Eating and Weight Disorders - Studies on Anorexia, Bulimia and Obesity (2022) 27:1395–1403
https://doi.org/10.1007/s40519-021-01276-4

ORIGINAL ARTICLE

Behavioral circadian phenotypes are associated with the risk of elevated body mass index

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Received: 13 May 2021 / Accepted: 22 July 2021 / Published online: 5 August 2021
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Abstract

Background Metabolic dysfunction and obesity rates are on the rise. Although the central modes of circadian disruption has been studied in relation to the risk of obesity, the role of eating time has remained unclear. Here, we aimed to assess circadian behavioral phenotypes and their association with the risk of elevated body mass index (BMI).

Methods This was a prospective cross-sectional study of individuals presenting for colorectal cancer screening colonoscopy. Participants completed demographic questionnaires, The Munich ChronoType Questionnaire (MCTQ), and Food Timing Screener (FTS). The primary outcome of the study was the association between circadian phenotypes and elevated BMI.

Results A total of 488 individuals completed the survey, with a mean (SD) age of 57.5 (10.8) years. The mean body mass index (BMI) was 28.8 (6.1) kg/m^2, with 72.3% of individuals met criteria for elevated BMI. Four circadian behavioral phenotypes were generated: early chronotype with regular food timing (ER) (34.7%), early chronotype with irregular food timing (EI) (11.7%), intermediate/late chronotype with regular food timing (LR) (33.9%), and intermediate/late chronotype with irregular food timing (LI) (19.7%). In a multivariable regression analysis, LI phenotype had 2.9 times higher odds of elevated BMI as compared to ER phenotype (OR 2.9, 95% CI 1.3–6.7, $P=0.01$).

Conclusion The combination of late chronotype and irregular food timing, representative of a behavioral circadian rhythm disruption, is associated with higher rates of elevated BMI. The majority of individuals with this abnormal circadian phenotype were younger than 60 years old. This observation is especially relevant because of the ongoing rise in the obesity rates among young adults.

Level III Evidence obtained from well-designed cohort or case–control analytic studies.

Keywords Circadian phenotype · Overweight · Obesity · Chronotype · Food timing · Metabolic dysfunction · Body mass index

Introduction

The circadian rhythm is roughly a 24-h physiologic sleep/wake cycle, which is generated by a self-sustained endogenous circadian clock [1]. The clock is regulated by external cues, such as light/dark cycles allowing the organism to anticipate changes in the external environment [1]. These changes enable the body to adapt to its environment though physiologic and behavioral responses, which is vital for survival. Besides the central circadian clock, the peripheral clocks located in most organs regulate the physiologic function of these organs based on environmental stimuli [2, 3]. The circadian clock in the central nervous system typically controls the clock in the periphery. This orchestrated central–peripheral circadian clock forms a state of healthy

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circadian homeostasis which is crucial in synchronizing physiological and biological processes, such as body temperature, metabolism, local, and systemic immunity, optimizing response to the surrounding environment [1, 4]. The peripheral clock could be influenced by other external cues such as food. For example, the time of meal consumption (i.e., timing of nutrient availability) actively regulates circadian clocks in the intestine and liver [4–7]. The modern lifestyle significantly affects the individual circadian rhythm by forcing it to adapt to the working or social environment. Although working at night shifts and frequent traveling across time zones are typical forms of circadian disruption, recent works by our group and others indicate that abnormal and irregular time of eating could also desynchronize the central and peripheral clock, leading to circadian rhythm disruption (CRD) [8–10]. The close interaction of circadian rhythms and metabolism [11] explains the deleterious effects of CRD in experimental models of metabolic dysfunction and obesity [4, 6, 7]. Controlled human studies have further supported the contribution of CRD to metabolic dysfunction [2, 7, 12]. While central modes of CRD, such as shift work has been well studied, data on the other forms of behavioral determinants of CRD (i.e., food timing) on obesity is still scarce. A number of epidemiological studies suggest that eating patterns such as breakfast skipping and eating large portions closer to the rest time in the evening could be associated with metabolic syndromes and obesity independent of the food type [7, 13–15]. However, such findings were reported as secondary outcomes of those studies that were otherwise designed for noncircadian primary outcomes. Here we aimed to comprehensively assess the behavioral circadian phenotypes (i.e., chronotype and food timing) in a cohort of consecutive individuals who presented for colon cancer screening in association with elevated body mass index (BMI).

Methods

Study design and data collection

A prospective cross-sectional study was conducted at a tertiary medical center. Individuals who presented to the endoscopy unit for colorectal cancer screening colonoscopy were approached. Patients were excluded for any of the following: lynch syndrome, familial adenomatous polyposis, inflammatory bowel disease, and any active malignancy under therapy. Participants completed questionnaires of demographics, the Munich ChronoType Questionnaire (MCTQ), and Food Timing Screener (FTS) [16, 17]. Demographics and clinical data, including body mass index (BMI) was extracted from the electronic medical records. Informed consent was obtained from all participants who agreed to participate in the study. There was no missing data as all the surveys were examined by the research assistant who assured the surveys were completed fully by participants. The study was approved by Institutional Review Board at Rush University (15011602).

The Munich chronotype questionnaire (MCTQ)

We assessed the chronotype of patients using the MCTQ [16]. It consists of questions about the individual's typical sleep behavior during work days and free days. The MCTQ provides information about sleep patterns in work and free days which allow to calculate different outcomes like chronotype, social jetlag, weekly sleep loss, and weekly light exposure. Chronotype is divided into three groups; early, intermediate, and late and was calculated based on the Mid-Sleep in free days (MSF) in patients who did not use the alarm to wake up on free days. Participants were considered early chronotype if their MSF fell before 3:00 am, intermediate chronotype if MSF fell between 3:00 am and 5:00 am, and late chronotype if MSF fell beyond 5:00 am [16].

Food timing screener

The Food Timing Screener (FTS) is a concise questionnaire to capture food timing that was validated using seven, 24-h recalls [17]. The FTS was also found to accurately assess timing of food intake compared to a more extensive Food Timing Questionniare, both of which were developed by experts in gastroenterology and nutrition at Rush University Medical Center [17]. The FTS was designed to be a concise form of the FTQ to be used independently when time to complete the full FTQ is limited. As with the FTQ, sleep–wake time is included to be able to identify the relation between food intake and sleep timing. Using the FTS, we collected information about exact meal times, and largest meal of the day in typical work days and free days. We calculated the average time for all the meals during work days and free days. Irregular food timing was defined as having more than a 2-h difference in the average meal time between work days and free days.

The FTS is a self-report questionnaire that assesses an individual's usual eating and sleep habits categorized into two types of days: school/work days and free days/days off. Respondents report, in one sitting, time of eating for three meals (breakfast, lunch, and dinner) and up to three snacks (snack 1, snack 2, and snack 3), the times of awakening and falling asleep, whether s/he awakens from sleep to eat, and the largest (self-defined most food) eating event of the day on each type of day.

In order to correct for the potential effects of the food types in our participants, we included major food categories (wheat, vegetables, fruit, fried food, pickled food, and

red meat) that have been linked to the risk of metabolic syndrome from population based studies [18–20]. Each participant reported the consumption of food types as regular, occasional, or never.

Study outcomes and statistical analysis

The aim of this hypothesis generating study was to test the association between circadian phenotypes and elevated BMI. Age was dichotomized into two groups (60 years and over and less than 60 years of age) because it was not normally distributed, so we created comparable age groups in numbers. Elevated BMI was defined as having a BMI ≥ 25 kg/m^2 [21]. We combined "occasional" and "never" categories of food types due to the low numbers in these categories. We also combined "intermediate" and "late" categories of chronotype because the majority of participants had early chronotype. We defined the behavioral circadian phenotypes based on the combination of two chronotypes and two eating habits, which resulted in four behavioral circadian phenotypes: early chronotype and regular food timing (ER), early chronotype and irregular food timing (EI), intermediate/late chronotype and regular food timing (LR), and intermediate/late chronotype and irregular food timing (LI).

Categorical variables were reported as counts and frequencies and continuous variables were reported as means and standard deviations. For categorical variables, we used χ^2 test or Fisher's exact test, as appropriate. For continuous variables, we used *t* test and one-way ANOVA, as appropriate. A univariate logistic regression analysis of the association between elevated BMI and other factors was performed. Furthermore, a multivariable logistic regression analysis of elevated BMI was conducted including all variables. A *P* value < 0.05 was considered statistically significant. All statistical analyses were performed using STATA/IC (version 14.2; StataCorp LLC, College Station, TX, USA).

Results

A total of 488 patients were recruited and included in the analysis (Table 1). The age ranged between 21 and 79 years with a mean (SD) of 57.5 (10.8) years. The majority (55.5%) of participants were under 60 years old. The mean BMI was 28.8 kg/m^2 (6.1), with 72.3% of individuals meeting criteria for elevated BMI (BMI ≥ 25 kg/m^2) (Table 1). A majority of the participants consumed vegetables, fruits, and foods containing wheat, while less consumed foods linked with cancers of the gastrointestinal tract (Table 1). There were no colorectal cancer cases in our cohort.

Table 1 Characteristics of participants

	N = 488 *n* (%)
Age (years) – mean (SD)	57.5 (10.8)
Age (< 60 years)	271 (55.5)
Sex	
Female	270 (55.3)
Male	218 (44.7)
BMI (kg/m^2) – mean (SD)	28.8 (6.1)
Elevated BMI (BMI ≥ 25 kg/m^2)	353 (72.3)
Food type*	
Vegetables	400 (82.5)
Fruit	338 (69.6)
Wheat	278 (57.3)
Red meat	145 (29.8)
Fried food	105 (21.7)
Pickled food	46 (9.5)
Largest meal of the day	
Dinner	335 (73.8)

*Regular consumption

Circadian characteristics of participants

Table 2 shows the circadian characteristics of participants stratified by age, sex, and BMI status. There were 196 (53.5%) participants who had intermediate/late chronotype. Younger participants (< 60 years old) had a higher rate of intermediate/late chronotype than older (≥ 60 years old) participants (122 (58.1%) vs. 74 (47.4%), *P* = 0.04). There was no significant association between chronotype and sex.

Dinner was the largest meal of the day in 335 (73.8%) participants, and only 64 (13.3%) participants skipped breakfast. Irregular food timing was present in 30.7% of participants and was associated with younger age (40.2% vs 18.9% in < 60 years old versus ≥ 60 years old, respectively; *P* < 0.01). There was no significant association between food timing and sex.

Circadian characteristics and elevated BMI

Participants with elevated BMI had a higher rate of intermediate/late chronotype than participants with normal BMI (56.6% vs. 44.7%, respectively; *P* = 0.04) (Table 2). Similarly, participants with elevated BMI tended to have a higher rate of irregular food timing compared to participants with normal BMI, but the results were not statistically significant (32.8% vs. 25.2%, respectively; *P* = 0.10).

Combining two behavioral determinants of circadian phenotypes based on the chronotype and food timing habits resulted in four behavioral circadian phenotypes: Early chronotype and regular food timing (ER, 34.7%), early

Table 2 Circadian characteristics of participants by age, sex, and BMI

	Total *n* (%)	Age *n* (%)			Sex *n* (%)			BMI (kg/m^2) *n* (%)		
		< 60	≥ 60	*P value*	Female	Male	*P*	< 25	≥ 25	*P value*
Chronotype				**0.04**			0.22			**0.04**
Early	170 (46.5)	88 (41.9)	82 (52.6)		89 (43.6)	81 (50.0)		52 (55.3)	118 (43.4)	
Intermediate/late	196 (53.5)	122 (58.1)	74 (47.4)		115 (56.4)	81 (50.0)		42 (44.7)	154 (56.6)	
Food timing				**< 0.01**			0.55			0.10
Regular	338 (69.3)	162 (59.8)	176 (81.1)		190 (70.4)	148 (67.9)		101 (74.8)	237 (67.2)	
Irregular	150 (30.7)	109 (40.2)	41 (18.9)		80 (29.6)	70 (32.1)		34 (25.2)	116 (32.8)	

P values <0.05 are bolded

BMI body mass index

chronotype and irregular food timing (EI, 11.7%), intermediate/late chronotype and regular food timing (LR, 33.9%), and intermediate/late chronotype and irregular food timing (LI, 19.7%) (Table 3). These phenotypes were distributed unequally according to the participants' age. While the majority of participants in LI group (76.4%) were < 60 years old, only 44% of the ER group were < 60 years old ($P < 0.001$).

There was an association of elevated BMI with circadian phenotypes (Fig. 1), where individuals in the LI group had the highest rates of having elevated BMI compared to those in the ER group (84.7% vs. 68.5%, $P = 0.01$).

Behavioral circadian phenotypes and elevated BMI

In a univariate analysis of the factors associated with elevated BMI, in addition to the LI group, regular consumption of fried food was positively associated with elevated BMI, while fruit consumption was negatively associated with the odds of having elevated BMI (Table 4). In a multivariable logistic regression analysis adjusted for all factors, LI group had 2.9 times higher odds of elevated BMI compared to ER group (OR 2.9, 95% CI 1.3–6.7, $P = 0.01$) (Table 5).

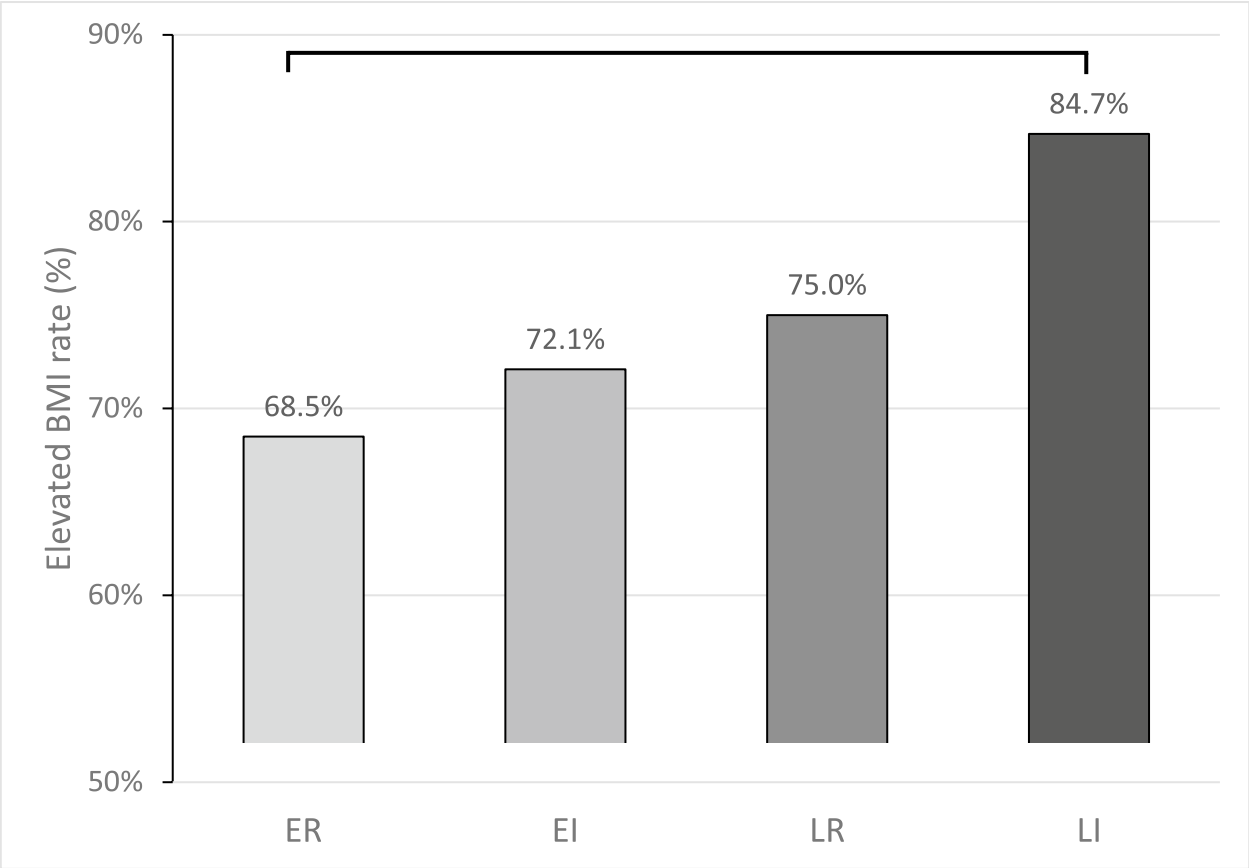
Table 3 Characteristics of participants stratified by circadian phenotypes

	Total *n* (%)	Early chronotype		Intermediate/late chronotype		*P* value
		Regular FT	Irregular FT	Regular FT	Irregular FT	
		ER *n* (%)	EI *n* (%)	LR *n* (%)	LI *n* (%)	
Age (< 60 years)	210 (57.4)	56 (44.1)	32 (74.4)	67 (54.0)	55 (76.4)	**< 0.001**
Sex						0.64
Female	204 (55.7)	67 (52.8)	22 (51.2)	74 (59.7)	41 (56.9)	
Male	162 (44.3)	60 (47.2)	21 (48.8)	50 (40.3)	31 (43.1)	
Elevated BMI (BMI ≥ 25 kg/m^2)	272 (74.3)	87 (68.5)	31 (72.1)	93 (75.0)	61 (84.7)	0.09
BMI (kg/m^2) – mean (SD)	29.0 (6.1)	28.4 (5.4)	28.3 (5.3)	29.1 (6.3)	30.1 (7.1)	0.23
Food type*						
Vegetables	297 (81.8)	103 (81.7)	38 (88.4)	104 (83.9)	52 (74.3)	0.23
Fruit	252 (69.2)	92 (72.4)	31 (72.1)	84 (67.7)	45 (64.3)	0.63
Wheat	201 (55.4)	73 (57.9)	21 (48.8)	69 (55.7)	38 (54.3)	0.77
Red meat	108 (29.7)	34 (26.8)	11 (25.6)	37 (29.8)	26 (37.1)	0.43
Fried food	80 (22.0)	24 (19.1)	7 (16.3)	34 (27.4)	15 (21.4)	0.30
Pickled food	38 (10.5)	16 (12.7)	2 (4.7)	13 (10.5)	7 (10.0)	0.52

P values <0.05 are bolded

BMI body mass index, *ER* individuals with early chronotype and regular food timing, *EI* individuals with early chronotype and irregular food timing, *LR* individuals with intermediate/late chronotype and regular food timing, *LI* individuals with intermediate/late chronotype and irregular food timing

*Regular consumption



BMI: body mass index; ER: individuals with early chronotype and regular food timing; EI: individuals with early chronotype and irregular food timing; LR: individuals with intermediate/late chronotype and regular food timing; LI: individuals with intermediate/late chronotype and irregular food timing.

Fig. 1 Elevated BMI rates in circadian phenotypes

Discussion

Circadian rhythm is closely linked to metabolic homeostasis, and once disrupted could lead to metabolic dysfunction [22]. This is supported by experimental models that showed the causal link between circadian rhythm disruption (CRD) and metabolic dysfunction and obesity in animals [11, 14, 23, 24]. Subsequently, evidence from human studies linked the CRD with chronic diseases including metabolic dysfunction and obesity [25]. Although prior studies mostly focused on the central modes of CRD, the data are still limited on the possible association of food timing habits on metabolism and obesity in humans [2, 12, 26–28]. In our study, using a complementary circadian phenotyping using both chronotype and food timing habits in 488 individuals, we found that irregular food timing particularly in those with intermediate/late chronotype was an independent factor for elevated BMI after adjusting for other factors. This circadian phenotype was more common among younger individuals. The rate of elevated BMI was increasing from one extrem phenotype (ER, 68.5%) to the other extreme phenotype (LI, 84.7%). Therefore, we compared these two phenotypes in a multivariable regression analysis and found that individuals with LI phenotype have 2.9 higher odds of elevated BMI compared to ER phenotype individuals.

The circadian clock has an essential role in metabolic health; circadian rhythm disruption can cause metabolic dysfunction, which in turn can result in weight gain and other chronic metabolic diseases [29]. Prior studies evaluated the role of circadian rhythm in metabolic homeostasis, where late chronotype was associated with metabolic dysfunction and obesity [8, 28, 30–32]. In a systematic review of the literature, Antunes et al. reported that the disruption of the circadian rhythm represented by rotating shift work schedule

Table 4 Predictors of elevated BMI

	OR (95% CI)	*P* value
Age (Ref: < 60 years old)	0.8 (0.5–1.2)	0.31
Sex (Ref: female)	1.6 (1.1–2.4)	**0.02**
Food type (Ref: occasional/never)		
Wheat—regular	0.8 (0.5–1.2)	0.34
Vegetables—regular	1.0 (0.6–1.7)	0.92
Fruit—regular	0.5 (0.3–0.8)	**< 0.01**
Fried food—regular	2.0 (1.2–3.4)	**0.01**
Pickled food—regular	1.1 (0.6–2.2)	0.80
Red meat—regular	1.4 (0.9–2.2)	0.10
Largest meal of the day (Ref: breakfast/lunch)		
Dinner	0.7 (0.4–1.1)	0.09
Circadian phenotypes (Ref: ER)		
EI	1.2 (0.6–2.6)	0.65
LR	1.4 (0.8–2.4)	0.25
LI	2.5 (1.2–5.4)	**0.01**

P values <0.05 are bolded

BMI body mass index, *ER* individuals with early chronotype and regular food timing, *EI* individuals with early chronotype and irregular food timing, *LR* individuals with intermediate/late chronotype and regular food timing, *LI* individuals with intermediate/late chronotype and irregular food timing

*Using univariate logistic regression analysis for each factor

Table 5 Multivariable logistic regression analysis of elevated BMI

	OR (95% CI)	*P* value
Age (Ref: < 60 years old)	1.1 (0.5–2.1)	0.97
Sex (Ref: female)	1.4 (0.7–2.9)	0.31
Food type (Ref: occasional/never)		
Wheat—regular	0.9 (0.4–1.8)	0.68
Vegetables—regular	1.8 (0.8–4.4)	0.18
Fruit—regular	0.6 (0.2–1.4)	0.21
Fried food—regular	1.5 (0.6–4.2)	0.39
Pickled food—regular	1.4 (0.4–4.9)	0.56
Red meat—regular	0.7 (0.3–1.8)	0.51
Largest meal of the day (Ref: breakfast/lunch)		
Dinner	0.6 (0.3–1.4)	0.22
Circadian phenotypes (Ref: ER)		
LI	2.9 (1.3–6.7)	**0.01**

P values <0.05 are bolded

BMI body mass index, *ER* individuals with early chronotype and regular food timing, *LI* individuals with intermediate/late chronotype and irregular food timing

*Using a multivariable logistic regression analysis including all factors in the model

can increase the risk of obesity, diabetes, and cardiovascular diseases. They hypothesized that both abnormal timing of sleep and eating may have contributed to this observed association [29]. Our study showed that elevated BMI was more prevalent among individuals with intermediate/late chronotype compared with early chronotype group, which is consistent with previous studies [8, 29]. Shift work in younger individuals results in the interruption of sleep during work days, which may lead to sleep loss. Sleep loss especially in individuals with late chronotype predispose them to circadian rhythm disruption, metabolic dysfunction and obesity [8].

Beside the effects of light/dark cycle on the circadian clock, food entrains the circadian rhythm in the digestive tract and plays a crucial role in metabolic homeostasis [22, 25, 33]. Animal studies suggest that abnormal time of eating (i.e. during inactive phase) predisposes mice to metabolic dysfunction and obesity [14, 23].

In humans, meal timing, independent from calorie intake and sleep patterns has been linked with metabolic dysfunction and body weight [2, 12, 31, 32]. Eating close to the rest time has been associated with decreased resting-energy expenditure, decreased glucose tolerance and body weight [33, 34]. Consistent with recently published studies [35], most participants in our study reported dinner as their largest meal of the day (70.1%). Some but not all previous studies suggested an association between obesity and late evening eating [13, 35]; however, we did not find the habit of dinner as the largest meal of the day to be associated with elevated BMI.

While inconsistent time of sleep between work and free days is considered an abnormal circadian phenotype [8, 29], there is not enough data regarding the effect of consistency of meal timing. In animals, regular feeding times are associated with healthier circadian rhythms and lower risk for metabolic dysfunction [14]. Our animal data also supports that inconsistent meal timing (i.e., rest phase eating during weekdays and ad-lib during weekends mimicking human condition) could lead to circadian rhythm disruption [7] and predispose to metabolic dysfunction and weight gain [36]. Recently, irregular food timing in humans was found to be associated with worsening inflammation among patients with inflammatory bowel disease [4]. Here, we found that irregular food timing as defined by inconsistent eating during work vs. free days tended to be more frequent among individuals with elevated BMI, a finding that did not reach statistical significance likely due to the sample size. When combined with central circadian phenotype, irregular food timing increased the risk of elevated BMI in subjects with intermediate/late chronotypes, an association which remained significant after adjusting for all other factors. The link between abnormal circadian phenotypes and elevated BMI in our study could be explainable by the role of circadian rhythm disruption in metabolic dysfunction [2, 7, 12, 35, 36], which could be in part mediated via changes in intestinal microbiota [6, 37–39].

Chronotype changes throughout the life from childhood to elderliness. Children usually have early chronotype that progresses to later chronotype by puberty and adolescence. In elderly individuals, chronotype continues to progress until it cycles back to early chronotype similar to children [40]. We also observed higher rates of intermediate/late chronotype among younger adults compared to older adults who had higher rates of early chronotype. Interestingly, the same group of younger adults also had higher rates of irregular food timing. This is particularly relevant to the current obesity epidemic in the modern societies including the US that is affecting the younger population, as younger adults could be more exposed to lifestyle habits such as CRD, which could predispose them to metabolic dysfunction [41, 42].

Our study has several limitations. It is a cross-sectional study and there are inherited limitations including recall bias and selection bias, especially that our study sample included indivudals who presented for colonoscopy. We expect that having a larger sample size with participants outside the clinical settings may result in similar finidngs to our study. This is a survey-based study which limits the ability to evaluate for other potential confounding factors as calorie intake, exercise, and other factors that may affect the BMI. It is noteworthy that our findings should be verified in younger population; for the current study we recruited healthy individuals at the screening age for colorectal cancer which explains why our study population was overall older.

In conclusion, we found that the behavioral circadian phenotypes illustrated by intermediate/late chronotype and irregular food timing is associated with higher rates of elevated BMI. The majority of individuals with this risky circadian phenotype were younger. Identifying risk factors for elevated BMI can help us develop new strategies in mitigating the obesity epidemic. Irregular food timing is a novel factor that could contribute to the risk of obesity, especially among younger adults; further studies in a younger population with larger sample size are needed to confirm our results.

What is already known on this subject?

The rise in obesity is closely linked to our lifestyle. Disruption of circadian clock which is a common lifestyle habit in our 24/7 modern society has been linked to predisposition to metabolic dysregulation and obesity. Shift in the light/dark cycles as occurs in shift workers is a widely studied model of central circadian disruption which can increase risk of obesity. Besides, studies from our lab and others show that eating during or close to the rest time could also lead to circadian rhythm disruption by desynchronizing the central from peripheral circadian clock. Animal studies show that the time of eating (independent from the type of diet) affects the risk of obesity.

What does this study add?

The combination of late chronotype and irregular food timing is associated with obesity. The association of behavioral circadian rhythm phenotypes with obesity is more evident in nonelderly population, an intriguing finding in light of the ongoing rise in the obesity rates among younger adults. Our observations introduce additional "targetable" lifestyle habits to decrease the risk of obesity.

Acknowledgements We thank Shahab Khan for his help in the recruitment of participants.

Funding FB was supported by NIH/AA025387 and Rush Translational Sciences Consortium/Swim Across America Organization, and is grateful for the support of the Brinson Foundation. MA was supported by the National Center For Advancing Translational Sciences of the National Institutes of Health under Award Number TL1TR002388. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by Institutional Review Board at Rush University (15011602).

Informed consent Informed consent was obtained from all individual participants included in the study.

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