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Moderating effects of insomnia on the association between urinary phthalate metabolites and depressive symptoms in Chinese college students: focus on gender differences

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Abstract

Objectives To investigate the rates of depressive symptoms in college students, explore the relationship between urinary phthalate metabolites and depressive symptoms and their gender differences, and further explore the moderating role of insomnia in this association.

Methods A total of 1 179 college students were recruited from 2 universities in Hefei and Shangrao cities from April to May 2019. The depressive symptoms and insomnia of college students were investigated by the Patient Health Questionnaire 9 and Insomnia Severity Index. The high-performance liquid chromatography-tandem mass spectrometry was adapted to determine the concentration of urinary phthalate metabolites. The generalized linear model was used to analyze the relationship of phthalate metabolites with depressive symptoms. Moderating analysis was used to examine whether insomnia moderated the relationship of phthalate metabolites with depressive symptoms.

Results The rates of mild depression, and moderate depression and above in college students were 31.9% and 9.2%, respectively. The phthalate metabolites exhibited a median and mean concentration spanning from 2.98 ~ 156.55 ng/mL and 6.12 ~ 205.53 ng/mL. The generalized linear model results showed that monobutyl phthalate (MBP) ($\beta = 1.160$, 95%*CI*: 0.423 ~ 1.896) and low molecular weight phthalate (LMWP) ($\beta = 1.230$, 95%*CI*: 0.348 ~ 2.113) were positively correlated with depressive symptoms, and MBP ($\beta = 1.320$, 95%*CI*: 0.453 ~ 2.187) and LMWP ($\beta = 1.396$, 95%*CI*: 0.351 ~ 2.440) were positively correlated with depressive symptoms only in female college students after stratified by

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gender. Furthermore, insomnia has a positive moderating role between MBP, LMWP, and depressive symptoms and has a sex-based difference.

Conclusions This study suggests that there is a positive association of phthalate metabolites with depressive symptoms among Chinese college students, as well as insomnia plays a positive moderating role in this association.

Keywords Phthalate metabolites, Depressive symptoms, Insomnia, College students

Introduction

College students are in a critical period of transitioning from adolescence to adulthood. Due to the decrease in social support, the change in social roles, and the increase in pressure, college students are more prone to developing depressive symptoms and other mental health problems [1]. A systematic review and meta-analysis of the rates of depressive symptoms among university students showed that the prevalence of depressive symptoms among university students was between 2.9% and 71.0% from 2009 to 2018, with a overall prevalence of 24.4% [2]. Another systematic review and meta-analysis on the incidence of depressive symptoms among Chinese university students revealed an approximate prevalence rate of 28.4% among this population [3]. Furthermore, in 2019, as the COVID-19 pandemic spread globally, it adversely affected the mental health of university students, leading to a heightened incidence of depression [4]. A meta-analysis revealed that the pooled incidence of depressive symptoms among university students worldwide during the COVID-19 pandemic was 34.0% [5]. These studies show that college students are at high-risk group for the occurrence of depressive symptoms. At present, various risk factors contributing to depressive symptoms among college students have been identified, such as sleep problems [6], insufficient physical activity [7], adverse childhood experiences [8] and so on. Meanwhile, more and more evidence suggests that phthalate exposure is associated with depressive symptoms [9, 10].

Phthalates, a class of widely employed non-persistent chemicals, serve as plasticizers to make several materials with temperature tolerance, malleability, and flexibility [11]. According to the different lengths of the carbon chain, phthalates are categorized into two distinct groups: high-molecular-weight phthalates and low-molecular-weight phthalates [12]. Exposure to high-molecular-weight phthalate compounds predominantly arises from dietary sources, while the presence of low-molecular-weight phthalate metabolites in the body can be attributed to diverse origins, including indoor air exposure, dust inhalation, and the use of personal care products [13]. Since phthalates exist in many consumer products, they frequently escape into the environment, elevating human exposure levels [14]. Human biomonitoring studies collect urine samples to evaluate phthalate exposure in individuals, given that the majority of metabolites of phthalate are eliminated through urine within a 48-hour period [15]. Interestingly, human biomonitoring studies have shown the presence of phthalates in urine samples across all age groups, and with females exhibiting higher concentrations than males [16]. In part, due to female using more personal care products and cosmetics, and therefore an increased susceptibility to skin phthalate exposure [15, 17]. This finding underscores the potential for a gender disparity in both the exposure to and the health impacts of phthalates on individuals [18].

Animal studies have revealed that phthalates exposure can affect brain development, alter the formation of the hippocampal, as well as lead to changes in emotions and behavior [12]. Furthermore, phthalates exposure not only disrupts glutamate and glutamine homeostasis, as well as glutamatergic neurotransmission activity in mice, inducing depressive behaviors [19], but also impairs the hypothalamic-pituitary-thyroid axis balance in rats, causing a decrease in serum thyroid hormone levels, which have been associated with psychological and behavioral problems [20]. For example, a study on mice showed that phthalate exposure can result in depression-like behavior and increase oxidative stress within the brain [21]. Similarly, another study on mice has uncovered that perinatal exposure to phthalates can have transgenerational effects, resulting in the manifestation of depression-like behaviors in the offspring [22]. In addition, a Korean study on the elderly revealed an association between elevated levels of specific phthalate metabolites and a heightened risk of developing depressive symptoms [23]. A United States study on general adults likewise revealed a positive correlation between certain phthalate metabolites and depressive symptoms [10]. Due to phthalates have reproductive toxicity similar to estrogen and antiandrogens [23]. Consequently, the occurrence of depressive symptoms may also be linked to the hormonal disruptions caused by phthalate exposure, given that the brain can be regulated by hormonal signals [24].

Previous research has already revealed the relationship of phthalate exposure with sleep problems [25, 26]. For instance, a study in the United States on females aged 20–39 found that phthalate exposure may increase their risk of developing sleep problems [27]. Similarly, another study using data from the 2005–2010 National Health and Nutrition Examination Survey cycle found that higher concentrations of several phthalate metabolites in urine among adolescents were associated with shorter sleep duration [28]. Animal studies have indicated that phthalates can disrupt the circadian rhythms of zebrafish, resulting in behavioral changes, increased daytime sleep, and reduced sleep latency [29]. Moreover, phthalates may disrupt neural circuits and hinder the maturation of hormone-mediated mechanisms essential for regulating sleep [30]. Specifically, phthalates have been linked to disrupting progesterone, cortisol, estrogen, and testosterone, all critical hormones regulating sleep [31]. At the same time, some research have suggested that sleep problems are also a significant predictor of the onset of depressive symptoms [31, 32]. Studies have demonstrated that insomnia can interfere with the brain's limbic circuits' ability to adapt at nighttime and resolve emotional distress at nighttime, thereby increasing the risk of developing mental disorders [33]. For example, a study on students from 4 universities in Yunnan province, China, found that insomnia was positively associated with depressive symptoms [34]. Another study on United States college students also found that compared to normal sleep, insomnia was associated with more depressive symptoms [35]. However, whether sleep issues play an important role in the correlation of phthalate exposure with depressive symptoms remains to be further investigated.

Therefore, to address these gaps, we conducted an epidemiological investigation to examine the association between phthalate metabolites, insomnia, and depressive symptoms among Chinese college students. The objectives of this study are threefold: (a) to investigate the rates of depressive symptoms in Chinese college students, (b) to examine the correlation of phthalate metabolites with depressive symptoms in Chinese college students and their gender differences, and (c) to further explore the moderating role of insomnia in the correlation of phthalate metabolites with depressive symptoms.

Methods

Participants

This survey was conducted in 2 universities in Shangrao, Jiangxi Province and Hefei, Anhui Province, China from April to May 2019. Firstly, a normal university in Shangrao City and a medical university in Hefei City were selected by convenient sampling. Subsequently, chemistry major and sports major in normal university, as well as public health major and nursing major in medical universities were selected by stratified cluster sampling. Finally, a comprehensive survey of all freshmen in these majors was conducted. Screening for depression among college freshmen could help identify students at risk for depression, thereby enhancing the development and implementation of targeted preventive interventions [36]. In the present study, a total of 1 179 freshmen were involved, 1 135 freshmen completed the questionnaire, and 1 012 freshmen provided urine samples for phthalate metabolites analysis. Before conducting the survey, all freshmen were given a unique code. Then, after matching the questionnaire data with urine sample data according to the freshmen' unique codes, the final data comprised 903 valid cases. The average age of the 903 freshmen surveyed was 18.7 years (SD = 1.2), and 31.6% (285/903) were male. The inclusion criteria were as follows: providing written informed consent; submitting a valid questionnaire; providing valid urine samples; no clinically diagnosed mental illness. The inclusion criteria in the analysis were as follows: both data of questionnaire and urinary phthalate metabolites were valid. Exclusion criteria: all participants who do not meet the above inclusion criteria are excluded.

Procedures

In this study, freshman gathered in a classroom and completed an electronic questionnaire utilizing their smartphones. The process generally lasted between 10 ~ 20 min after the investigators introduces the objectives of the investigation, and principles of anonymity, confidentiality, and voluntary participation. Upon finishing the questionnaire, each freshmen willingly submitted a morning urine sample, which was gathered in a 15 mL polypropylene tube for subsequent analysis. The urine samples underwent centrifugation at a speed of 3500 revolutions per minute for a duration of 10 min, following which the supernatant was extracted and stored in a polypropylene cryotube for further processing. The urine samples were temporarily stored in a -20 ℃ refrigerator for 1 ~ 2 week and long-term frozen in a -80 ℃ refrigerator in the laboratory of Anhui Medical University until analysis. The Ethics Committee of Anhui Medical University approved this study (NO: 20170291). All participants provided written informed consent prior to their involvement.

Sample size calculation

To determine the sample size, we used the evidence that approximately 28.4% of Chinese college students experience depressive symptoms [3]. We utilized the formula $S = Z^2 \times P \times (1-P)/M^2$ ($Z = 1.96$, representing the standard normal deviate for a 95% confidence level; $P = 28.4\%$, reflecting the proportion of students with depressive symptoms; $M = 0.05$, denoting a 5% margin of error) to calculate a sample size was 312 [37]. Consequently, the sample size of 903 college students for this study was fully met.

Questionnaire survey data

A questionnaire was utilized to collect information, encompassing age, gender, height, weight, major (public health, nursing, chemistry, sports), residence area (rural, urban), number of siblings (0, ≥ 1), family economy status, monthly living expenses, learning burden, academic performance, number of friends, parental education level, bodily form, physical activity level, sleep quality, smoking, drinking, family history of depression, family accidents, hospitalization experiences, insomnia, and depressive symptoms.

Family economy was evaluated through the question: "How do you perceive your family's economic condition compared to other students?" The answers were reclassified as "high", "medium" and "low". Monthly living expenses (Yuan) were categorized as "<1 000", "1 000 ~ 1 500", "1 501 ~ 2 000", and ">2 000". To assess learning burden, participants were asked: "How much burden do you feel by studying recently?" The answers were categorized as "much", "some", and "a little". Academic performance was assessed by asking: "How do you think your academic performance is in your class?" Responses were recoded into "poor", "average", and "good". Number of friends was reclassified as "0 ~ 2", "3 ~ 5", and "≥6" [38]. The parental education level was recoded into "senior high school and above", "middle school", and "primary school and below". Bodily form was assessed by asking: "What type of body do you think you have?" The answers were recoded as "thin", "medium", and "fat".

Body mass index (BMI) was calculated by dividing weight by the square of height. Based on Chinese standards, college students aged 18 and above were categorized into four weight statuses: underweight (< 18.5 kg/m^2), normal weight (18.5 to 23.9 kg/m^2), overweight (24.0 to 27.9 kg/m^2), and obesity (≥ 28.0 kg/m^2) [39]. For college students under 18 years of age, BMI percentiles were used to determine their weight status and were classified into four categories: underweight (BMI < 5th percentile), normal weight (5th-≤BMI < 85th percentile), overweight (85th-≤BMI < 95th percentile), and obesity (BMI ≥ 95th percentile) [40].

The International Physical Activity Questionnaire Short Form (IPAQ-SF) was used to assess the physical activity levels of college students in the past week [41]. Total physical activity was computed by metabolic equivalents (METs) × hour/week. Subsequently, physical activity was categorized into three levels: low, middle, and high [42].

College students' sleep quality over the past month was assessed utilizing the Pittsburgh Sleep Quality Index (PSQI) [43]. The score range of the scale is 0 to 21, where a score of ≥ 8 signifies poor sleep quality, whereas a score of < 8 indicates good sleep quality [44]. The PSQI has been verified among Chinese college students and has demonstrated good validity and reliability [44].

Current smoking and alcohol use of college student were assessed using the Young Risk Behavior Surveillance System questionnaire [45]. Smoking status was determined by the question: "In the past month, how many days did you smoke at least one cigarette per day?" Similarly, alcohol use was evaluated by asking: "In the past month, how many days did you have at least one drink per day?" Responses of "<1 day" were considered as "no", whereas responses of "≥1 day" were deemed as "yes".

Family history of depression was assessed by asking "Do you have a family history of depression (i.e., one or more family members including father, mother, or siblings have been diagnosed with depression)?" Family accidents was assessed by asking "In the last year, have you experienced a family accidents (such as divorce of parents)?" Hospitalization was assessed by asking "Have you been hospitalized in the last year (e.g., sick, injured, etc.)?" Responses were categorized as "yes" and "no".

The Insomnia Severity Index (ISI) was adopted to measure the insomnia symptoms of college students in the past two weeks [46]. The ISI is a self-reported measurement designed to evaluate the extent of insomnia severity. The measure comprises 7 distinct items, yielding a total score that spans from 0 to 28. The higher the score, the more severe the insomnia is considered to be. A score of ≥ 9 is indicative of insomnia, while a score of < 9 signifies no insomnia. The ISI has been verified in the Chinese populations, demonstrating robust reliability and validity [47].

College students' depressive symptoms over the past month were assessed using the Patient Health Questionnaire 9 (PHQ-9) [48]. The PHQ-9 is a questionnaire with 9 items, and each item is scored from 0 ~ 3 using the Likert scale. The score range of the scale is 0 to 27, where higher scores serve as an indicator of more severe depressive symptoms. A score of ≤ 4 indicates no depression, whereas a score ranging from 5 to 9 indicates mild depression, and a score of ≥ 10 indicates moderate depression and above. The PHQ-9 has undergone validation in the Chinese population, demonstrating its robust validity and reliability in accurately assessing depressive symptoms [49].

Urinary phthalate metabolites analysis

Our prior reports have detailed the procedures employed for the analysis of urinary phthalate metabolites [12]. Briefly, we used high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS-MS) (6410LC-MS, Agilent Technologies Co., Santa Clara, CA, USA) to analyze 6 phthalate metabolites, including monobutyl phthalate (MBP), monoethyl phthalate (MEP), monomethyl phthalate (MMP), mono-2-ethylhexyl phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), and mono(2-ethyl-5-oxohexyl) phthalate (MEOHP). Furthermore, in this study, the method used by Zota et al. was used to calculate the concentration of high molecular weight phthalate (HMWP) metabolites and low molecular weight phthalate (LMWP) metabolites [50, 51]. HMWP were equal to the sum of the molar concentrations of MEHP, MEHHP, and MEOHP. LMWP were equal to the sum of the molar concentrations of MBP, MEP, and MMP.

Covariates

In this study, variables with statistically significant difference in the detection rate of depressive symptoms in college student were used as covariates (Table 1). Thus, confounding factors controlled for in this study included age, major, academic performance, number of friends, paternal education level, self-rated bodily form, sleep quality, smoking, drinking, family history of depression, and hospitalization experiences.

Statistical analysis

In this research, when the concentrations of urinary phthalate metabolites were below the limits of detection (LOD), it was substituted with a value calculated as the LOD divided by the square root of 2 [52]. We employed urine specific gravity (SG) to correct the individual urinary phthalate metabolite concentrations to account for variations in urine dilution among individuals [53]. All of the SG-calibrated concentrations were subsequently transformed into log-10.

All statistical analyses were carried out utilizing SPSS 23.0 software. Categorical variables were presented as frequency (percentages) and continuous variables were reported as mean ± standard deviation. The measured non-normal distribution was represented by the median and interquartile range. The chi-square test was adopted to compare the prevalence of depressive symptoms in college students. Pearson correlations between phthalate metabolites, insomnia, and depressive symptoms were calculated. The generalized linear model was adopted to determine the relationship between urinary phthalate metabolites, insomnia, and depressive symptoms. We calculated β value and 95% confidence intervals (95%*CI*) for the explanatory factors, with adjustments made for potential confounding factors. Utilizing the PROCESS plug-in within SPSS software, we conducted an analysis to examine the moderating role of insomnia on the correlation of phthalate metabolites with depressive symptoms. Within the PROCESS plug-in, model 1 was chosen and the confidence interval was set to 95%. Prior to conducting the moderation analyses, we employed mean centering to mitigate multicollinearity. A two-tailed P value < 0.05 was considered statistically significant.

Results

Distribution of depressive symptoms among college students

In this research, the rates of mild depression, and moderate depression and above among college students was 31.9% and 9.2%, respectively. The prevalence of moderate depression and above in college students was sport majors > chemistry majors > public health majors > nursing majors ($P < 0.05$). The prevalence of moderate depression and above in college students whose number of friends was 0 ~ 2 was higher than that of college students whose number of friends was 3 ~ 5, ≥6 ($P < 0.05$). The prevalence of moderate depression and above in students whose father's education level was primary school and below was higher than that of students whose father's education level was middle school, senior high school and above ($P < 0.05$). The prevalence of moderate depression and above of college students with a poor academic performance, fat bodily form, poor sleep quality, smoking, drinking, family history of depression, hospitalization, and insomnia was higher than that in those with a average or good academic performance, medium or thin bodily form, good sleep quality, no smoking, no drinking, no family history of depression, no hospitalization, and no insomnia ($P < 0.05$). However, there was no statistically significant difference in other variables ($P > 0.05$). As shown in Table 1.

Distribution of phthalate metabolites concentration and SG-calibrateds concentration among college students

In this study, MBP, MEP, MMP, MEHP, MEHHP, and MEOHP of the college students were detected in 99.6%, 99.1%, 98.3%, 79.2%, 99.6%, and 99.7%, respectively. Table 2 displays the distribution of urinary phthalate metabolites concentration, along with their respective SG-calibrated concentration. The SG-standardized concentrations (median) of MBP, MEP, MMP, MEHP, MEHHP, MEOHP, LMWP, and HMWP were 123.71 ng/mL, 17.62 ng/mL, 10.20 ng/mL, 2.98 ng/mL, 14.63 ng/mL, 8.88 ng/mL, 156.55 ng/mL, and 26.11 ng/mL, respectively. According to gender and further stratified analysis, in male college students, the SG-standardized concentrations (median) of MBP, MEP, MMP, MEHP, MEHHP, MEOHP, LMWP, and HMWP were 131.24 ng/mL, 15.75 ng/mL, 10.24 ng/mL, 3.06 ng/mL, 14.26 ng/mL, 8.73 ng/mL, 162.42 ng/mL, and 25.59 ng/mL, respectively. In female college students, the SG-standardized concentrations (median) of MBP, MEP, MMP, MEHP, MEHHP, MEOHP, LMWP, and HMWP were 119.05 ng/mL, 18.69 ng/mL, 10.09 ng/mL, 2.88 ng/mL, 14.94 ng/mL, 8.91 ng/mL, 153.93 ng/mL, and 26.72 ng/mL, respectively.

Table 1 Distribution of depressive symptoms in college students

Variable	n (%)	Depressive symptoms			χ^2 value	P value
		No depression	Mild depression	Moderate depression and above		
Gender					1.54	0.463
Male	285(31.6)	167(58.6)	87(30.5)	31(10.9)		
Female	618(68.4)	365(59.1)	201(32.5)	52(8.4)		
Major					14.76	0.022
Public health	223(24.7)	146(65.5)	61(27.4)	16(7.1)		
Nursing	326(36.1)	193(59.2)	112(34.4)	21(6.4)		
Chemistry	178(19.7)	99(55.6)	58(32.6)	21(11.8)		
Sports	176(19.5)	94(53.4)	57(32.4)	25(14.2)		
Residential area					5.97	0.051
Rural	497(55.0)	276(55.5)	175(35.2)	46(9.3)		
Urban	406(45.0)	256(63.1)	113(27.8)	37(9.1)		
Number of siblings					0.33	0.848
0	228(25.2)	138(60.5)	70(30.7)	20(8.8)		
≥ 1	675(74.8)	394(58.4)	218(32.3)	63(9.3)		
Self-reported family economy					6.17	0.187
Low	204(22.6)	110(53.9)	71(34.8)	23(11.3)		
Medium	645(71.4)	384(59.5)	206(31.9)	55(8.6)		
High	54(6.0)	38(70.4)	11(20.4)	5(9.2)		
Monthly living expenses (Yuan)					8.75	0.188
< 1000	181(20.0)	105(58.0)	61(33.7)	15(8.3)		
1000～1500	565(62.6)	323(57.2)	189(33.5)	53(9.3)		
1501～2000	119(13.2)	78(65.5)	32(26.9)	9(7.6)		
> 2000	38(4.2)	26(68.4)	6(15.8)	6(15.8)		
Self-reported learning burden					8.34	0.080
A little	14(1.6)	9(64.3)	3(21.4)	2(14.3)		
Some	545(60.4)	340(62.4)	159(29.2)	46(8.4)		
Much	344(38.0)	183(53.2)	126(36.6)	35(10.2)		
Self-reported academic performance					19.75	0.001
Good	167(18.5)	101(60.5)	58(34.7)	8(4.8)		
Average	557(61.7)	331(59.4)	182(32.7)	44(7.9)		
Poor	179(19.8)	100(55.9)	48(26.8)	31(17.3)		
Number of friends					19.14	0.001
0～2	101(11.2)	43(42.6)	45(44.6)	13(12.8)		
3～5	247(27.4)	135(54.7)	84(34.0)	28(11.3)		
≥ 6	555(61.4)	354(63.8)	159(28.6)	42(7.6)		
Paternal education level					16.35	0.003
Primary school and below	191(21.2)	100(52.4)	63(33.0)	28(14.6)		
Middle school	434(48.1)	247(56.9)	151(34.8)	36(8.3)		
Senior high school and above	278(30.7)	185(66.5)	74(26.6)	19(6.8)		
Maternal education level					8.62	0.071
Primary school and below	393(43.5)	220(56.0)	129(32.8)	44(11.2)		
Middle school	316(35.0)	183(57.9)	109(34.5)	24(7.6)		
Senior high school and above	194(21.5)	129(66.5)	50(25.8)	15(7.7)		
Self-rated bodily form					13.45	0.009
Thin	225(24.9)	133(59.1)	72(32.0)	20(8.9)		
Medium	417(46.2)	265(63.5)	124(29.7)	28(6.8)		
Fat	261(28.9)	134(51.3)	92(35.2)	35(13.5)		
BMI groups					8.93	0.178
Underweight	150(16.6)	84(56.0)	51(34.0)	15(10.0)		
Normal weight	662(73.3)	400(60.4)	205(31.0)	57(8.6)		
Overweight	72(8.0)	39(54.2)	27(37.5)	6(8.3)		
Obesity	19(2.1)	9(47.4)	5(26.3)	5(26.3)		

Table 1 (continued)

Variable	n (%)	Depressive symptoms			χ^2 value	P value
		No depression	Mild depression	Moderate depression and above		
Physical activity level					7.88	0.096
Low	131(14.5)	69(52.7)	44(33.6)	18(13.7)		
Medium	469(51.9)	290(61.8)	146(31.1)	33(7.1)		
High	303(33.6)	173(57.1)	98(32.3)	32(10.6)		
Sleep quality					137.55	< 0.001
Good	798(88.4)	514(64.4)	239(29.9)	45(5.7)		
Poor	105(11.6)	18(17.1)	49(46.7)	38(36.2)		
Smoking					24.65	< 0.001
Yes	53(5.9)	25(47.2)	13(24.5)	15(28.3)		
No	850(94.1)	507(59.6)	275(32.4)	68(8.0)		
Drinking					16.36	< 0.001
Yes	184(20.4)	89(48.4)	66(35.9)	29(15.7)		
No	719(79.6)	443(61.6)	222(30.9)	54(7.5)		
Family history of depression					15.59	< 0.001
Yes	32(3.5)	12(37.5)	11(34.4)	9(28.1)		
No	871(96.5)	520(59.7)	277(31.8)	74(8.5)		
Family accidents					1.19	0.551
Yes	115(12.7)	63(54.8)	39(33.9)	13(11.3)		
No	788(87.3)	469(59.5)	249(31.6)	70(8.9)		
Hospitalization					8.05	0.018
Yes	95(10.5)	48(50.5)	31(32.6)	16(16.9)		
No	808(89.5)	484(59.9)	257(31.8)	67(8.3)		
Insomnia					217.14	< 0.001
Yes	119(13.2)	13(10.9)	57(47.9)	49(41.2)		
No	784(86.8)	519(66.2)	231(29.5)	34(4.3)		

Pearson correlations between phthalate metabolites, insomnia, and depressive symptoms

Pearson coefficients of correlation between phthalate metabolites, insomnia, and depressive symptoms were presented in the heatmap (Figs. 1, 2 and 3) and Table S1. The MBP ($r = 0.097$, $P < 0.05$), LMWP ($r = 0.084$, $P < 0.05$), and insomnia ($r = 0.671$, $P < 0.01$) were positively correlated with depressive symptoms. According to gender and further stratified analysis, in female college students, the MBP ($r = 0.130$, $P < 0.01$), LMWP ($r = 0.112$, $P < 0.05$), and insomnia ($r = 0.618$, $P < 0.01$) were positively correlated with depressive symptom, while only insomnia ($r = 0.761$, $P < 0.01$) was positively correlated with depressive symptoms among male college students.

Association between phthalate metabolites, insomnia, and depressive symptoms by adjusted generalized linear model

After controlling for age, major, self-reported academic performance, number of friends, paternal education level, self-rated bodily form, sleep quality, smoking, drinking, family history of depression, and hospitalization, the generalized linear model results showed that MBP ($\beta = 1.160$, 95%CI: 0.423 ~ 1.896), LMWP ($\beta = 1.230$, 95%CI: 0.348 ~ 2.113), and insomnia ($\beta = 0.656$, 95%CI: 0.597 ~ 0.716) were positively correlated with depressive symptoms. According to gender and further stratified analysis, in female college students, the generalized linear model results showed that MBP ($\beta = 1.320$, 95%CI: 0.453 ~ 2.187), LMWP ($\beta = 1.396$, 95%CI: 0.351 ~ 2.440), insomnia ($\beta = 0.608$, 95%CI: 0.532 ~ 0.684) were positively correlated with depressive symptoms. In male college students, the generalized linear model results showed that only insomnia ($\beta = 0.745$, 95%CI: 0.645 ~ 0.845) was positively correlated with depressive symptoms (Table 3).

Moderating effects of insomnia on the correlation of phthalate metabolites with depressive symptoms

After controlling for confounding factors, the moderating effects analysis revealed that insomnia had positive moderating effects between MBP, MEHP, LMWP, and depressive symptoms, with respective β values for the interaction terms of 0.21, 0.08, and 0.23. According to gender and further stratified analysis, in male college students, insomnia positively moderated the relationships between MEP, MMP, LMWP, and depressive symptoms, with respective β values for the interaction terms of 0.26, 0.43, and 0.27. In female college students, insomnia positively moderated the relationships between MBP, MEHHP, and depressive symptoms, with respective β values for the interaction terms of 0.22 and 0.20. As shown in Table 4.

Table 2 Distribution of phthalate metabolites concentration and SG-calibrateds concentration in college students

Gender	Phthalate metabolite	Concentration (ng/mL)	Percentiles								Detected (%)	*r* value	*P* value
			mean ± SD	5th	10th	25th	50th	75th	90th	95th			
Overall	MBP	Uncalibrated	158.36± 143.36	37.48	47.80	69.88	115.45	195.77	314.87	444.43	99.6	0.86	< 0.001
		SG-calibrated	171.74± 166.49	40.48	52.38	79.60	123.71	205.93	342.84	492.43			
	MEP	Uncalibrated	34.09± 65.62	3.72	5.30	8.99	16.82	34.12	70.79	120.23	99.1	0.92	< 0.001
		SG-calibrated	36.40± 64.11	4.98	6.08	9.96	17.62	35.28	80.12	139.91			
	MMP	Uncalibrated	12.95± 12.99	2.41	3.55	5.86	9.95	15.95	24.47	32.85	98.3	0.86	< 0.001
		SG-calibrated	13.21± 11.88	3.79	5.08	7.18	10.20	15.41	23.21	32.45			
	MEHP	Uncalibrated	5.65± 18.32	0.10	0.10	0.51	2.80	6.26	10.26	15.53	79.2	0.96	< 0.001
		SG-calibrated	6.12± 15.61	0.09	0.11	0.59	2.98	6.15	11.03	18.19			
	MEHHP	Uncalibrated	25.16± 72.43	4.51	5.91	8.79	13.81	22.45	37.11	57.01	99.6	0.84	< 0.001
		SG-calibrated	25.64± 61.31	5.53	6.79	9.78	14.63	22.91	40.56	64.08			
	MEOHP	Uncalibrated	14.97± 39.77	2.96	3.63	5.51	8.42	13.56	22.20	35.59	99.7	0.83	< 0.001
		SG-calibrated	15.20± 33.69	3.63	4.40	6.10	8.88	13.98	23.69	39.82			
	LMWP	Uncalibrated	190.97± 156.91	50.20	61.41	94.21	147.24	233.76	370.90	498.05	-	0.85	< 0.001
		SG-calibrated	205.53± 185.19	58.29	71.52	103.43	156.55	247.98	395.75	514.90			
	HMWP	Uncalibrated	45.70± 128.00	8.42	10.72	16.53	25.25	40.70	65.95	108.01	-	0.83	< 0.001
		SG-calibrated	46.45± 108.11	10.43	12.56	18.28	26.11	41.73	72.46	112.04			
Male	MBP	Uncalibrated	183.08± 155.74	46.38	57.09	86.32	142.13	218.73	356.73	460.06	99.6	0.92	< 0.001
		SG-calibrated	170.75± 140.43	43.82	51.95	81.75	131.24	213.69	316.94	457.52			
	MEP	Uncalibrated	38.16± 92.84	4.02	5.60	9.28	17.65	31.18	71.44	135.88	98.9	0.95	< 0.001
		SG-calibrated	32.93± 66.87	4.42	5.71	9.16	15.75	29.47	69.69	117.77			
	MMP	Uncalibrated	13.70± 10.30	3.36	4.65	7.22	11.27	17.42	24.26	30.31	98.9	0.91	< 0.001
		SG-calibrated	12.35± 9.91	4.43	5.12	7.12	10.24	15.15	19.43	25.52			
	MEHP	Uncalibrated	7.69± 21.14	0.10	0.10	1.14	3.35	6.82	11.90	22.19	85.6	0.98	< 0.001
		SG-calibrated	6.95± 16.00	0.08	0.11	1.26	3.06	6.34	11.67	24.03			
	MEHHP	Uncalibrated	33.56± 84.72	5.37	7.15	10.28	15.62	26.15	46.44	80.72	99.6	0.91	< 0.001
		SG-calibrated	29.37± 64.39	5.71	6.68	9.92	14.26	22.55	39.85	85.20			
	MEOHP	Uncalibrated	19.27± 46.01	3.38	4.32	6.36	9.43	15.26	25.41	41.37	99.6	0.91	< 0.001
		SG-calibrated	16.90± 35.36	3.44	4.41	6.04	8.73	13.81	23.85	44.54			
	LMWP	Uncalibrated	218.06± 175.92	57.24	75.08	110.17	180.98	257.42	393.72	522.06	-	0.91	< 0.001
		SG-calibrated	200.14± 147.72	56.94	68.39	104.18	162.42	249.77	350.98	479.49			
	HMWP	Uncalibrated	60.11± 149.69	9.84	12.61	18.40	28.16	47.19	83.31	137.80	-	0.90	< 0.001
		SG-calibrated	52.64± 113.93	9.54	12.55	18.71	25.59	42.43	71.73	143.58			
Female	MBP	Uncalibrated	146.97± 135.89	35.78	44.05	64.70	105.00	173.09	312.64	419.40	99.5	0.84	< 0.001
		SG-calibrated	172.19± 177.32	39.64	53.59	78.36	119.05	200.04	360.82	495.64			
	MEP	Uncalibrated	32.21± 48.12	3.55	5.07	8.71	16.51	34.88	70.92	115.41	99.2	0.91	< 0.001
		SG-calibrated	38.00± 62.79	5.16	6.26	10.14	18.69	37.64	83.16	147.93			
	MMP	Uncalibrated	12.60± 14.06	2.03	3.12	5.41	9.42	15.00	24.66	33.16	98.1	0.84	< 0.001
		SG-calibrated	13.61± 12.67	3.40	5.05	7.19	10.09	15.55	25.57	36.15			

Table 2 (continued)

Gender	Phthalate metabolite	Concentration (ng/mL)		Percentiles							Detected (%)	*r* value	*P* value
			mean ± SD	5th	10th	25th	50th	75th	90th	95th			
	MEHP	Uncalibrated	4.71± 16.80	0.10	0.10	0.12	2.49	5.92	9.31	13.36	76.2	0.96	< 0.001
		SG-calibrated	5.74± 15.43	0.09	0.11	0.27	2.88	6.10	10.45	17.83			
	MEHHP	Uncalibrated	21.29± 65.71	4.18	5.55	8.37	12.71	20.64	32.81	48.14	99.5	0.82	< 0.001
		SG-calibrated	23.91± 59.81	5.48	6.79	9.71	14.94	23.11	41.10	59.84			
	MEOHP	Uncalibrated	12.98± 36.40	2.75	3.43	5.27	8.04	12.89	20.48	32.67	99.7	0.80	< 0.001
		SG-calibrated	14.42± 32.89	3.68	4.40	6.13	8.91	14.13	24.03	37.69			
	LMWP	Uncalibrated	178.47± 145.77	47.10	57.67	87.46	137.70	215.44	361.63	495.19	-	0.83	< 0.001
		SG-calibrated	208.01± 200.19	59.61	73.09	102.88	153.93	245.12	404.27	532.74			
	HMWP	Uncalibrated	39.06± 116.17	7.80	9.98	15.42	23.91	37.29	60.83	97.24	-	0.81	< 0.001
		SG-calibrated	43.59± 105.29	10.59	12.54	17.88	26.72	41.66	72.73	109.46			

Discussion

The primary objective of this research was to investigate whether urinary phthalate metabolites were correlated with depressive symptoms among Chinese college students. Our research results indicate that MBP and LMWP were positively correlated with depressive symptoms among college students, and this association only remained for female college students after stratified by gender. Moreover, we further found that insomnia had positive moderating effects on the correlation of MBP and LMWP with depressive symptoms, as well as there were gender differences. This study offers valuable scientific insights that can significantly contribute to the prevention and control of depressive symptoms among college students.

In this study, the rates of mild depression, and moderate depression and above in college students was 31.9% and 9.2%, respectively. Compared with domestic and foreign studies, the rates of mild depression was at a higher level, while moderate depression and above were at a lower level. For example, a study of university students in Spain showed that the rates of mild depression, and moderate depression and above in university students were 7.5% and 10.9%, respectively [54]. Another study of university students in Poland showed that the prevalence of mild depression, and moderate depression and above in university students was 25.1% and 9.6%, respectively [55]. Likewise, a study of Chinese university students showed that the rates of mild depression, and moderate depression and above were 13.8% and 17.3%, respectively [56]. However, another study of 3 891 university students in China showed that the rate of both mild depression (14.8%) and moderate depression and above (7.7%) was lower than that of our study [57]. Meanwhile, we also found that the prevalence of mild depression was higher in females (32.5%) than in males (30.5%), while the prevalence of moderate depression and above was higher in males (10.9%) than in females (8.4%), but the difference was not statistically significant.

Additionally, the results of this study showed that urinary phthalate metabolites were detected in 79.2%~100.0% of study participants. The higher detection rate indicates that Chinese college students have widespread exposure to phthalates. This finding aligns with the results of a study on phthalate exposure among college students in China, which reported a detection rate of 98.0% [58]. While phthalate exposure is widespread among humans, the levels of exposure differ among various populations and even between gender. Several studies have found higher levels of urinary phthalate metabolites in women and non-white ethnic groups [59, 60]. Meanwhile, several studies have also revealed that females exhibit higher concentrations of phthalate metabolites compared to males, potentially attributable

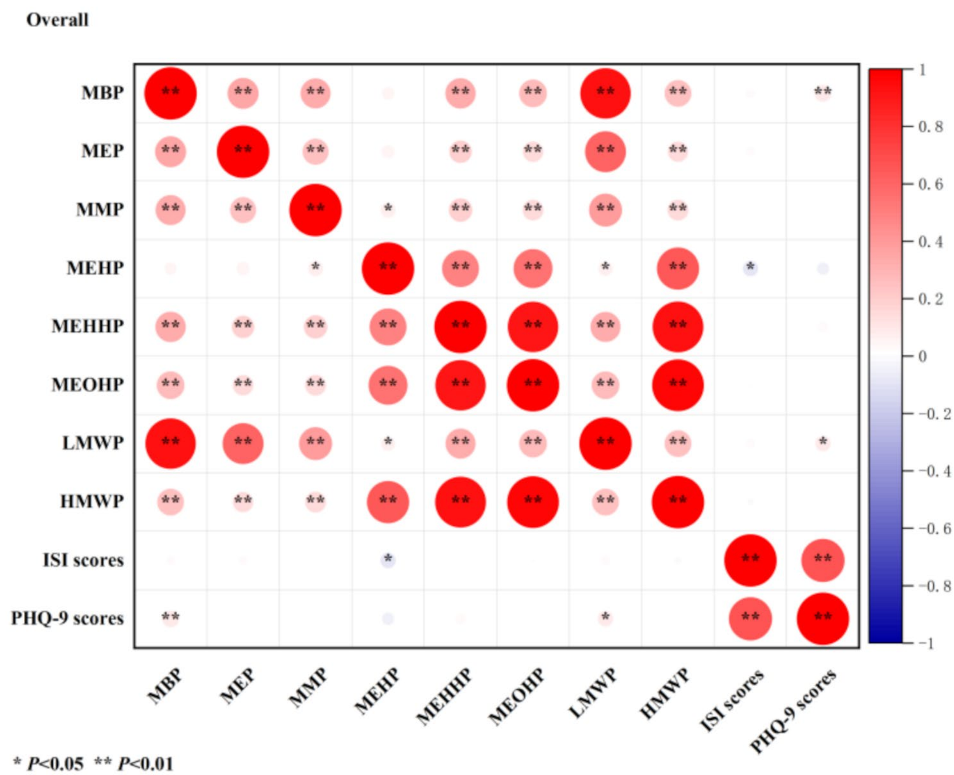

Fig. 1 Heatmap of the correlation of phthalate metabolites, insomnia, with depressive symptoms in college students

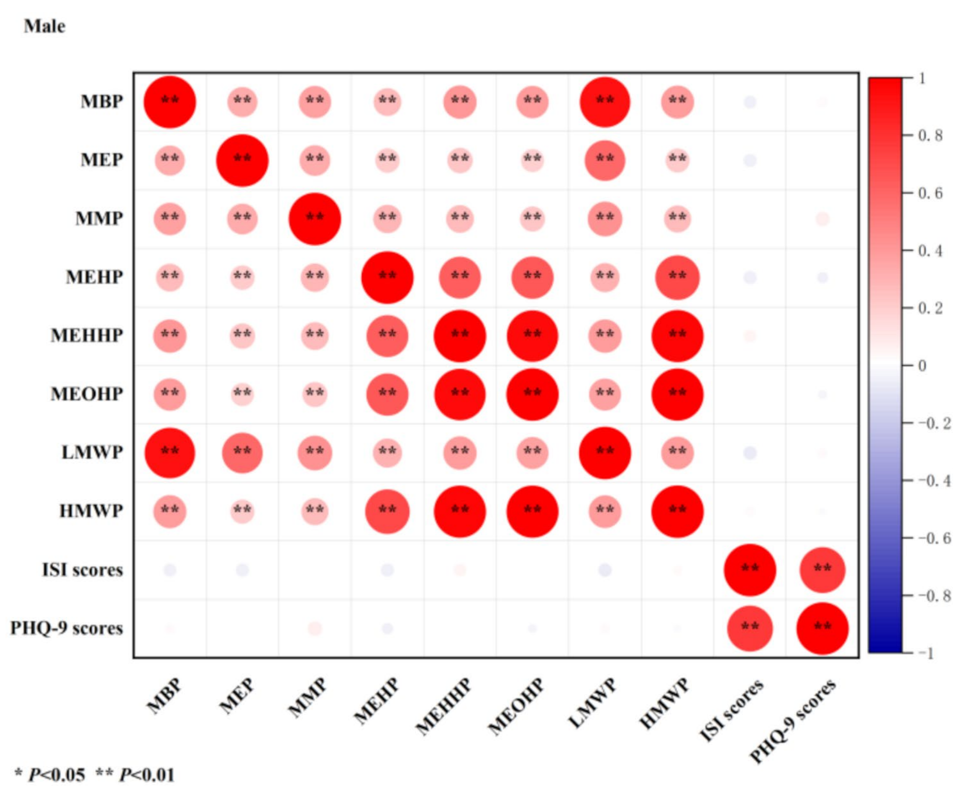

Fig. 2 Heatmap of the correlation of phthalate metabolites, insomnia, with depressive symptoms in male college students

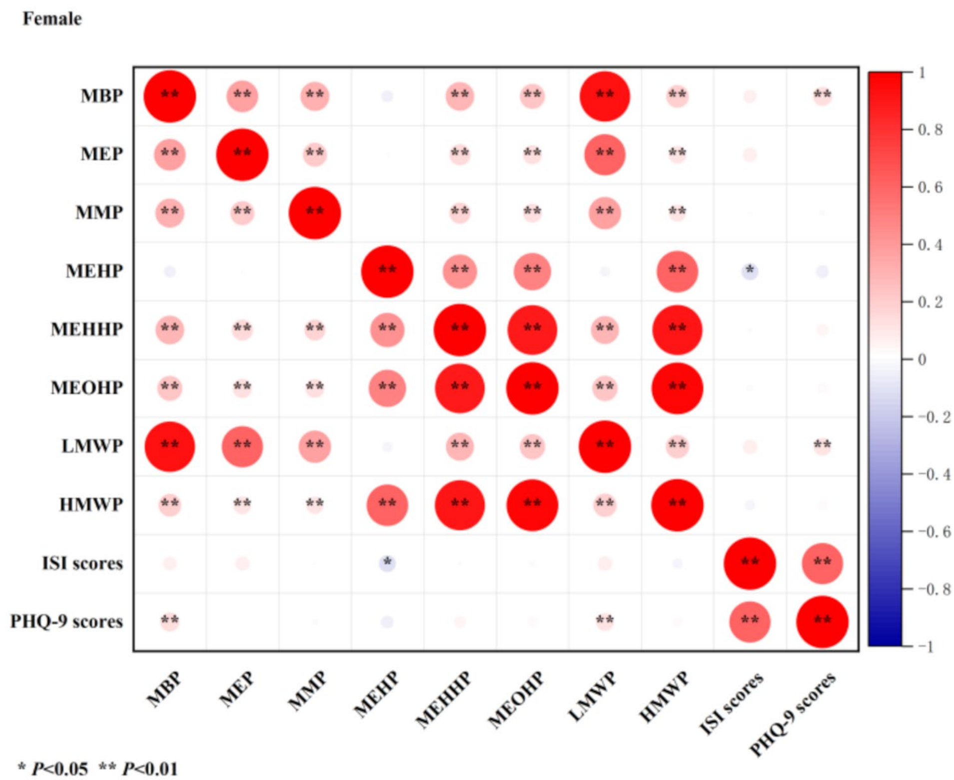

Fig. 3 Heatmap of the correlation of phthalate metabolites, insomnia, with depressive symptoms in female college students

to their higher use of personal hygiene products and cosmetics [61, 62]. In fact, studies frequently discover that phthalate metabolites are detectable in 99.0%~100.0% of samples provided by females [63]. However, another study conducted on adults in the United States revealed that males had higher levels of each phthalate metabolites compared to females [64]. In this study, we found that the SG-standardized concentrations (mean) of MBP, MEP, and LMWP was slightly higher in females than in males, while the SG-standardized concentrations (mean) of MMP, MEHP, MEHHP, MEOHP, and HMWP wass lightly higher in males than in females.

At present, there is growing concern about the relationship of phthalate exposure with depressive symptoms. However, current research have focused more on phthalate exposure in the elderly [24, 65] and adult populations [10] and rarely focused on college students. For example, a study of the elderly in Anhui Province, China found that the highest tertiles of MEHP and MBP were positively related to depressive symptoms [24]. Similarly, another study examining the adult population in the United States uncovered positive correlations between MEHHP and mono (2-ethyl-5-carboxypentyl) phthalate (MECPP) and depressive symptoms [10]. However, another survey using the National Health and Nutrition Examination Survey 2005–2008 data suggests no such association [66]. In this study, we found that the MBP and LMWP were positively correlated with depressive symptoms, and this association only remained for female college students after stratified by gender. One possible explanation is that females use more personal hygiene products and cosmetics, resulting in increased skin sensitivity to phthalate exposure [15, 17], which in turn contributes to the onset of depressive symptoms. Similarly, animal studies have aslo shown that perinatal phthalate exposure increases anxiety-like responses only in adult females mice [22]. However, a study involving 351 mother-child pairs revealed that higher urinary phthalate concentrations during the second trimester of pregnancy were correlated with higher scores for externalization and internalization problems only in boys [67].

Previous studies have suggested that phthalate exposure or sleep problems were risk factors for the development of depressive symptoms [10, 32]. However, the specific role that sleep problems play in the progression of depressive symptoms induced by phthalate exposure remains undiscovered and unexplored. In this survey, we found that insomnia had a positive moderating role on the correlation of MBP and LMWP with depressive symptoms, as well as there were gender differences. Our findings indicate that phthalate exposure may have a potential mechanism for increasing the risk of depressive symptoms through sleep problems. In fact, prior research has established that exposure to phthalates can

Table 3 Association between phthalate metabolites, insomnia, and depressive symptoms by adjusted generalized linear model

Gender	Variable	Depressive symptoms		
		β value	95% CI	*P* value
Overall	MBP	1.160	0.423 ~ 1.896	0.002
	MEP	0.141	−0.472 ~ 0.755	0.652
	MMP	0.144	−0.761 ~ 1.050	0.755
	MEHP	−0.120	−0.477 ~ 0.236	0.507
	MEHHP	0.280	−0.469 ~ 1.030	0.463
	MEOHP	0.070	−0.734 ~ 0.873	0.865
	LMWP	1.230	0.348 ~ 2.113	0.006
	HMWP	0.125	−0.660 ~ 0.910	0.755
	Insomnia	0.656	0.597 ~ 0.716	< 0.001
Male	MBP	0.737	−0.611 ~ 2.084	0.284
	MEP	−0.120	−1.239 ~ 0.998	0.833
	MMP	1.786	−0.101 ~ 3.674	0.064
	MEHP	−0.012	−0.677 ~ 0.654	0.973
	MEHHP	−0.319	−1.574 ~ 0.937	0.619
	MEOHP	−0.657	−1.973 ~ 0.658	0.327
	LMWP	0.711	−0.889 ~ 2.312	0.384
	HMWP	−0.459	−1.741 ~ 0.824	0.483
	Insomnia	0.745	0.645 ~ 0.845	< 0.001
Female	MBP	1.320	0.453 ~ 2.187	0.003
	MEP	0.120	−0.610 ~ 0.851	0.747
	MMP	−0.244	−1.258 ~ 0.770	0.637
	MEHP	−0.138	−0.560 ~ 0.284	0.522
	MEHHP	0.452	−0.478 ~ 1.381	0.341
	MEOHP	0.355	−0.654 ~ 1.365	0.490
	LMWP	1.396	0.351 ~ 2.440	0.009
	HMWP	0.325	−0.663 ~ 1.313	0.519
	Insomnia	0.608	0.532 ~ 0.684	< 0.001

Note: Model adjusted for age, major, self-reported academic performance, number of friends, paternal education level, self-rated bodily form, sleep quality, smoking, drinking, family history of depression, and hospitalization

cause disruption of circadian rhythms, which in turn can lead to sleep disorders, such as insomnia [29, 68], leading to the onset of depressive symptoms. In addition, studies have demonstrated a correlation between early exposure to phthalates and emotional problems, poorer language development, and reduced mental and psychomotor development, these neurobehavioral traits may share a biological basis with sleep health [27]. At the same time, phthalates are endocrine disrupting chemicals that influence endogenous hormones. Exposure to phthalates not only disrupts neural circuits, but also impedes the maturation of hormone-mediated mechanisms that regulate development and sleep [28], leading to sleep deprivation and depressive symptoms.

Our study has some limitations. Firstly, the cross-sectional design, while revealing significant associations, does not establish a definitive causal relationship between phthalate metabolites and depressive symptoms among college students. Secondly, retrospective investigations inevitably involve information bias. To mitigate this, we have implemented rigorous measures to minimize information bias by conducting comprehensive training and evaluation for investigators and conducting anonymous surveys among participants through electronic questionnaires. Thirdly, while many potential confounding factors were considered, we were not able to adjust for all possible covariates in our analysis and potential residual confounding could lead to bias in reported estimates. Fourth, phthalate exposure was estimated based on metabolite concentrations in a single urine sample, which may not represent the average daily exposure level. However, research indicates that single spot-sampling reflects average exposure and moderate sensitivity [67]. Fifth, due to the concentrations of most phthalate metabolites in morning urine samples was significantly higher than in other time periods [69]. Considering the nonpersistent nature of phthalates in vivo and the corresponding variation in phthalate exposure levels, future studies are encouraged to investigate the relationship of phthalate concentrations with mental health outcomes at multiple sampling timepoints. Moreover, future studies can also measure the concentration of phthalate metabolites through blood samples due to the established method (ultra-performance liquid chromatography-mass spectrometry) is accurate and highly sensitive [70]. However, there were also some benefits that should be acknowledged. A notable strength of our study lies in its substantial sample size, which enabled us to conduct a robust examination of the potential correlation between urinary phthalate metabolites and depressive symptoms. Additionally, the population-based design of our study allows us to generalize our findings to a broader group of college students.

Conclusion

Overall, we found that Chinese college students were widely exposed to phthalates. The results of the current study reveal significant cross-sectional associations between MBP, LMWP, and depressive symptoms among college students, and this association only remained for female college students after stratified by gender. Furthermore, we also found that insomnia has a positive moderating role on the correlation of MBP and LMWP with depressive symptoms, as well as there were sex differences. These findings have the potential to inform strategies designed to decrease phthalate exposure and improve both physical and mental health outcomes among college students. Meanwhile, further longitudinal investigations are also imperative to both replicate and expand upon the existing findings.

Table 4 The moderating effects of insomnia on the correlation of phthalate metabolites with depressive symptoms

Phthalate metabolites	Variable	Depressive symptoms (Overall)				Depressive symptoms (Male)				Depressive symptoms (Female)			
		β value	t value	R^2 value	F value	β value	t value	R^2 value	F value	β value	t value	R^2 value	F value
MBP	constant	11.55	4.63**	0.49	61.00**	8.05	2.12*	0.60	29.15**	13.88	3.97**	0.44	34.11**
	MBP	1.11	3.62**			1.06	1.99*			1.18	3.14*		
	Insomnia	0.65	21.35**			0.75	14.50**			0.59	15.24**		
	MBP×Insomnia	0.21	2.71*			0.17	1.46			0.22	2.12*		
MEP	constant	11.16	4.42**	0.48	58.47**	8.37	2.21*	0.61	29.72**	12.93	3.64**	0.43	32.33**
	MEP	0.03	0.12			0.52	1.18			−0.20	−0.61		
	Insomnia	0.65	21.36**			0.76	14.72**			0.61	15.39**		
	MEP×Insomnia	0.10	1.64			0.26	2.86*			0.01	0.08		
MMP	constant	10.90	4.33**	0.48	58.41**	7.36	1.96	0.61	30.27**	13.16	3.73**	0.43	32.50**
	MMP	0.17	0.45			0.59	0.78			−0.19	−0.43		
	Insomnia	0.66	21.51**			0.74	14.46**			0.61	15.48**		
	MMP×Insomnia	0.13	1.43			0.43	3.21*			−0.17	−1.27		
MEHP	constant	10.63	4.23**	0.48	58.91**	7.17	1.87	0.59	28.27**	12.84	3.64**	0.43	32.71**
	MEHP	0.02	0.16			0.02	0.09			0.04	0.24		
	Insomnia	0.66	21.52**			0.74	14.26**			0.61	15.68**		
	MEHP×Insomnia	0.08	2.43*			0.07	1.23			0.08	1.82		
MEHHP	constant	10.94	4.34**	0.48	58.24**	7.41	1.95	0.60	28.68**	13.47	3.82**	0.43	33.11**
	MEHHP	0.23	0.74			−0.63	−1.25			0.69	1.71		
	Insomnia	0.66	21.43**			0.75	14.44**			0.61	15.76**		
	MEHHP×Insomnia	0.06	0.75			−0.19	−1.67			0.20	2.03*		
MEOHP	constant	10.92	4.34**	0.48	58.11**	7.48	1.97	0.60	28.84**	13.54	3.83**	0.43	32.83**
	MEOHP	0.10	0.30			−0.66	−1.27			0.58	1.31		
	Insomnia	0.66	21.43**			0.75	14.40**			0.61	15.64**		
	MEOHP×Insomnia	0.01	0.16			−0.22	−1.89			0.18	1.68		
LMWP	constant	11.70	4.68**	0.49	60.47**	8.49	2.24*	0.61	29.60**	13.97	3.97**	0.44	33.44**
	LMWP	1.13	3.08**			1.30	2.07*			1.12	2.46*		
	Insomnia	0.65	21.37**			0.76	14.66**			0.59	15.18**		
	LMWP×Insomnia	0.23	2.70*			0.27	2.10*			0.21	1.75		
HMWP	constant	10.92	4.34**	0.48	58.21**	7.52	1.97*	0.60	28.59**	13.41	3.86**	0.43	33.04**
	HMWP	0.21	0.65			−0.58	−1.14			0.67	1.55		
	Insomnia	0.66	21.45**			0.75	14.39**			0.61	15.76**		
	HMWP×Insomnia	0.05	0.67			−0.18	−1.54			0.21	1.94		

Note: *$P<0.05$; **$P<0.01$. Model adjusted for age, major, self-reported academic performance, number of friends, paternal education level, self-rated bodily form, sleep quality, smoking, drinking, family history of depression, and hospitalization

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-025-21986-z.

Supplementary Material 1

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Author contributions

Designed the experiments: Xiaoyan Wu, Fangbiao Tao. Conducted the experiments: Wanyu Che, Yajuan Yang, Shuman Tao. Contributed materials: Tangjun Jiang, Liwei Zou, Shuman Tao. Analyzed the data: Tingting Li. Wrote the essay: Tingting Li.

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Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request (Xiaoyan Wu, xywu@ahmu.edu.cn).

Declarations

Ethics approval and consent to participate

The Ethics Committee of Anhui Medical University approved this study (NO: 20170291). All data procedures were carried out in accordance with relevant ethical guidelines and regulations associated with the declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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