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Circadian rhythm abnormalities during the COVID-19 outbreak related to mental health in China: a nationwide university-based survey

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A B S T R A C T

Objective/background: School closure and home quarantine has been implemented worldwide during the coronavirus disease 2019 (COVID-19) outbreak. The study aims to assess the associations of circadian rhythm abnormalities (CRA) during the COVID-19 outbreak with mental health in Chinese undergraduates.

Methods: A nationwide cross-sectional university-based survey was conducted from 4th February to 12th, 2020. Based on different geographical locations and purposive sampling approach, 19 universities from 16 provinces or municipalities in the mainland of China were selected. A total of 14,789 participants were recruited by using multistage stratified random sampling. The data of CRA were collected by self-reported questionnaires consist of four items involved rest—activity cycle, diet rhythm, wake up rhythm and sleep rhythm. The Patient Health Questionnaire and the Generalized Anxiety Disorder were applied to evaluate the symptoms of depression and anxiety. Chi-square test and ordinal logistic regression models were used to describe the distributions and associations of CRA and mental health.

Results: A total of 11,787 students [female: 6731(57.1%)] aged 15–26 years old (M = 20.45, SD = 1.76) were analyzed (response rate: 79.7%). The results showed the percentage of CRA were 17.5–28.7%. The prevalence of depression and anxiety were significantly higher in students with single CRA. Students who reported the coexistence of four CRA were more likely to be with the symptoms of depression (OR: 4.43, 95% CI: 3.91–5.03) and anxiety (OR: 3.11, 95% CI: 2.70–3.60). Dose-response relationships were found between multiple CRA and mental problems.

Conclusion: Circadian rhythm abnormalities are positively associated with mental health among university studies. Mental health care is needed for college students during the COVID-19 epidemic period.

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1. Introduction

In order to prevent the global transmission of the coronavirus disease 2019 (COVID-19), many countries have implemented a nationwide school closure to prevent contact and reduce cases [1]. Since 23rd January 2020, the Chinese government promotes home quarantine, which obviously is proved to be effective, and home-based online learning has become the main mode for Chinese...
students. Up to April third 2020, a total of 1454 colleges and universities provide online teaching. 1.18 billion students are taking online courses [2]. However, circadian rhythm abnormalities caused by home quarantine should be proposed. Circadian rhythm is an endogenous timing system, organisms have established the conventional physiology and behaviour (eg regular diet, good sleep habits and outdoor activities) to adapt to regular environmental changes (eg time, light and temperature) in 24-h cycle [3]. Genetic, behavioural and environmental factors contribute to changes in circadian timing, such as screen time, pressure from parental involvement in bedtime [4]. Home quarantine might disrupt the congruity between intrinsic circadian rhythm and lifestyle which is known as social jetlag [5]. There is evidence that the development of healthy habits depends on the timing of daily cycle [6]. It has been showed that circadian rhythm abnormalities can damage the maintenance of healthy lifestyle, such as eating behavior [7].

Previous studies have shown links between loss of normal circadian rhythms and mental health among children or youths. The degree of circadian rhythm abnormalities seems to be a reason of mental disorder severity [8]. For example, a network survey in Japan reported that preschool children with more irregular diet and sleep times showed worse physical and mental health [9]. Lower morningness or eveningness abnormal rest–activity cycle were correlated with increased clinical psychosocial impairment among American youths aged 12–21 years at baseline or at 1-year follow-up [10]. A cross-sectional study has showed that sleep debt and daytime sleepiness would mediate the relationship between evening chronotype and depression or anxiety in American university students [11]. A prospective study in the Netherlands found that eveningness at baseline was a significant predictor of depressive symptoms at follow-up in a sample of university students [12]. More depressive symptoms were predicted by lower morning circadian preference in Polish university students [13]. A study showed that lower Morningness–Eveningness Questionnaire scores (eveningness preference) was significantly related to the Hospital Anxiety and Depression Scale–Depression scores in a young Swedish population aged 16–26 years [14]. Longitudinal studies also demonstrated higher levels of the baseline cortisol awakening response significantly predict higher major depression or depressive symptoms by structured Clinical Interview or self-reported after 2.5–3 years [15,16].

However, much of this work has limitations, the associations of circadian rhythms abnormalities caused by home quarantine with mental health in undergraduate students are not well established, considering that psychological fear towards the viruses might have an additive effect on mental health in university students. Thus, the aim of this study is to assess the associations of circadian rhythm abnormalities caused by home quarantine during the COVID-19 outbreak with mental health among Chinese undergraduate students. The results will have important implications for mental health care for college students during the COVID-19 epidemic period.

2. Methods

2.1. Study design and participants

We conducted a nationwide cross-sectional university-based survey in 19 universities from 16 provinces or municipalities in the mainland of China during 4th February to 12th February 2020. Students were selected by using multistage stratified random sampling strategy. First, universities were selected by using a purposive sampling approach, which is based on different geographical locations and cooperation intention. Four universities were included from Wuhan, Hubei province where the COVID-19 was firstly reported in China. Six universities were located in the central of China (Anhui, Hunan, Shanxi, Jiangxi, Chongqing, Henan province) and they were adjacent province of Hubei province. Two universities were located in first-tier city (Beijing and Shanghai). One university was located in the eastern of China (Jiangsu province). Two universities were from the southern of China (Guangdong and Guangxi province). One university was located in the western of China (Xinjiang province) and another one was located in the southwest of China (Yunnan province). The remaining two were in the northeast of China (Jilin and Heilongjiang province). Meantime, in consideration of the type of university, comprehensive and medical university were both recruited. Second, based on sample proportion of universities and medical schools, 100 to 120 students were randomly selected in each grade (in general, 5 years for medical students and 4 years for non-medical students) of a faculty from each university, as listed in supplemental file. A total of 14,789 students were selected. The participants were invited to complete the survey using an electronic online questionnaire.

The study protocol was approved by the Ethics Committee of Anhui Medical University. Electronic informed consents were obtained from all participants before completing the survey, which was conducted in accordance with the principles of the Declaration of Helsinki.

2.2. Measures

2.2.1. Descriptive information

Descriptive information included age, gender, grade, residential area (rural/urban), types of faculty (medical/non-medical), school location (Wuhan, adjacent provinces of Hubei and other provinces), current residence (Wuhan, other cities in Hubei, adjacent provinces of Hubei, and other provinces), exercise at home during the past 7 days (No/Yes, regularly/Yes, irregularly), screen time on the computer (including playing video or computer games or using a computer for something) and watching TV/video programs (less than 2 h per day/2 h or more per day), duration of browsing the COVID-19 information (less than 2 h per day/2 h or more per day), fear of infection (yes/no), the timing of sleep and wake up, any housework in the last week (yes/no), and argued with others in the last week (yes/no).

2.2.2. Circadian rhythm abnormalities

Home quarantine began on January 23rd 2020. Data of circadian rhythm were collected by four self-reported questions: “During the past week, whether your rest–activity cycle was more regular than in school”, “During the past week, whether your diet rhythm was more regular than in school”, “During the past week, whether your wake up rhythm was more regular than in school” and “During the past week, whether your sleep rhythm was more regular than in school”. The answers of “more irregular than in school” were defined as “abnormal rest–activity cycle”, “abnormal diet rhythm”, “abnormal wake up rhythm” or “abnormal sleep rhythm”. Multiple circadian rhythm abnormalities were calculated by the sum of four single circadian rhythm abnormalities.

2.2.3. Mental health

The Patient Health Questionnaire (PHQ-9) [17] and the Generalized Anxiety Disorder (GAD-7) [18] were applied to measure the symptoms of depression and anxiety during the last two weeks. The PHQ-9 is a self-rating scale with nine items for depression screening which commonly used as screening tool in most primary care settings. The GAD-7 is a standardized instrument designed to assess symptoms of generalized anxiety disorder during the last 14 days. The response of each item is 0 (not at all), 1 (several days), 2...
score for GAD-7 range from 0 to 21 which are categorized as
levels: none (0–4); mild (5–9); moderate (10–14); moderately severe (15–19); severe (20–27). A sum score for GAD-7 range from 0 to 21 which are categorized as four levels: none (0–4); mild (5–9); moderate (10–14); severe (15–21). The cut-off scores for mild depression/anxiety were five, and for moderate-severe depression/anxiety were 10.

2.3. Statistical analysis
Categorical variables were showed as frequencies (n) and percentages (%). Continuous variables were presented as the mean and standard deviation (SD) or median and interquartile. Chi-square tests were used to assess the associations of demographic factors with mental health. Ordinal logistic regression analyses were used for the independent effects of circadian rhythm abnormalities on mental health. Multivariable ordinal logistic regressions adjusting for gender, grade, types of faculty, school location, residential area, current residence, exercise at home during the past 7 days, screen time, duration of browsing the COVID-19 information, fear of infection, any housework in the last week, and argued with others in the last week were used to examine the associations of multiple circadian rhythm abnormalities and mental health among university students. Statistical analysis is conducted by SPSS software version 23.0 (SPSS Inc, Chicago, IL, USA) and significance is defined as \( P < 0.05 \) (two-tailed).

3. Results
A total of 11,787 university students (57.1% aged 15–26 years (M = 20.45, SD = 1.76) were analyzed (response rate: 79.7%). The prevalence rates of mild (PHQ-9: ≥5) and moderate-severe depression (PHQ-9: ≥10) were 17.2% or 8.7% while they were 12.4% or 5.4% for mild (GAD-7: ≥5) and moderate-severe anxiety (GAD: ≥10), respectively. Circadian rhythm abnormalities including “abnormal rest—activity cycle”, “abnormal diet rhythm”, “abnormal wake up rhythm” and “abnormal sleep rhythm” accounts for 27.9%, 17.5%, 28.7%, and 24.6% of the study population, respectively. Multiple circadian rhythm abnormalities were categorized into five levels: 0 (none), 1 (single), 2 (two types of circadian rhythm abnormalities), 3 (three types of circadian rhythm abnormalities), and 4 (the coexistence of four circadian rhythm abnormalities), and the percentages were 61.2%, 10.4%, 7.8%, 9.8%, 10.8%, respectively. In addition, 30.4% of the students' bedtime were 1 h later than in school (median: 60 min; Q1: 30min, Q3: 120min). Seventy percent of the students woke up 2 h later than in school (median: 120 min; Q1: 60 min, Q3: 180 min). A total of 80.6% of the study population were worried about infection of the COVID-19. Sixty-one percent of the students spend 2 h/d or more on the computer (including playing video or computer games or using a computer for something) and watching TV/video programs, only 13.9% of the students spend 2 h/d or more on browsing the COVID-19 information. A total of 23.9% of the students had an argument with others during the last week (Table 1).

Table 2 lists the distribution of mental problems. The presence of mental problems was found to be more common in girls compared with boys (\( P < 0.001 \)). Medical students reported lower rates of mental problems than non-medical students (\( P < 0.001 \)). The symptoms of depression and anxiety were more frequent in the students in Hubei province compared with their counterparts in other provinces (\( P < 0.01 \)). Students who did exercise or housework at home during the last week were less likely to be with mental problems (\( P < 0.001 \)). Students who were worried about infection, spend 2 h/d or more on the computer and watching TV/video programs, spend 2 h/d or more on browsing the COVID-19 information or argued with others were more frequent to be with mental problems (\( P < 0.001 \)). The prevalence of mental problems was significantly higher in students with multiple circadian rhythm abnormalities than normal students or those who reported single circadian rhythm abnormality (\( P < 0.001 \)).

Table 3 depicts the prevalence of depressive symptoms and the symptoms of anxiety in different groups of circadian rhythm abnormalities. The prevalence of mental problems was significantly higher in students with single circadian rhythm abnormality or multiple circadian rhythm abnormalities than those of normal students (\( P < 0.001 \)), and the approximate dose—response relationship was presented.

We examined the relationships between multiple circadian rhythm abnormalities and the symptoms of depression or anxiety ordinal logistic regression models. Table 4 shows the crude and adjusted OR (95% CI) for each group in comparison with the reference group (normal circadian rhythm) for the symptoms of depression or anxiety. After adjusting for age, gender, grade, types of faculty, school location, current residence, exercise at home, screen time, browsing the COVID-19 information, fear of infection, any housework, and argued with others, students who reported the coexistence of four circadian rhythm abnormalities were more likely to be with the symptoms of depression (OR: 4.43, 95% CI: 3.91–5.03) or anxiety (OR: 3.11, 95% CI: 2.70–3.60) than those of normal students. Dose—response relationships between were found between multiple circadian rhythm abnormalities and mental problems. Students who reported single circadian rhythm abnormality were more likely to be with the symptoms of depression or anxiety (\( P < 0.001 \)).

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Then we have subdivided multiple circadian rhythm abnormalities and analyzed the correlations between sub-classifications of multiple circadian rhythm abnormalities and mental problems. Fig. 1 indicated students who reported the coexistence of four circadian rhythm abnormalities were more likely to be with the symptoms of depression (OR: 5.25, 95% CI: 4.65–5.92) than those of normal students, and the second-highest odd ratio for depressive symptoms was found in students who reported abdominal rest—activity cycle, abnormal diet rhythm and sleep rhythm (OR: 5.19, 95% CI: 3.10–8.68). However, students who reported the coexistence of abnormal rest—activity cycle, diet rhythm and sleep rhythm were more likely to be with the symptoms of anxiety (OR: 4.71, 95% CI: 2.73–4.71) than those of normal students, and the second-highest odd ratio for the symptoms of anxiety was found in students who reported the coexistence of four circadian rhythm abnormalities (OR: 3.59, 95% CI: 3.14–4.11), which indicated students have a certain combination of abnormal wake up rhythm, the associations of circadian rhythm abnormalities with mental health might be might be less severe.

4. Discussion
Negative impacts of home quarantine on mental health have been proposed but the mechanism underlying this observation remains unclear [19]. To our knowledge, the study firstly supports that circadian rhythm abnormalities caused by home quarantine during the COVID-19 outbreak had a detrimental effect on mental health among undergraduates.

Assessments of circadian rhythms in humans include subjective assessment (eg Morningness-Eveningness Questionnaire, sleep log/diary), core body temperature, melatonin levels, and dieting timing and rest—activity cycles. Obviously, sleep—wake cycle is the most prominent circadian rhythm in human [8]. Evening chronotype
(preference for later timing of sleep and activity) is common in circadian misalignment, which is proved to be associated with more mental problems. Our findings indicated the timing of sleep or wake up is 1–2 h later than in school and 78.7% of the students spend 2 h/d or more on the computer or watching TV/video programs. Recently a cross-sectional study showed 82.0% of the study population reported frequently social media exposure during the COVID-19 outbreak [20]. It suggests that time spent on screens replaces sleeping [21]. Previous studies focused on the relationships between sleep disorder and mental health. For example, sleepiness and sleep debt mediated the relationship between short sleep or evening-type preferences and depression and anxiety risk in the university sample [11]. Morning circadian preference was related to less depressive symptoms in Polish university students [13].

In addition, the phenotypes of circadian rhythm abnormalities are interlinked. For instance, sleep–wake cycle may have an impact on diet timing. Circadian abnormality also describes a misalignment of sleep/wake with feeding rhythms [22]. Results from the UK National Diet and Nutrition Survey showed scores of healthy eating patterns dropping when people slept 1 h and 45 min more on weekends than on weekdays [23]. Circadian rhythm of rest and activity was influenced by the chronotype [24]. Our study collected the data of four phenotypes of circadian rhythm abnormalities, and identified the associations between subclassifications of multiple circadian rhythm abnormalities and mental health, which is also an advantage of our study.

There are several evidences on the associations between circadian rhythm abnormalities and mental health, which are consistent with our findings. A cohort study on Australian adults found that skipped/delayed breakfast with higher evening intakes at baseline had a higher incidence of mood disorder during the 5-year follow-up [25]. Adolescents with major depressive disorder had lower activity levels, damped circadian amplitude than healthy controls [26]. A study showed that the depressed boys showed eveningness preference and later-timed phases than healthy controls on weekends [27].

The coexistence of multiple circadian rhythm abnormalities might have a greater impact on mental health than single one, as

| Table 1 |
|------------------|------------------|------------------|------------------|------------------|------------------|
| Variables | Categories | n (%)/M±SD/Median (Q1,Q3) |
| Age | 20.45 ± 1.76 |
| Gender | Males | 5056 (42.9) |
| | Females | 6731 (57.1) |
| Grade | Year 1 | 2930 (24.9) |
| | Year 2 | 2609 (22.1) |
| | Year 3 | 2667 (22.5) |
| | Year 4 | 2314 (29.6) |
| | Year 5 | 1267 (10.7) |
| Residential area | Rural | 5660 (48.0) |
| | Urban | 6127 (52.0) |
| Types of faculty | Medical | 5770 (49.0) |
| | Non-medical | 6017 (51.0) |
| School location | Hubei provinces | 4887 (41.5) |
| | Adjacent provinces of Hubei | 2800 (23.8) |
| | Other provinces | 4100 (34.8) |
| Current residence | Wuhan city | 597 (5.1) |
| | Other cities in Hubei | 2237 (19.0) |
| | Adjacent provinces of Hubei | 2750 (23.3) |
| | Other provinces | 6203 (52.6) |
| Exercise at home | No | 4597 (39.0) |
| | Yes, regularly | 1653 (14.0) |
| | Yes, irregular | 5537 (47.0) |
| Screen time | Less than 2 h/d | 2511 (21.3) |
| | 2 h/d or more | 9276 (78.7) |
| Browsing the COVID-19 information | Less than 2 h/d | 10144 (86.1) |
| | 2 h/d or more | 1643 (13.9) |
| Fear of infection | Yes | 9501 (80.6) |
| | No | 2286 (19.4) |
| Any housework | Yes | 10163 (86.2) |
| | No | 1624 (13.8) |
| Argued with others | Yes | 2821 (23.9) |
| | No | 8966 (76.1) |
| Bedtime later than in school | 60 (30, 120) |
| Wake up later than in school | 120 (60, 180) |
| Circadian rhythm abnormalities | Abnormal rest–activity cycle | 3284 (27.9) |
| | Abnormal diet rhythm | 2059 (17.5) |
| | Abnormal wake up rhythm | 3377 (28.7) |
| | Abnormal sleep rhythm | 2904 (24.6) |
| Multiple circadian rhythm abnormalities | 0 | 7210 (61.2) |
| | 1 | 1231 (10.4) |
| | 2 | 919 (7.8) |
| | 3 | 1153 (9.8) |
| | 4 | 1274 (10.8) |
| The symptoms of depression | None | 8734 (74.1) |
| | Mild | 2022 (17.2) |
| | Moderate-severe | 1031 (8.7) |
| The symptoms of anxiety | None | 9689 (82.2) |
| | Mild | 1465 (12.4) |
| | Moderate-severe | 633 (5.4) |
Table 2
Distributions of mental problems among 11,787 undergraduate students.

|                         | The symptoms of depression | The symptoms of Anxiety | P value |
|-------------------------|----------------------------|-------------------------|---------|
| Age                     |                            |                         |         |
|                         | Mild                       | Moderate-severe         | 0.16    |
|                         | 20.42 ± 1.72               | 20.54 ± 1.71            |         |
| Gender                  |                            |                         | 0.001   |
| Males                   | 709 (14.0)                 | 422 (8.3)               |         |
| Females                 | 1313 (19.5)                | 609 (9.0)               |         |
| Types of faculty        |                            |                         | <0.001  |
| Medical                 | 898 (15.6)                 | 440 (7.6)               |         |
| Non-medical             | 1124 (18.7)                | 591 (9.8)               |         |
| School location         |                            |                         | <0.001  |
| Hubei provinces         | 924 (18.9)                 | 469 (9.6)               |         |
| Adjacent provinces of Hubei | 480 (17.1)  | 217 (7.8)               |         |
| Others                  | 618 (15.1)                 | 345 (8.4)               |         |
| Current location        |                            |                         | 0.001   |
| Wuhan city              | 114 (19.1)                 | 73 (12.2)               |         |
| Other cities in Hubei   | 409 (18.3)                 | 170 (7.6)               |         |
| Adjacent provinces of Hubei | 481 (17.5)  | 237 (8.6)               |         |
| Others                  | 1018 (16.4)                | 551 (8.9)               |         |
| Grade                   |                            |                         | <0.001  |
| Year 1                  | 484 (16.5)                 | 224 (7.6)               |         |
| Year 2                  | 453 (17.4)                 | 254 (9.7)               |         |
| Year 3                  | 481 (18.0)                 | 243 (9.1)               |         |
| Year 4                  | 407 (17.6)                 | 212 (9.2)               |         |
| Year 5                  | 197 (15.5)                 | 98 (7.7)                |         |
| Residential area        |                            |                         | 0.001   |
| Rural                   | 942 (16.6)                 | 489 (8.6)               |         |
| Urban                   | 1080 (17.6)                | 542 (8.8)               |         |
| Exercise at home        |                            |                         | <0.001  |
| No                      | 861 (18.7)                 | 542 (11.8)              |         |
| Yes, regularly          | 224 (13.6)                 | 113 (6.8)               |         |
| Yes, irregular          | 937 (16.9)                 | 376 (6.8)               |         |
| Screen time             |                            |                         | <0.001  |
| Less than 2 h/d         | 336 (13.4)                 | 220 (8.8)               |         |
| 2 h/d or more           | 1686 (18.2)                | 811 (8.7)               |         |
| Browsing the COVID-19 information | 1693 (16.7) | 795 (7.8) |         |
| Less than 2 h/d         | 329 (20.0)                 | 236 (14.4)              |         |
| Fear of infection       |                            |                         | <0.001  |
| Yes                     | 1780 (18.7)                | 875 (9.2)               |         |
| No                      | 242 (10.6)                 | 156 (6.8)               |         |
| Any housework           |                            |                         | <0.001  |
| Yes                     | 1719 (16.9)                | 790 (7.8)               |         |
| No                      | 303 (18.7)                 | 241 (14.8)              |         |
| Argued with others      |                            |                         | <0.001  |
| Yes                     | 734 (26.0)                 | 510 (18.1)              |         |
| No                      | 1288 (14.4)                | 521 (5.8)               |         |

Table 3
Prevalence of mental problems in different groups of circadian rhythm abnormalities.

|                         | The symptoms of depression | The symptoms of Anxiety | P value |
|-------------------------|----------------------------|-------------------------|---------|
| Rest-activity cycle     |                            |                         | <0.001  |
| Normal                  | 6860 (80.7)                | 1186 (13.9)             |         |
| Abnormal                | 1874 (57.1)                | 836 (25.5)              |         |
| Diet rhythm             |                            |                         | <0.001  |
| Normal                  | 7614 (78.3)                | 1487 (15.3)             |         |
| Abnormal                | 1120 (54.4)                | 535 (26.0)              |         |
| Wake up rhythm          |                            |                         | <0.001  |
| Normal                  | 6729 (80.0)                | 1188 (14.1)             |         |
| Abnormal                | 2005 (59.4)                | 834 (24.7)              |         |
| Sleep rhythm            |                            |                         | <0.001  |
| Normal                  | 7123 (80.2)                | 1263 (14.2)             |         |
| Abnormal                | 1611 (55.5)                | 759 (26.1)              |         |
| Multiple circadian rhythm abnormalities | 0 | 5968 (82.8) | 909 (12.6) | <0.001 |
|                         | 1                         | 862 (70.0)              | 246 (9.0) |         |
|                         | 2                         | 599 (65.2)              | 211 (23.0) |         |
|                         | 3                         | 670 (58.1)              | 328 (28.4) |         |
|                         | 4                         | 635 (49.8)              | 328 (25.7) |         |
|                         | None                      | Mild                    | Moderate-severe |         |
|                         | 6860 (80.7)                | 1186 (13.9)             | 457 (5.4) |         |
|                         | 1874 (57.1)                | 836 (25.5)              | 574 (17.5) |         |
|                         | 7614 (78.3)                | 1487 (15.3)             | 627 (6.4) |         |
|                         | 1120 (54.4)                | 535 (26.0)              | 404 (19.6) |         |
|                         | 6729 (80.0)                | 1188 (14.1)             | 493 (5.9) |         |
|                         | 2005 (59.4)                | 834 (24.7)              | 538 (15.9) |         |
|                         | 7123 (80.2)                | 1263 (14.2)             | 497 (5.6) |         |
|                         | 1611 (55.5)                | 759 (26.1)              | 534 (18.4) |         |
|                         | None                      | Mild                    | Moderate-severe |         |
|                         | 6860 (80.7)                | 1186 (13.9)             | 457 (5.4) |         |
|                         | 1874 (57.1)                | 836 (25.5)              | 574 (17.5) |         |
|                         | 7614 (78.3)                | 1487 (15.3)             | 627 (6.4) |         |
|                         | 1120 (54.4)                | 535 (26.0)              | 404 (19.6) |         |
|                         | 6729 (80.0)                | 1188 (14.1)             | 493 (5.9) |         |
|                         | 2005 (59.4)                | 834 (24.7)              | 538 (15.9) |         |
|                         | 7123 (80.2)                | 1263 (14.2)             | 497 (5.6) |         |
|                         | 1611 (55.5)                | 759 (26.1)              | 534 (18.4) |         |
shown in Table 4, and dose–response relationships were found. However, Fig. 1 showed that the associations between sub-classifications of multiple circadian rhythm abnormalities and depressive symptoms or the symptoms of anxiety were discrepant. A combination of four circadian rhythm abnormalities has the supreme effect on depressive symptoms, but students who reported the coexistence of abnormal rest–activity cycle; diet rhythm; wake up rhythm; and sleep rhythm were more likely to be with the symptoms of anxiety. If students have a certain combination of abnormal wake up rhythm, the associations of circadian rhythm abnormalities and mental health might be less severe. The reasons are difficult to figure out, but it might be explained because some previous studies indicated that students delayed their weekday wake-up time (15 min) showed improved mental health [28], and delaying school start time benefits adolescent sleep and mental well-being [29]. Therefore, we speculate that irregular waking time (getting up later) might attenuate the associations of other phenotypes of circadian rhythm abnormalities and the mental health.

The underlying mechanisms for the associations between circadian rhythm abnormalities and mental health are driven by clock genes. A systematic review showed that circadian genes CRY1, CRY2, PER2 and NPAS2 have a higher risks for major depressive disorder [30]. There is relatively few findings on the role of clock genes in anxiety disorders. A animal experiment show that lack of CRY 1 and 2 proteins show an abnormally high level of anxiety in mice [31]. Although researches in adolescents or young adults on clock genes and mental health are still less, clock genes provide novel strategies for intervention of mental disorders. The circadian rhythm is also a vital regulator of a variety of systems which play a role in the development of mood disorders, such as monoamine signaling, immune function, HPA axis regulation, metabolic peptides, redox/mitochondria/apoptosis, and neurogenesis [32].

Whether circadian rhythm abnormalities might be the cause or the effect of mental disorder remains unclear because of the cross-sectional nature of the study. Secondly, most of the measurements in our study are subjective and information biases might distort the association. Future work with prospective design and objective measurements (eg accelerometry data, melatonin levels, clinical interview) are warranted. In addition, lifestyle would be quite different if college students were living with parents/grandparents than college students living by themselves. The covariates adjusted did not include many household level factors, such as how many people were living with them and who they were. However, the majority of Chinese undergraduates were living with family, so the influences of family factors can be mitigated. Given that the circadian timing system changes during adolescence, older adolescents prefer later timing of activities than younger students [33]. The present study is conducted in a sample of nationwide university-based students.
as Holmes EA et al. [34] proposed that population-based studies on mental health and COVID-19 should be established by using epidemiologically methodology for both the whole population and specific groups (eg children and young people), which could more persuasively deepen our understanding of the causes and prevention of mental problems during the COVID-19 outbreak. Finally, non-respondent bias can not be avoided in our study; however, as listed in supplemental file, the sample size based on the research design is basically obtained, which might reduce the impact of non-respondent bias.

In summary, evidence based on observational data indicates the associations between circadian rhythm abnormalities caused by home quarantine during the COVID-19 outbreak and mental problems among university students. It is urgent to established normal circadian rhythm and maintains a healthy routine which might reduce the burden of mental problems during the COVID-19 epidemic period.

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Authors' contributions

Shuman Tao: Writing - Original Draft, Investigation, Formal analysis, Data Curation.
Xiaoyan Wu: Investigation, Writing - Review & Editing, Project administration.
Shiyue Li: Investigation.
Le Ma: Investigation.
Yizhen Yu: Investigation.
Guilong Sun: Investigation.
Yi Zhang: Investigation.
Tingting Li: Investigation.
Fangbiao Tao: Conceptualization, Writing - Review & Editing, Supervision, Funding acquisition.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Anhui Medical University. Electronic informed consents were obtained from all participants before completing the survey, which was conducted in accordance with the principles of the Declaration of Helsinki.

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Conflict of interest

The authors declare there are no competing interests.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2021.05.028.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2021.05.028.

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