AKADÉMIAI KIADÓ

Journal of Behavioral Addictions

13 (2024) 2, 554–564

DOI:
10.1556/2006.2024.00027

FULL-LENGTH REPORT

Moderating effects of PER3 gene DNA methylation on the association between problematic mobile phone use and chronotype among Chinese young adults: Focus on gender differences

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Received: April 13, 2023 • Revised manuscript received: August 6, 2023; February 25, 2024 • Accepted: April 25, 2024
Published online: June 3, 2024

ABSTRACT

Objective: To investigate the rates of problematic mobile phone use (PMPU) and chronotypes in young adults, and examine the associations of PMPU with chronotypes, as well as its gender differences. Furthermore, we explored the moderating role of *PER3* gene DNA methylation on the associations. *Methods:* From April to May 2019, a total of 1,179 young adults were selected from 2 universities in Anhui and Jiangxi provinces. The Self-rating Questionnaire for Adolescent Problematic Mobile Phone Use (SQAPMPU) and reduced Morningness-Eveningness Questionnaire (rMEQ) were adopted to investigate PMPU and chronotypes in young adults, respectively. Moreover, 744 blood samples were collected to measure *PER3* gene DNA methylation. Multivariate logistic regression models were established to analyze the associations between PMPU and chronotypes. Moderating analysis was used to determine whether *PER3* gene DNA methylation moderated the relationships between PMPU and chronotypes. *Results:* The prevalence of PMPU, morning chronotypes (M-types), neutral chronotypes (N-types), and evening chronotypes (E-types) of young adults were 24.6%, 18.4%, 71.1%, and 10.5%, respectively. Multivariate logistic regression results indicated that PMPU was positively correlated with E-types (*OR* = 3.53, 95%*CI*: 2.08–6.00), and the association was observed only in females after stratified by gender (*OR* = 5.36, 95%*CI*: 2.70–10.67). Furthermore, *PER3* gene DNA methylation has a negative moderating role between PMPU and chronotypes and has a sex-based difference. *Conclusions:* This study can provide valuable information for the prevention and control of circadian rhythm disturbance among young adults from the perspective of epidemiology and biological etiology.

KEYWORDS

problematic mobile phone use, chronotypes, circadian rhythms, young adults, smartphone addiction, genetics, behavioral addictions

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INTRODUCTION

Circadian rhythms are biological oscillations of about 24 h that play fundamental roles in regulating biological functions, including sleep and wake preferences, hormonal secretion, and cognitive and physical performance (Chi-Castañeda & Ortega, 2020). Circadian rhythms vary between individuals and determine circadian preferences in the development of daily life, which can be expressed in the concept of chronotype (Aguilar-Galarza et al., 2021). Three different chronotypes can be distinguished: morning chronotypes (M-types), neutral chronotypes (N-types), and evening chronotypes (E-types) (Gowen, Filipowicz, & Ingram, 2019). M-types, also called early chronotypes, prefer to be active in the morning, going to bed early and getting up early. E-types, also called late chronotypes, prefer to be active in the evening, going to bed late and waking up late (Zou, Zhou, Yan, Yao, & Lu, 2022). Most individuals with no apparent circadian preference are classified as N-types (Montaruli et al., 2021). Studies have found that genetic factors, age, gender, cultural, social, and environmental threats might impact on individuals' chronotypes (Demirhan, Randler, & Horzum, 2016).

With the increasing popularity of information and communication technology, mobile phones and smartphones have become an indispensable part of the current society (Wu & Siu, 2020). However, smartphone dependence has been a major concern in our society (Cui et al., 2021). Problematic mobile phone use (PMPU) is also called mobile phone dependence, mobile phone addiction, and smartphone addiction, which refers to the excessive use or uncontrolled use of mobile phones or smartphones, resulting in problems in daily life (Nowak et al., 2022). According to Ofcom, 37.0% of adults and 60.0% of adolescents were highly addicted to electronic communication devices (Ofcom Report, 2018). Meanwhile, it has been reported that in India (Choudhury et al., 2019), Nepal (Thapa, Lama, Pokharel, Sigdel, & Rimal, 2020), China (Long et al., 2016), and Switzerland (Haug et al., 2015), 14.9, 21.8, 21.3, and 16.9% of young adults exhibit signs of PMPU, respectively. It can be found from domestic and foreign studies that mobile phone or smartphone overuse was widespread among young adults.

In addition, studies found gender differences between chronotypes (Adan & Natale, 2002; Duarte et al., 2014). For instance, Adan et al. (Adan & Natale, 2002) studies on more than 2,000 college students found significant differences in the distribution of chronotype between males and females, with the male showing a more evening-oriented. However, Duarte et al. (2014) studies on 14,650 Brazilian adults found that females greater than 45 years tended to be more evening preference than males. At the same time, studies found that there were gender differences in PMPUs. Some studies found that males have a higher risk of PMPU than females (Li, Wang, et al., 2023; Takao, Takahashi, & Kitamura, 2009). However, other studies have shown that females are more addicted to their phones than males (De-Sola et al., 2016; Demirci, Akgönül, & Akpinar, 2015). Finally, some studies have found that gender makes no effect at all (Chen et al., 2017; Fang et al., 2019). As can be seen, gender differences in chronotype and mobile phone use are also an issue worth discussing.

In recent years, increasing studies have found that excessive use of smartphones can significantly affect circadian rhythm (Li et al., 2022). For example, Lin et al. (2021) have found that some behavioral addictions (e.g. Internet addiction, smartphone addiction, and problematic social media use) were associated with higher eveningness. Similarly, Bartel et al. (Bartel, Gradisar, & Williamson, 2015) found that information and communication technologies usage, such as the Internet, computer, video games, and mobile phone use, were associated with later bedtimes and sleep latency. One possible explanation is that the blue light emitted by the mobile phone may inhibit melatonin secretion and thus delay the circadian rhythm (Crowley, Cain, Burns, Acebo, & Carskadon, 2015). For example, Shrivastava et al. (Shrivastava & Saxena, 2014) studies on medical students found that duration of mobile phone use was negatively correlated with melatonin secretion. Furthermore, light exposure at night has also increased by the excessive use of mobile phones or smartphones (Smolensky, Sackett-Lundeen, & Portaluppi, 2015). Previous studies have shown that the *PER3* gene, as a molecular component of the circadian clock, was linked to changes in sleep-wake patterns when exposed to light (Martynhak et al., 2017). Likewise, Chellappa et al. (2012) found that the *PER3* allele was related to enhanced inhibition of nocturnal melatonin by nighttime light. Animal studies have also shown that the long-term effects of light on circadian rhythms appear to be related to the *PER3* genotype (Van & Archer, 2010). These studies suggest that *PER3* variants may interact with the light environment to influence circadian rhythms (Archer, Schmidt, Vandewalle, & Dijk, 2018).

The *PER3* gene is a highly rhythmic, circadian-related gene expressed in the central nervous system and peripheral tissues, and plays an important role in determining the circadian cycle and phase (Weiss, Woods, Filipowicz, & Ingram, 2020). There is some evidence that in humans, the *PER3* gene may be associated with circadian preference, or an individual's tendency to be active at different times of the waking day (Turco et al., 2017). The associations of *PER3* with circadian preference may be mediated by the effect of *PER3* on light perception and transduction processes and their rhythmic regulation (Archer et al., 2018). Moreover, recent studies in mice have also reported the role of *PER3* in regulating sleep/wake time, sleep homeostasis, and retinal physiology (Hasan, van, Winsky-Sommerer, Dijk, & Archer, 2011). Among human tissues, *PER3* levels are highest in the retina, thyroid, and pineal (Archer et al., 2018). Changes in *PER3*-dependent light sensitivity may be related to high expression of *PER3* in the retina and may contribute to changes in the brain's response to light and diurnal preference (Archer et al., 2018).

Therefore, given the excessive use of mobile phones or smartphones and the higher prevalence of late bedtimes in young adults (Lu et al., 2021; Xie, Tao, Zhang, Tao, & Wu,

2019), we conducted an epidemiological investigation of the associations between PMPU and chronotypes in Chinese young adults. The aim of the current study is threefold: a) to describe the prevalence of PMPU and chronotypes in Chinese young adults, b) to examine the association between PMPU and chronotypes in Chinese young adults, and gender-based difference in the associations of PMPU with chronotypes, and c) to further explore the moderating role of *PER3* gene DNA methylation in the association between PMPU and chronotypes.

METHODS

Participants

From April to May 2019, the cluster random sampling method was adopted to select one medical university in Hefei City, Anhui Province, and one comprehensive normal university in Shangrao City, Jiangxi Province. All freshmen from 2 faculties at each university were selected to complete a questionnaire survey. A total of 1,179 questionnaires were distributed, 1,151 were returned and 1,135 were valid. The effective questionnaire rate was 98.6%. Young adults completed the electronic anonymous questionnaire by scanning quick response code with smartphones. A total of 744 blood samples were collected by medical care personnel. Participants who provided informed consent, and did not report or have not been diagnosed with a psychiatric disorders were included.

Sociodemographic data

The following sociodemographic characteristics were obtained: age, gender, number of friends, number of siblings, residential area, self-reported family economy, self-reported academic performance, self-rated health status, self-reported learning burden, parental education level, smoking, and drinking. Number of friends was recoded into 3 categories: "0–2", "3–5, and "≥6". Number of siblings was divided into "0" or "≥1". Residential area was divided into 2 categories: "urban", and "rural". Family economy was assessed by asking "What do you think your family's economic condition was compared with other students?" The answers were recoded into "low", "medium" or "high". Academic performance was assessed by asking "What do your think about your academic performance in the class?" The answers were recoded into "poor", "average", and "good". Health status was assessed by asking "What do you think of your health status?" The answers were recoded into "poor", "fair", and "good". Learning burden was assessed by asking "How much burden do you feel by studying recently?" The answers were recoded into "a little", "some", and "much". Parental educational level was recoded into "primary school or lower", "middle school", and "senior high school and above". Current smoking and drinking were measured based on the Young Risk Behavior Surveillance System questionnaire (Eaton et al., 2012). Cigarette use was assessed by asking "How many days did you smoke at least one cigarette per day during the past month?" With <1 day defined as the non-cigarette-use group, and ≥1 day defined as the cigarette-use group. Alcohol use was assessed by asking "How many days did you drink at least one glass of alcohol per day during the past month?" With <1 day classified as the non-alcohol use group, and ≥1 day classified as the alcohol use group.

Problematic mobile phone use

The Self-rating Questionnaire for Adolescent Problematic Mobile Phone Use (SQAPMPU) (Tao, Fu, Wang, Hao, & Tao, 2013) was used to measure PMPU in young adults. The scale contains 13 items and was divided into 3 dimensions: physical and mental health status, craving, and withdrawal symptoms. Each item was weighted from 1 to 5, generating one global score ranging from 13 to 65, where SQAPMPU scores ≥28 were defined as the PMPU. The Cronbach's alpha coefficient in this study was 0.87.

Chronotype

The reduced Morningness-Eveningness Questionnaire (rMEQ) was used to assess chronotype in young adults (Adan & Almirall, 1991), and rMEQ was well-validated in China and also regarded as the MEQ-5 items (MEQ-5). The total score ranges from 4 to 25 points, where 4–11 points were defined as the E-types, 12–17 points were defined as the N-types and 18–25 points were defined as the M-types (Adan & Almirall, 1991). The Cronbach's alpha coefficient in this study was 0.68.

DNA methylation detection of the *PER3* gene

Between 6:00 and 8:00 in the morning, 5 mL of peripheral blood was collected from each participant and placed in a test tube containing ethylenediaminetetraacetic acid and stored in a −80 °C refrigerator. Genomic DNA was extracted from participants' peripheral blood using the TGuide Cells/Tissue Genomic DNA Kit (Tiangen Biotech Co., Ltd., Beijing, China) according to the manufacturer's instructions. DNA methylation levels were analyzed using MethylTarget™ (Genesky Biotechnologies Inc., Shanghai, China), a multiple-targeted CpG methylation analysis method based on NGS. Specifically, genomic regions of interest were analyzed by geneCpG software and transformed into bisulfite-converted sequences. CpG islands located in the proximal promoter of the *PER3* gene from 2 kb upstream of the transcription start point to 1 kb downstream of the first exon were selected for measurement according to the following criteria: (1) 200 bp minimum length; (2) 50% or higher GC content; (3) 0.60 or higher ratio of observed/expected dinucleotides CpG. PCR primer sets were designed from bisulfate-converted DNA using methylation primer software (reference human genome 19). Genomic DNA (400 ng) was treated with sodium bisulfite using the EZ DNA Methylation™-GOLD Kit (Zymo Research) following the manufacturer's protocol. Multiplex PCR was performed using an optimized combination of primer sets. The PCR amplicons were diluted and amplified with the index primers. The PCR amplicons (170 bp - 270 bp) were separated by agarose electrophoresis and purified using a

QIAquick Gel Extraction kit (QIAGEN). Libraries from different samples were quantified, normalized, and pooled, and then sequenced using 2 × 150 bp paired-end mode on the Illumina NextSeq platform according to the manufacturer's protocols (Li, Xie, et al., 2023). Quality control of sequencing reads was performed by FastQC. After read recalibration using USEARCH, the filtered reads were mapped to the genome using BLAST, and methylation was analyzed using Perl script. The methylation level at each CpG site was calculated as the percentage of methylated cytosines over the total tested cytosines.

Statistical analysis

SPSS software (version 23.0) was used for statistical analysis (SPSS, Chicago, IL, United States). Categorical variables were presented as frequencies and percentages, and continuous variables as mean ± standard deviation ($M \pm SD$). First, Chi-square tests were used to compare the differences of PMPU as well as chronotypes between different groups. A Bonferroni correction test was then applied to identify which specific groups (PMPU groups: Non-PMPU and PMPU; chronotypes: M-types, N-types, and E-types) differed from each other for each groups within each variable. Second, multivariate logistic regression was used to analyze the PMPU association with chronotype, including chronotype as outcomes, and PMPU as predictors. Moreover, age, gender, self-reported family economy, self-reported academic performance, self-reported academic burden, self-rated health status, smoking, and drinking as covariates. Finally, to explore whether *PER3* gene DNA methylation moderates the associations between PMPU and chronotype, we conducted a moderation model using PROCESS (Hayes, 2017). PROCESS was an SPSS macro for moderation and mediation analysis. In PROCESS, model 1 was selected and the confidence interval (*CI*) was set at 95%. Before performing the moderation analyses, we used the mean center to reduce multicollinearity. A moderation analysis was conducted with PMPU as an independent variable, *PER3* gene DNA methylation as a moderator, chronotype as a dependent variable, and the covariates were the same as above. Furthermore, in order to further understand the moderating effect of *PER3* gene DNA methylation in the relationship between PMPU and chronotype, a Johnson-Neymann procedure was used. $p < 0.05$ was considered statistically significant.

Ethics

The research protocol approved by the Ethics Committee of Anhui Medical University (NO: 20170291). Written informed consent was obtained from all participants.

RESULTS

Comparison of PMPU and chronotypes among young adults with different characteristics

In this study, the mean age of participants was 18.8 years (SD = 1.2), and 38.1% (432/1,135) were male. The prevalence of PMPU among young adults was 24.6%. The rate of PMPU was higher in young adults with a low family economy, much learning burden, poor academic performance, and poor or fair health status, smoking, and drinking than that of those with a high family economy, some learning burden, average or good academic performance, good health status, no smoking, no drinking. The rates of M-types, N-types, and E-types were 18.4%, 71.1%, and 10.5%, respectively. The rate of M-types was higher in males than in females. The rate of E-types was higher in young adults with fair health status than that of good health status. However, the rate of M-types of young adults with good health status was higher than the fair health status, and the difference was statistically significant (Table 1).

Comparison of chronotypes among different PMPU groups in young adults

The rate of M-types in the PMPU group was lower than that in the non-PMPU group, while the rate of E-types in the PMPU group was higher than that in the non-PMPU group. In addition, there was a gender-based difference in the rate of chronotype among different groups of PMPU. In female young adults, the rates of M-types and N-types in the PMPU group were lower than that in the non-PMPU group, while the rate of E-types in the PMPU group was higher than that in the non-PMPU group. In male young adults, the difference was not statistically significant (Table 2).

Association of PMPU and chronotypes among young adults

The multivariate logistic regression indicated that there was a positive correlation between PMPU and E-types (OR = 3.53, 95%*CI*: 2.08–6.00) after controlling for age, gender, self-reported family economy, self-reported academic performance, self-reported learning burden, self-rated health status, smoking, and drinking. According to further analysis stratified by gender, in female young adults, PMPU was positively correlated with E-types (OR = 5.36, 95%*CI*: 2.70–10.67), while among male young adults, there was no significant statistical associations (Table 3).

Moderating effects of *PER3* gene DNA methylation on the correlation between PMPU and chronotype

In this study, the mean levels of *PER3* gene DNA methylation were 0.34 (SD = 0.02), and 0.33 (SD = 0.02) in males, and 0.34 (SD = 0.03) in females. The results of moderating effects analysis indicated that *PER3* gene DNA methylation had negative moderating effects between PMPU and chronotype, with the β values of the interaction terms being −1.72, after controlling for age, gender, self-reported family economy, self-reported academic performance, self-reported learning burden, self-rated health status, smoking, and drinking (Table 4). The Johnson-Neyman procedure suggested that when the *PER3* gene DNA methylation level exceeded −0.04, the PMPU had a significantly negative effect on the chronotype ($B = -2.04$, $t = -2.78$, $p < 0.05$) (Fig. 1).

Table 1. Comparison of differences in the prevalence of PMPU and chronotypes by characteristics among young adults (n = 1,135)

Variable	n (%)	PMPU groups				Chronotypes				
		Non-PMPU	PMPU	χ^2 value	p value	M-types	N-types	E-types	χ^2 value	p value
Gender				0.47	0.495				6.70	0.035
Male	432 (38.1)	321 (74.3)[a]	111 (25.7)[a]			95 (22.0)[a]	298 (69.0)[a]	39 (9.0)[a]		
Female	703 (61.9)	535 (76.1)[a]	168 (23.9)[a]			114 (16.2)[b]	509 (72.4)[a]	80 (11.4)[a]		
Residential area				1.36	0.244				1.79	0.408
Rural	633 (55.8)	469 (74.1)[a]	164 (25.9)[a]			123 (19.4)[a]	449 (70.9)[a]	61 (9.6)[a]		
Urban	502 (44.2)	387 (77.1)[a]	115 (22.9)[a]			86 (17.1)[a]	358 (71.3)[a]	58 (11.6)[a]		
Number of siblings				0.00	0.984				4.00	0.136
0	268 (23.6)	202 (75.5)[a]	66 (24.5)[a]			43 (16.0)[a]	189 (70.5)[a]	36 (13.4)[a]		
≥1	867 (76.4)	654 (75.4)[a]	213 (24.6)[a]			166 (19.1)[a]	618 (71.3)[a]	83 (9.6)[a]		
Self-reported family economy				7.32	0.026				3.16	0.532
Low	272 (24.0)	192 (70.6)[a]	80 (29.4)[a]			58 (21.3)[a]	189 (69.5)[a]	25 (9.2)[a]		
Medium	800 (70.5)	610 (76.2)[a,b]	190 (23.8)[a,b]			138 (17.3)[a]	576 (72.0)[a]	86 (10.8)[a]		
High	63 (5.6)	54 (85.7)[b]	9 (14.3)[b]			13 (20.6)[a]	42 (66.7)[a]	8 (12.7)[a]		
Self-reported learning burden				8.70	0.013				4.50	0.339
A little	21 (1.9)	15 (71.4)[a,b]	6 (28.6)[a,b]			5 (23.8)[a]	14 (66.7)[a]	2 (9.5)[a]		
Some	695 (61.2)	545 (78.4)[b]	150 (21.6)[b]			130 (18.7)[a]	502 (72.2)[a]	63 (9.1)[a]		
Much	419 (36.9)	296 (70.6)[a]	123 (29.4)[a]			74 (17.7)[a]	291 (69.5)[a]	54 (12.9)[a]		
Self-reported academic performance				23.64	<0.001				7.03	0.134
Good	200 (17.6)	162 (81.0)[b]	38 (19.0)[b]			47 (23.5)[a]	135 (67.5)[a]	18 (9.0)[a]		
Average	696 (61.3)	542 (77.9)[b]	154 (22.1)[b]			125 (18.0)[a]	502 (72.1)[a]	69 (9.9)[a]		
Poor	239 (21.1)	152 (63.6)[a]	87 (36.4)[a]			37 (15.5)[a]	170 (71.1)[a]	32 (13.4)[a]		
Number of friends				2.05	0.360				2.23	0.694
0–2	135 (11.9)	97 (71.9)[a]	38 (28.1)[a]			28 (20.7)[a]	89 (65.9)[a]	18 (13.3)[a]		
3–5	306 (27.0)	226 (73.9)[a]	80 (26.1)[a]			56 (18.3)[a]	219 (71.6)[a]	31 (10.1)[a]		
≥6	694 (61.1)	533 (76.4)[a]	161 (24.6)[a]			125 (18.0)[a]	499 (71.9)[a]	70 (10.1)[a]		
Paternal education level				3.22	0.199				3.85	0.426
Primary school and below	257 (22.6)	187 (72.8)[a]	70 (27.2)[a]			48 (18.7)[a]	182 (70.8)[a]	27 (10.5)[a]		
Middle school	539 (47.5)	402 (74.6)[a]	137 (25.4)[a]			93 (17.2)[a]	396 (73.5)[a]	50 (9.3)[a]		
Senior high school and above	339 (29.9)	267 (78.8)[a]	72 (21.2)[a]			68 (20.0)[a]	229 (67.6)[a]	42 (12.4)[a]		
Maternal education level				1.41	0.494				1.05	0.903
Primary school and below	497 (43.8)	367 (73.8)[a]	130 (26.2)[a]			91 (18.3)[a]	358 (72.0)[a]	48 (9.7)[a]		
Middle school	396 (34.9)	301 (76.0)[a]	95 (24.0)[a]			71 (17.9)[a]	282 (71.2)[a]	43 (10.9)[a]		
Senior high school and above	242 (21.3)	188 (77.7)[a]	54 (22.3)[a]			47 (19.4)[a]	167 (69.0)[a]	28 (11.6)[a]		
Self-rated health status				14.87	0.001				20.39	<0.001
Good	672 (59.2)	530 (78.9)[a]	142 (21.1)[a]			148 (22.0)[a]	468 (22.0)[a]	56 (8.3)[a]		
Fair	418 (36.8)	300 (71.8)[b]	118 (28.2)[b]			56 (13.4)[b]	307 (73.4)[a]	55 (13.2)[b]		
Poor	45 (4.0)	26 (57.8)[b]	19 (42.2)[b]			5 (11.1)[a,b]	32 (71.1)[a]	8 (17.8)[a,b]		
Smoking				6.07	0.014				4.63	0.099
Yes	101 (8.9)	66 (65.3)[b]	35 (34.7)[b]			26 (25.7)[a]	63 (62.4)[a]	12 (11.9)[a]		
No	1,034 (91.1)	790 (76.4)[a]	244 (23.6)[a]			183 (17.7)[a]	744 (72.0)[a]	107 (10.3)[a]		

(continued)

Table 1. Continued

Variable	n (%)	PMPU groups				Chronotypes				
		Non-PMPU	PMPU	χ^2 value	*p* value	M-types	N-types	E-types	χ^2 value	*p* value
Drinking				8.54	0.003				2.01	0.366
Yes	261 (23.0)	179 (68.6)[b]	82 (31.4)[b]			50 (19.2)[a]	178 (68.2)[a]	33 (12.6)[a]		
No	874 (77.0)	677 (77.5)[a]	197 (22.5)[a]			159 (18.2)[a]	629 (72.0)[a]	86 (9.8)[a]		

Note: Chi-square test with the Bonferroni correction; "a versus a,b" or "b versus a,b" denotes no statistical differences in the percentage of PMPU and chronotypes between different groups; "a versus b" denotes the statistical differences in the percentage of PMPU and chronotypes between different groups; "a versus a" and "b versus b" denote no statistical difference in the percentage of PMPU and chronotypes between different groups.

According to further analysis stratified by gender, in male young adults, *PER3* gene DNA methylation negatively moderated the relationships between PMPU and chronotypes, but there was no statistically significance (Table 4). When *PER3* gene DNA methylation level was higher than 0.01, the relationship between PMPU and chronotypes was non-significant ($B = -0.20$, $t = -0.13$, $p > 0.05$) (Fig. 2). Among female young adults, *PER3* gene DNA methylation had negative moderating effects between PMPU and chronotype, with the β value of the interaction term being −1.90, after controlling for confounding factors (Table 4). The Johnson-Neyman procedure suggested that when the *PER3* gene DNA methylation level was higher than −0.04, the PMPU had a significantly negative effect on the chronotype ($B = -2.20$, $t = -2.53$, $p < 0.05$) (Fig. 3).

DISCUSSION

Our research illuminates the association between PMPU and chronotypes in Chinese young adults, as well as gender differences in the association. Moreover, we further found that *PER3* gene DNA methylation had negative moderating effects on the association between PMPU and chronotype and had sex differences. Our research can provide more favorable scientific value for the prevention and control of circadian rhythm disturbance among young adults.

This research indicates that the rate of PMPU in young adults was 24.6%, which was at a higher level compared to other domestic and foreign studies. For instance, in a survey of young adults in Changsha, China, the prevalence of PMPU among young adults was 21.3% (Long et al., 2016). Similarly, a study from America found that the prevalence of PMPU was 11.2% (Lee, 2015). However, another study of 28,669 young adults found that the rate of PMPU was 46.1%, which was higher than that of our study (Gokce & Ozer, 2021). Furthermore, we found that the prevalence of PMPU was higher in males (25.7%) than in females (23.9%). However, at odds with our findings, a survey of 1,794 adolescents in Korea found that females tended to use their mobile phones more frequently and were at a higher risk of PMPU than males (Park, Yang, Shin, Jang, & Park, 2019). Similarly, a study of Swedish adolescents found that females have a greater possibility of having excessive smartphone use than males (Claesdotter-Knutsson et al., 2021).

In the present study, the rates of the M-types, N-types, and E-types were 18.4%, 71.1%, and 10.5%, respectively. The prevalence of E-types in our study was lower than that in other studies. For instance, a study of 2,857 young adults in Korea indicated that the rate of E-types was 20.4% (Lee, Lee, Jhung, & Park, 2017). Similarly, a survey of 3,160 young adults in Canadian found that the rate of E-types was 36.0% (Walsh, Repa, & Garland, 2022). However, another study of 5,497 young adults in China showed that the rate of E-types (6.4%) was lower than that of our study (Sun et al., 2019). Furthermore, we found that the rate of E-types was higher in females (11.4%) than in males (9.0%), while the rate of

Table 2. Comparison of chronotypes among different PMPU groups in young adults

Gender	PMPU groups	Chronotypes			χ^2 value	*p* value
		M-types	N-types	E-types		
Overall	Non-PMPU	173 (20.2)[a]	618 (72.2)[a]	65 (7.6)[a]	34.45	<0.001
	PMPU	36 (12.9)[b]	189 (67.7)[a]	54 (19.4)[b]		
Male	Non-PMPU	77 (24.0)[a]	217 (67.6)[a]	27 (8.4)[a]	3.14	0.208
	PMPU	18 (16.2)[a]	81 (73.0)[a]	12 (10.8)[a]		
Female	Non-PMPU	96 (17.9)[a]	401 (75.0)[a]	38 (7.1)[a]	42.12	<0.001
	PMPU	18 (10.7)[b]	108 (64.3)[b]	42 (25.0)[b]		

Note: Chi-square test with the Bonferroni correction; "a versus b" denotes the statistical differences in the percentage of chronotypes between different groups; "a versus a" and "b versus b" denote no statistical difference in the percentage of chronotypes between different groups.

Table 3. The associations between PMPU and chronotypes by adjusted multivariate logistic regression analysis

Gender	PMPU groups	N-types		E-types	
		OR value (95%*CI*)	*p* value	*OR* value (95%*CI*)	*p* value
Overall	Non-PMPU	1.00		1.00	
	PMPU	1.40 (0.93~2.11)	0.105	3.53 (2.08~6.00)	<0.001
Male	Non-PMPU	1.00		1.00	
	PMPU	1.42 (0.78~2.61)	0.255	1.65 (0.67~4.02)	0.275
Female	Non-PMPU	1.00		1.00	
	PMPU	1.40 (0.80~2.44)	0.236	5.36 (2.70~10.67)	<0.001

Note: Model adjusted for age, gender, self-reported family economy, self-reported learning burden, self-reported academic performance, health status, smoking, and drinking.

Table 4. The moderating effects of *PER3* gene DNA methylation on the associations between PMPU and chronotypes

Gender	Chronotypes		
	Variable	β value	*t* value
Overall	constant	8.84	4.06**
	PMPU	−0.08	−6.29**
	PER3	−2.70	−0.61
	PMPU × *PER3*	−1.72	−2.38*
	R^2 value	0.12	
	F value	8.95**	
Male	constant	2.90	0.73
	PMPU	−0.04	−2.06*
	PER3	4.21	0.39
	PMPU × *PER3*	−0.81	−0.55
	R^2 value	0.13	
	F value	3.51**	
Female	constant	10.59	4.00**
	PMPU	−0.10	−6.67**
	PER3	−4.03	−0.83
	PMPU × *PER3*	−1.90	−2.19*
	R^2 value	0.13	
	F value	7.40**	

Note: *$p < 0.05$; **$p < 0.001$. Model adjusted for age, gender, self-reported family economy, self-reported learning burden, self-reported academic performance, health status, smoking, and drinking.

M-types was higher in males (22.0%) than in females (16.2%). A study of the young adult in Saudis found that M-types were more common in males, which was similar to our study (BaHammam, Almistehi, Albatli, & AlShaya, 2011).

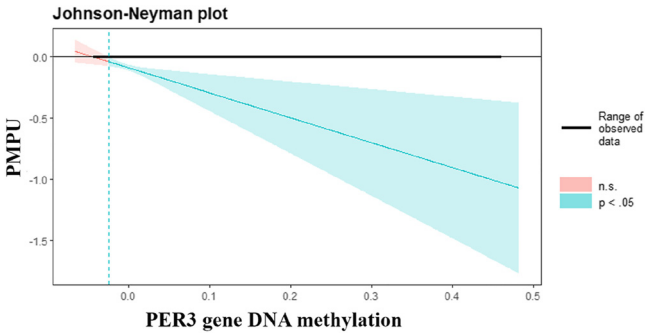

Fig. 1. The moderating effects of PER3 gene DNA methylation on the associations of PMPU with chronotypes among young adults

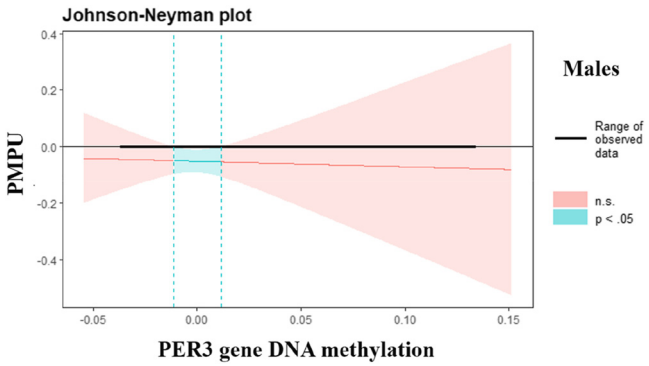

Fig. 2. The moderating effects of PER3 gene DNA methylation on the associations of PMPU with chronotypes among male young adults

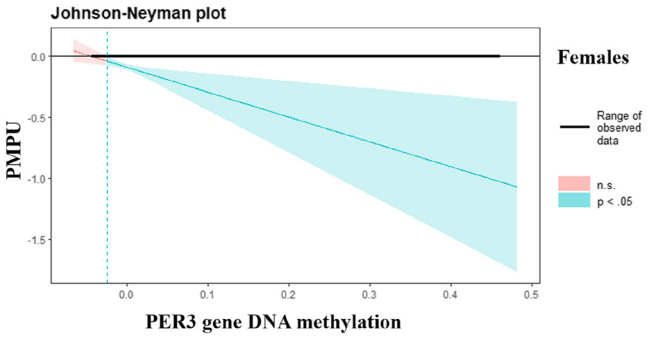

Fig. 3. The moderating effects of PER3 gene DNA methylation on the associations of PMPU with chronotypes among female young adults

However, Kim et al. (Kim, Han, Heo, Kim, & Chu, 2020) study found that the rate of E-types was higher in males (16.9%) than in females (14.0%).

At present, the adverse health effects caused by the excessive use of mobile phones were attracting more and more attention. According to the research results, E-type individuals are more problematic mobile phone users. For instance, Asarnow et al. (Asarnow, Gasperetti, Gumport, & Harvey, 2021) found that Internet use in the middle of the night was correlated with a later bedtime. In addition, Fossum et al. (Fossum, Nordnes, Storemark, Bjorvatn, & Pallesen, 2014) recruited 532 students aged 18 to 39 through lectures or emails and found mobile phone use and gaming were positively associated with E-types. In this study, we similarly found that the PMPU was positively correlated with E-types. After further analysis stratified by gender, we found that PMPU was positively correlated with E-types only in female young adults. Demirhan et al. (2016) found that E-type college students had higher scores on the mobile phone problem usage scale. However, they found that gender was not a predictor of PMPU.

PMPU was associated with E-types and this may happen through many interrelated biological mechanisms, including alteration of the expression of circadian genes, changes in sex hormone levels, and suppression of melatonin production (Ritonja, Aronson, Flaten, et al., 2022). DNA methylation is an epigenetic modification that plays a critical role in the regulation of gene expression (Lahtinen et al., 2019). Once the DNA methylation pattern is established, it is considered stable in a non-pathological context (Lahtinen et al., 2021). However, data emerging on aging have shown that DNA methylation changes throughout a person's life and is susceptible to environmental influence (Day et al., 2013; Field et al., 2018). Light is the major component of clock control. Studies have shown that light can alter the timing of suprachiasmatic nucleus clock gene expression, which subsequently leads to adjustment in timing in the periphery (Reppert & Weaver, 2002). In fact, in different, rare human *PER3* variants, light induces a larger phase delay (or smaller phase advance), which leads to abnormal entrainment (Zhang et al., 2016). Therefore, light emitted by E-type individuals using mobile phones may interact with the expression of clock-related genes, further affecting circadian rhythm. In the present study, we found that DNA methylation of the *PER3* gene negatively moderates the relationship between PMPU and chronotype, and there is a sex difference.

Nowadays, young adults are widely exposure to electronic devices (including smartphones, tablets, computers and consoles) before bedtime, LEDs emit more blue light than white incandescent bulbs, therefore have a greater impact on the biological clock (Touitou, Touitou, & Reinberg, 2016). Experimental studies have demonstrated that exposure to short wavelengths of light (ie, blue light exposure), can suppress melatonin secretion and subsequently induce aberrant global DNA methylation (Schwimmer et al., 2014; Zubidat, Fares, Fares, & Haim, 2018). On the contrary, the treatment of exogenous melatonin was found to mitigate the impact of light exposure on global DNA methylation (Schwimmer et al., 2014; Zubidat et al., 2018). In addition, studies have indicated that patterns in melatonin secretion were associated with differential circadian gene methylation among night shift workers (Ritonja, Aronson, Leung, et al., 2022). Melatonin may also exert an influence on DNA methyltransferases, enzymes that catalyse the addition of methyl groups to DNA (Agbaria, Haim, Fares, & Zubidat, 2019). In this study, we found that *PER3* gene DNA methylation interacting with PMPU increased the risk of E-types, which may be due to the fact that light emitted by mobile phones inhibits the secretion of melatonin and further affects the expression of the clock gene, causing the chronotype to trend towards E-types.

So far, similar survey analyses have been rare. However, there were several limitations to this study. First, the cross-sectional design limits the ability to determine causal relationships. Further, longitudinal studies were needed to clarify the causal relationships between PMPU and chronotypes. Second, we used a self-reported questionnaire to assess PMPU and chronotypes. recall bias is inevitable. However, the two questionnaires were both have been verified. Despite the above limitations, our study firstly found that PMPU was positively correlated with E-types in a relatively impressive sample size of young adults and found that *PER3* gene DNA methylation negatively moderated the association of PMPU with the chronotypes and had sex-based differences.

CONCLUSIONS

To sum up, PMPU may have a potential impact on chronotypes among young adults, and this effect was significantly different varied by gender. Thus, by restricting mobile phone overuse among young adults may reduce the adverse impact on circadian rhythm. In addition, the circadian rhythm gene plays an important role in the relationship between PMPU and chronotypes. Further studies are warranted to determine the exact mechanism of the mediating

effect circadian rhythm gene in the associations between behavioral addiction and circadian rhythm disturbance.

Funding sources: The National Natural Science Foundation of China supported this work (grant number: 82173542, 82373592, 82304169).

Author contributions: Conceived and designed the experiments: Fangbiao Tao. Wrote the paper: Tingting Li. Performed the experiments: Shuman Tao, Yajuan Yang. Analyzed the data: Tingting Li, Yuming Chen. Contributed reagents/materials/analysis tools: Yang Xie, Liwei Zou. Contributed to study design: Xiaoyan Wu.

Conflict of interest: None.

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