25.0)
Circadian characteristics, habitual meal/snack consumption and feeling of hunger		
Chronotype MSFsc (o'clock)[2]	3:26 (2:55; 3:38)	6:00 (5:35; 6:23)

TABLE 1: *continued*.

Time when falling asleep (o'clock)		
Workdays[3]	22:50 (22:25; 23:11)	1:00 (00:15; 1:10)
Free days[3]	23:32 (23:10; 00:00)	2:00 (1:20; 2:10)
At evenings before intervention[4*]	22:44 (22:44; 23:06)	23:38 (23:21; 00:29)
Wake-up time (o'clock)		
Workdays[3]	7:00 (6:30; 7:30)	9:00 (8:00; 9:05)
Free days[3]	8:00 (7:15; 8:30)	10:00 (9:00; 10:45)
At intervention days[5*]	6:29 (6:17; 6:42)	6:44 (6:26; 6:49)
Breakfast timing (o'clock)[3]		
Workdays	7:52 (7:00; 8:15)	10:00 (9:00; 10:00)
Free days	9:00 (8:37; 9:30)	11:00 (10:00; 12:00)
Dinner timing (o'clock)[3]		
Workdays	19:00 (18:30; 19:00)	19:30 (19:00; 20:00)
Free days	19:00 (18:00; 19:00)	19:30 (18:30; 20:46)
Snacking in the morning (n (%))[3]		
Workdays	8 (36)	5 (22)
Free days	5 (23)	4 (17)
Diurnal feeling of hunger/satiety at		
intervention[5], cm	0.0 (-1.8; 0.0)	0.0 (-3.4; 1.6)
Before breakfast	-0.2 (-3.6; 0.3)	0.0 (-1.8; 1.6)
Midmorning	-4.1 (-5.4; -1.7)	-1.8 (-4.1; 0.1)
Lunch	-1.8 (-4.0; 0.0)	-1.7 (-4.6; 0.0)
Afternoon snack	-5.1 (-6.7; -4.0)	-5.1 (-6.7; -3.6)
Before dinner[4]		

Abbreviations: hsCRP, high-sensitivity C-reactive protein; HDL, high-density; LDL, low-density; MSFsc, midpoint of sleep corrected, GI, glycemic index. [1] only for n=44 available. [2] estimated time of the previous month at screening (Roenneberg et al., 2019).[3] estimated time of the past 4 weeks before intervention when lectures were still held online due to the COVID-19 pandemic. [4] mean of days 4 and 6. [5] mean of intervention days 5 and 7. * These data were examined to show if the early meal timing at the intervention days had an impact on the habitual sleep timing. Negative values indicate feeling of hunger (-9,5 cm), positive values a feeling of fullness (9,5 cm), and value of 0 a feeling of neither hunger nor full (Zalifha et al., 2008). Data are frequencies, means ± standard deviation, or medians (Q1, Q3).

Table 2: Glucose parameters after a medium- or high-GI breakfast or dinner by chronotype group.

	breakfast		dinner		P for GI[1]	p for meal[1]
	Medium GI	**High-GI**	**Medium GI**	**High-GI**		
participants with an early chronotype (n=22)						
glucose $dip_{2\text{-}3h}$ (%)[2,3]	-4.89 (-7.61, -0.54)	1.59 (-9.58, 13.3)	5.45 (-7.26, 11.6)	5.16 (-1.5, 27.3)	0.03	0.001
lowest $glucose_{0\text{-}3h}$ (mmol/l)	4.81 (0.60)	4.66 (0.74)	4.46 (0.69)	4.42 (0.83)	0.5	0.050
highest $glucose_{0\text{-}3h}$ (mmol/l)	7.04 (0.80)	9.00 (1.36)	7.35 (1.00)	9.64 (1.32)	<0.0001	0.055
glucose $rise_{0\text{-}2h}$ (%)	34 (13)	74 (27)	38 (18)	77 (27)	<0.0001	0.5
participants with a late chronotype (n=23)						
glucose $dip_{2\text{-}3h}$ (%)	0 (-8.49, 4.92)	3.14 (-5.38, 18.4)	2.52 (-7.39, 11.3)	6.85 (-0.45, 20.4)	0.03	0.09
lowest $glucose_{0\text{-}3h}$ (mmol/l)	4.93 (0.49)	4.96 (0.62)	4.81 (0.60)	4.93 (0.52)	0.5	0.5
highest $glucose_{0\text{-}3h}$ (mmol/l)	7.21 (0.75)	9.68 (1.58)	7.51 (0.82)	9.42 (1.19)	<0.0001	0.9
glucose $rise_{0\text{-}2h}$ (%)	34 (13)	78 (27)	35 (13)	69 (28)	<0.0001	0.4

Data are means ± standard deviation or medians (Q1, Q3).

[1] p values are derived from combined multilevel models with glucose parameters as the dependent variables and categories of GI and meal as independent variables. Models were additionally adjusted for sex and age at intervention.

[2] Glucose dips were calculated as the difference between the lowest glucose reading in 2-3 hours postprandial after i) high/medium GI breakfast or directly before midmorning snack consumption (whichever came first) and ii) high/medium GI dinner and the average baseline glucose level (glucose readings -5 min and min 0), presented as a percentage of average baseline level. The glucose $dip_{2\text{-}3hr}$ is expressed as a percentage to adjust for differences in participants' baseline glucose levels. Negative glucose dip values indicate states of mild hypoglycemia while positive glucose dip values indicate that glucose levels remain elevated above baseline level.

[3] n=21, since one participant had snack 120 min. after breakfast

Table 3: Association between selected glucose parameters and the feeling of hunger 2-3h after breakfast (n=45)

	ß	SE	p[1]
Participants with an early chronotype (n=22)			
glucose dip$_{2\text{-}3h}$ (%) [2,3]			
unadjusted[4]	-0.051	0.045	0.3
adjusted[5]	-0.049	0.046	0.3
lowest glucose$_{0\text{-}3h}$ (mg/dl)			
unadjusted[4]	0.030	0.749	>0.9
adjusted[5]	0.127	0.753	0.9
highest glucose$_{0\text{-}3h}$ (mg/dl)			
unadjusted[4]	0.043	0.452	0.9
adjusted[5]	0.060	0.455	0.9
glucose rise$_{0\text{-}2h}$ (%)			
unadjusted[4]	-0.003	0.024	0.9
adjusted[5]	-0.004	0.024	0.9
Participants with a late chronotype (n=23)			
glucose dip$_{2\text{-}3h}$ (%)[2]			
unadjusted[4]	0.024	0.037	0.5
adjusted[5]	0.027	0.038	0.5
lowest glucose$_{0\text{-}3h}$ (mg/dl)			
unadjusted[4]	-0.051	0.912	>0.9
adjusted[5]	0.233	0.941	0.8
highest glucose$_{0\text{-}3h}$ (mg/dl)			
unadjusted[4]	0.469	0.404	0.3
adjusted[5]	0.858	0.430	0.053
glucose rise$_{0\text{-}2h}$ (%)			
unadjusted[4]	0.020	0.024	0.4
adjusted[5]	0.034	0.025	0.2

[1] p derived from mixed models with the selected glucose parameter as the independent variable and hunger after breakfast as the dependent;

[2] Glucose dips were calculated as the difference between the lowest glucose reading in 2-3 hours postprandial after i) high/medium GI breakfast or directly before midmorning snack consumption (whichever came first) and ii) high/medium GI dinner and the average baseline glucose level (glucose readings -5 min and min 0), presented as a percentage of average baseline level. The glucose dip$_{2\text{-}3hr}$ is expressed as a percentage to adjust for differences in participants' baseline glucose levels. Negative glucose dip values indicate states of mild hypoglycemia while positive glucose dip values indicate that glucose levels remain elevated above baseline level.

[3] n=21, since one participant had snack 120 min after breakfast

[4] model adjusted for GI of breakfast (medium or high)

[5] model adjusted for GI of breakfast (medium or high), sex, chronotype, age

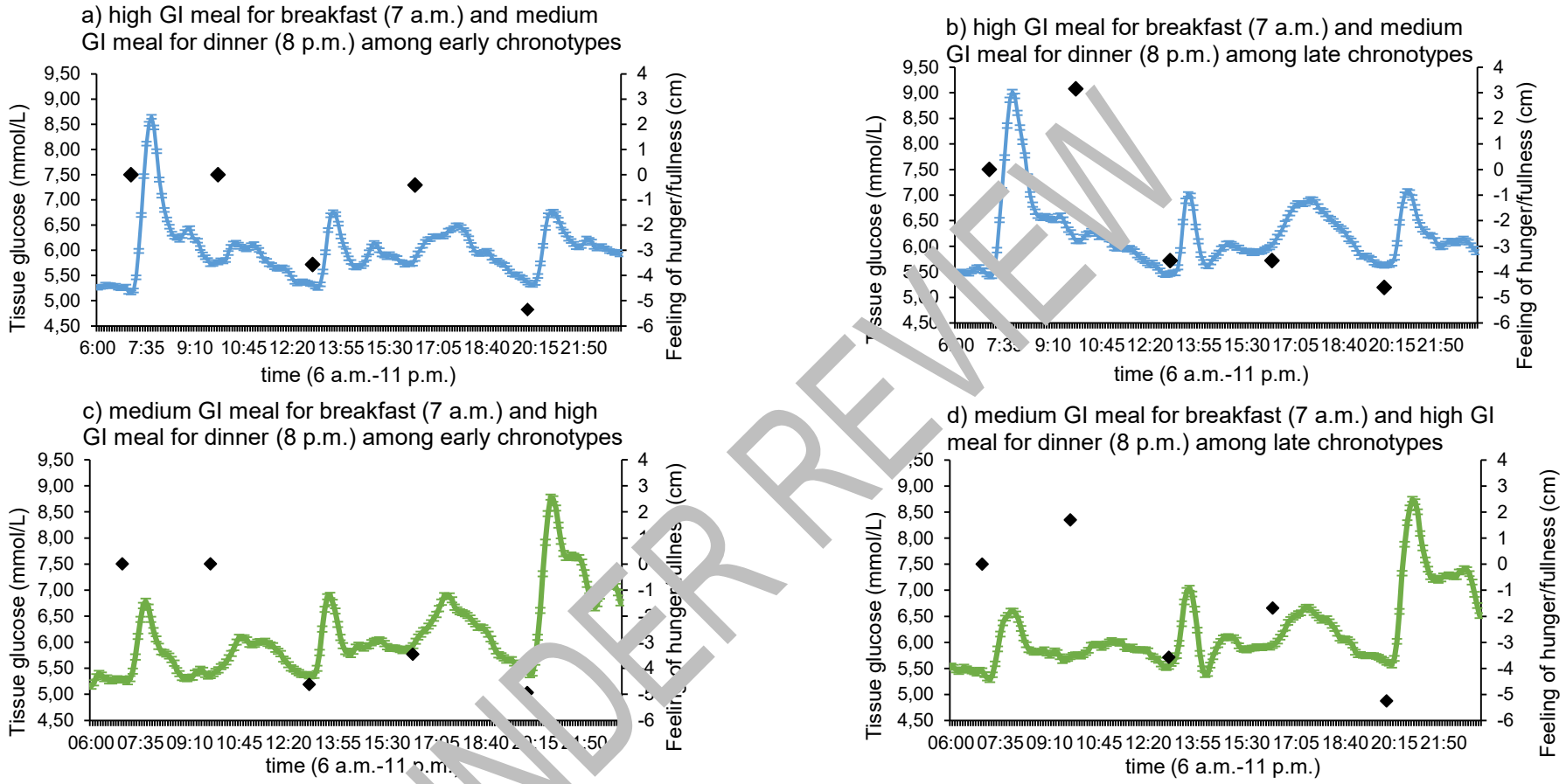


Figure 2: Mean diurnal glucose (± SE) (lines) and median feeling of hunger/fullness (diamonds) after breakfast with high glycemic index (GI) (a+b) and after medium GI breakfast (c+d) among early (c) and late (d) chronotypes. [1]Negative values indicate feeling of hunger, positive values a feeling of fullness, and value of 0 a feeling of neither hunger nor full (Zalifha et al., 2008).

Supplemental Table 1: Glucose parameters after a medium- or high-GI breakfast or dinner by chronotype group for those participants with complete 180min postprandial data*

	breakfast		dinner		P for GI[1]	p for meal[1]
	Medium GI	**High-GI**	**Medium GI**	**High-GI**		
participants with an early chronotype	(n=11)		(n=22)			
glucose $dip_{2\text{-}3h}$ (%)[2]	-6.11 (-9.30, -1.62)	-8.33 (-13.37, 6.76)	5.45 (-7.26, 11.6)	5.16 (-1.5, 27.3)	0.1	0.004
lowest $glucose_{0\text{-}3h}$ (mmol/l)	4.94 (0.57)	4.68 (0.73)	5.02 (0.55)	4.87 (0.72)	0.6	0.045
highest $glucose_{0\text{-}3h}$ (mmol/l)	7.22 (0.78)	9.21 (1.36)	7.32 (0.82)	9.85 (1.41)	<0.0001	0.6
participants with an late chronotype	(n=15)		(n=23)			
glucose $dip_{2\text{-}3h}$ (%)	0 (-6.47, 3.26)	1.64 (-15.79, 18.72)	2.52 (-7.39, 11.3)	6.85 (-0.45, 20.4)	0.07	0.09
lowest $glucose_{0\text{-}3h}$ (mmol/l)	4.46 (0.69)	4.42 (0.83)	4.81 (0.60)	4.93 (0.52)	1.0	0.6
highest $glucose_{0\text{-}3h}$ (mmol/l)	7.35 (1.00)	9.64 (1.32)	7.51 (0.82)	9.42 (1.19)	<0.0001	0.5

*please note that due to the study design, some of the participants have an incomplete 180 min time period after breakfast, as they had an earlier midmorning snack. Hence, complete 180 min data for breakfast postprandial data was available for n=27 participants after the medium GI breakfast and for n=26 participants after high-GI breakfast. As dinner was the last meal of the day, all participants had complete 180 min postprandial data.

Data are means ± standard deviation or medians (Q1, Q3).

[1] p values are derived from combined multilevel models with glucose parameters as the dependent variables and categories of GI and meal as independent variables. Models were additionally adjusted for sex and age at intervention.

Supplemental Table 2: Association between selected glucose parameters and the feeling of hunger 2-3h after breakfast for those participants with complete 180 min postprandial data (n=26).

	ß	SE	p[1]
participants with an early chronotype (n=11)			
glucose dip$_{2\text{-}3h}$ (%) [2,3]			
unadjusted[4]	-0.124	0.079	0.1
adjusted[5]	-0.129	0.079	0.1
lowest glucose$_{0\text{-}3h}$ (mg/dl)			
unadjusted[4]	-0.541	1.277	0.7
adjusted[5]	-0.692	1.236	0.6
highest glucose$_{0\text{-}3h}$ (mg/dl)			
unadjusted[4]	0.110	0.764	0.9
adjusted[5]	0.236	0.748	0.8
participants with a late chronotype (n=15)			
glucose dip$_{2\text{-}3h}$ (%) [2]			
unadjusted[4]	-0.008	0.048	0.9
adjusted[5]	-0.016	0.048	0.7
lowest glucose$_{0\text{-}3h}$ (mg/dl)			
unadjusted[4]	-0.802	1.056	0.5
adjusted[5]	-0.569	1.051	0.6
highest glucose$_{0\text{-}3h}$ (mg/dl)			
unadjusted[4]	0.524	0.584	0.4
adjusted[5]	0.825	0.543	0.1

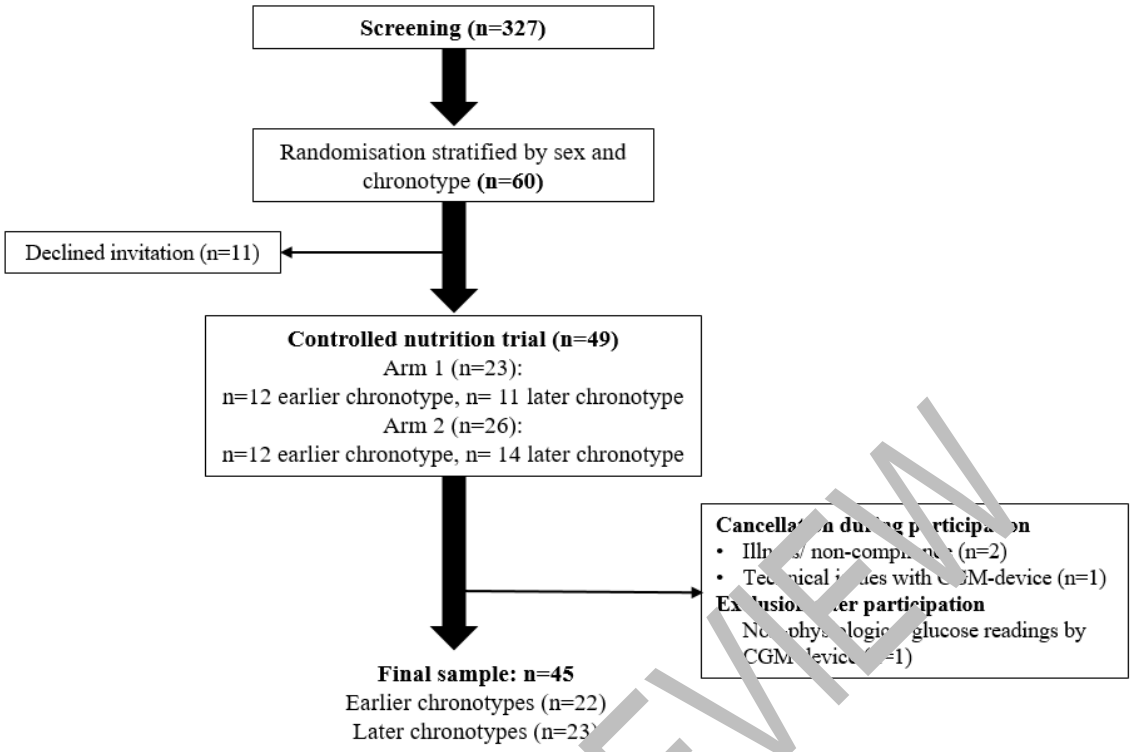
[1] p derived from mixed models with the selected glucose parameter as the independent variable and hunger after breakfast as the dependent;

[2] Glucose dips were calculated as the difference between the lowest glucose reading in 2-3 hours postprandial after i) high/medium GI breakfast or directly before midmorning snack consumption (whichever came first) and ii) high/medium GI dinner and the average baseline glucose level (glucose readings -5 min and min 0), presented as a percentage of average baseline level. The glucose dip$_{2\text{-}3hr}$ is expressed as a percentage to adjust for differences in participants' baseline glucose levels. Negative glucose dip values indicate states of mild hypoglycemia while positive glucose dip values indicate that glucose levels remain elevated above baseline level.

[3] n=10, since one participant had snack 120min after breakfast

[4] model adjusted for GI of breakfast (medium or high)

[5] model adjusted for GI of breakfast (medium or high), sex, chronotype, age



Supplemental figure 1: Flow chart of study population.

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APPENDIX E

Appendix Table 2: Midpoint of sleep examined by accelerometry and the participant's diary entries during the controlled nutrition trial (study 2).

Partici-pant	MSF (h:min) by accelerometry	MSF_{sc} (h:min) by accelerometry	MSF (h:min) by diary entries	MSF_{sc} (h:min) by diary entries	Absolute difference of MSF (h:mm:ss) (accelerometry vs. diary)	Absolute difference of MSFsc (h:mm:ss) (accelerometry vs. diary)
1	5:19	2:42	5:24	2:20	0:04:15	00:21:51
2	4:36	3:27	4:38	3:34	0:02:30	00:06:42
3	6:33	4:13	6:33	4:10	0:00:00	00:03:00
4	4:17	3:27	4:23	3:29	0:06:00	00:01:54
5	6:31	3:25	6:38	3:29	0:07:00	00:04:18
6	2:43	2:30	3:00	2:51	0:17:15	00:20:57
7	5:13	1:34	5:14	1:40	0:01:00	00:06:18
8	4:03	1:53	4:01	1:53	0:02:30	00:00:48
9	5:49	1:57	5:51	1:51	0:01:45	00:06:09
10	4:12	3:04	4:22	3:01	0:10:00	00:03:24
11	4:57	3:37	5:06	4:13	0:08:45	00:35:33
12	5:02	3:37	5:00	3:21	0:01:45	00:15:57
13	3:58	2:35	4:03	2:38	0:05:30	00:02:42
14	4:14	4:14	4:21	4:06	0:07:45	00:07:03
15	3:42	2:49	3:48	2:57	0:06:30	00:08:06
16	5:36	4:56	5:42	5:00	0:06:15	00:04:03
17	7:39	3:50	7:38	3:45	0:00:30	00:04:18
18	3:21	3:21	3:26	3:26	0:05:00	00:05:00
19	3:34	3:34	3:29	3:29	0:05:00	00:04:30
20	5:10	3:50	5:07	3:47	0:03:30	00:02:54
21	5:01	4:50	5:06	4:54	0:05:15	00:03:51
22	4:01	2:35	3:41	2:47	0:20:15	00:11:51
23	6:09	2:22	6:04	1:43	0:05:45	00:39:42
24	3:33	2:21	3:27	2:27	0:05:30	00:06:18
25	6:09	2:27	6:07	2:30	0:01:30	00:03:18
26	3:48	2:42	3:51	3:13	0:03:15	00:31:09
27	5:46	5:22	5:52	5:26	0:06:15	00:04:27
28	5:57	3:50	5:43	4:10	0:14:00	00:19:48
29	3:59	1:46	4:06	1:48	0:07:00	00:01:18

Appendix Table 2: *Continued.*

Partici-pant	MSF (h:min) by accelerometry	MSFsc (h:min) by accelerometry	MSF (h:min) by diary entries	MSF_{sc} (h:min) by diary entries	Absolute difference of MSF (h:mm:ss) (accelerometry vs. diary)	Absolute difference of MSFsc (h:mm:ss) (accelerometry vs. diary)
30	3:34	1:53	3:42	1:54	0:07:45	00:00:39
31	3:38	3:06	3:38	3:19	0:00:30	00:13:00
32	5:21	3:00	5:21	2:55	0:00:30	00:05:18
33	5:42	3:16	5:29	3:35	0:13:00	00:18:54
34	5:09	3:33	4:19	3:49	0:50:30	00:15:54
35	2:25	1:45	2:31	1:48	0:06:15	00:03:33
36	3:21	3:10	3:27	3:19	0:06:30	00:08:36
37	6:24	3:03	6:18	3:16	0:06:00	00:12:48
38	3:42	2:24	3:50	2:30	0:07:45	00:05:09
39	3:34	2:26	3:43	2:34	0:09:00	00:08:48
40	4:03	3:25	4:05	3:18	0:02:30	00:06:30
41	5:15	3:35	5:18	3:31	0:03:45	00:03:27
42	9:56	3:39	9:55	3:37	0:00:45	00:02:27
43	4:40	2:48	4:36	2:35	0:04:30	00:12:54
44	4:39	2:03	4:50	1:59	0:10:45	00:04:33
45	7:29	7:29	8:05	6:54	0:36:00	00:35:45

Abbreviations: MSF, midpoint of sleep; MSF_{sc}; midpoint of sleep corrected

MSF (h:mm) was based on mean values of study days 4-8. MSF_{sc} (h:mm) was calculated based on mean values of study days 1-4 (denoted work-free days) and 4-8 (denoted workdays) [26]. Absolute mean difference (± standard deviation) of MSF and MSF_{sc} between accelerometry and diary was 0:07:30 (± 0:08:56) and 0:09:54 (± 0:09:44) h:mm:ss, respectively, i.e., 0,7% difference of MSF_{sc}.

APPENDIX F

Appendix Table 3: Melatonin levels among participants of the controlled nutrition trial.

Participant	MSFsc at screening	Chronotype	Melatonin
1	03:55:43	early chronotype	16,2
2	02:40:21	early chronotype	18,6
3	03:35:21	early chronotype	20,2
4	03:10:00	early chronotype	21,0
5	03:31:26	early chronotype	21,6
6	03:17:30	early chronotype	22,7
7	03:03:13	early chronotype	22,7
8	03:12:30	early chronotype	23,4
9	03:51:26	early chronotype	24,1
10	03:28:56	early chronotype	25,1
11	03:45:21	early chronotype	27,1
12	03:27:30	early chronotype	27,7
13	03:48:56	early chronotype	28,6
14	02:52:30	early chronotype	29,7
15	03:24:47	early chronotype	32,3
16	03:38:56	early chronotype	37,3
17	03:27:09	early chronotype	38,1
18	02:52:30	early chronotype	38,2
19	04:10:00	early chronotype	38,4
20	02:30:00	early chronotype	39,5
21	03:33:34	early chronotype	42,2
22	02:55:00	early chronotype	54,4
23	06:00:00	late chronotype	18,4
24	05:55:00	late chronotype	19,0
25	06:00:00	late chronotype	27,1
26	05:34:17	late chronotype	28,3
27	06:47:30	late chronotype	28,3
28	07:29:17	late chronotype	29,4
29	06:00:00	late chronotype	31,0
30	05:50:00	late chronotype	31,5
31	05:45:00	late chronotype	32,8
32	05:35:00	late chronotype	32,9
33	06:40:43	late chronotype	32,9
34	06:23:00	late chronotype	39,1
35	06:44:17	late chronotype	40,6
36	06:05:21	late chronotype	43,0
37	06:37:09	late chronotype	44,1
38	07:22:30	late chronotype	50,9
39	05:35:00	late chronotype	57,1
40	05:34:17	late chronotype	61,0
41	06:00:30	late chronotype	64,6
42	05:52:30	late chronotype	90,3
43	06:05:00	late chronotype	98,5
44	05:48:17	late chronotype	98,6
45	07:00:00	late chronotype	no plasma sample available

Abbreviation: MSF_{sc}, midpoint of sleep.

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Selbstständigkeitserklärung

Hiermit erkläre ich, dass ich die vorliegende Arbeit mit dem Titel

THE RELEVANCE OF CHRONOTYPE FOR MEAL TIMING, GLYCEMIC RESPONSE AND HUNGER SENSATIONS
THE CHRONU STUDY

selbstständig und ohne unerlaubte fremde Hilfe angefertigt, keine anderen als die angegebenen Quellen und Hilfsmittel* verwendet und die den verwendeten Quellen und Hilfsmitteln wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.

Paderborn, 2.04.2024
_____
Ort, Datum


_____
Unterschrift

*ChatGPT wurde verwendet, um die englische Sprache und Lesbarkeit dieser Doktorbarbeit zu überprüfen und zu verbessern. ChatGPT wurde nicht fie die Erstellung der Manuskripte verwendet.