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# Attitude toward COVID-19 vaccines and its association with depressive symptoms in 386,924 Chinese primary school students during COVID-19 epidemic normalization



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## ABSTRACT

*Aim:* Before Chinese primary school students were generally vaccinated against the COVID-19 vaccine, this study evaluated the willingness of this population and its influencing factors before vaccination, and evaluate its association between attitudes toward the vaccine and depressive symptoms.

*Methods*: A cross-sectional study involved 386,924 primary school students using a cluster sampling method during May 21–27, 2021. The Chinese version of the Children Depression Inventory (CDI) was used to assess depressive symptoms. Multiple logistic regression analysis models were used to estimate the relationship between attitudes toward COVID-19 vaccines and depressive symptoms.

*Results:* Among the participants, the prevalence of depressive symptoms was higher in higher grades. The prevalence was higher in fifth and sixth grade students than third and fourth grade students and first and second grades (10.22% vs. 6.07% vs. 3.04%). In addition, 20.79% of students do not know whether the vaccine can protect him from the COVID-19 infection, and 40.60% of students do not know whether the vaccine is safe. Of note, in terms of attitudes toward COVID-19 vaccines, students with more positive attitudes have a lower risk of depressive symptoms (adjusted odds ratio (aOR) = 0.151; 95% confidence interval (CI): 0.140-0.164). *Conclusion:* Based on these findings, it is necessary for the government and schools to promote vaccine safety and

## 1. Introduction

The COVID-19 outbreak has caused millions of deaths worldwide due to its respiratory spread and the continued mutation of the virus [1,2]. Since during the outbreak of the COVID-19 epidemic, global medical researchers are actively participating in the research and development of the COVID-19 vaccine. Vaccination is now a key global public health intervention to control the pandemic [3,4]. However, people's misunderstanding of vaccines has led to hesitation in vaccination in many countries [5,6]. World Health Organization (WHO) regarded vaccine hesitation as one of the public health threats [7]. Hence, as the pace of vaccine development and vaccination accelerates, it will have a certain impact on the public's psychology, and it may also affect the public's acceptance of vaccines [8].

In children and adolescents, depression is one of the more common mental illnesses [9], and depressive symptom more common in schoolage children [10]. As children's COVID-19 infection rate and mortality rate are lower than adults, children's mental health has received less attention during the epidemic [11]. Of note, children's physical and psychological characteristics are different compared to adults, so children are more susceptible to psychologically effects [12,13]. Meanwhile, previous studies have shown that adverse childhood experiences (ACEs) are the cause of approximately 40% of depression cases [14]. Therefore, it is very necessary to understand the depression state of

reliability information in a timely manner to increase vaccination uptake.

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#### children in time.

At this stage, the COVID-19 vaccine has not yet been commonly vaccinated among Chinese primary school students. Of note, previous studies have found that the vaccine acceptance rate is related to anxiety and depression symptoms [15,16]. Therefore, it is necessary to investigate the willingness of this population and its influencing factors before vaccination, and to evaluate the relationship between attitudes toward the vaccine and depressive symptoms. It is helpful to take targeted measures to strengthen the vaccination strategy and increase the vaccination rate in order to promote the popularization of vaccine.

## 2. Methods

#### 2.1. Study population

Data were collected through online questionnaires in this crosssectional study to investigate attitudes toward the COVID-19 vaccines and its relationship with depressive symptoms from May 21 to May 27, 2021. A cluster sampling method was used to recruit Chinese primary school students aged 6–12 years in Henan Province, China (Xinxiang city, Zhengzhou city and Xinyang city), and invited them to participate in a questionnaire survey through an online survey platform ("SurveyStar", Changsha Ranxing Science and Technology, Shanghai, China). In total of 438,978 people participated in the online survey and submitted their answers. Participants with incomplete questionnaires, younger than 6 years old or older than 12 years old or the time it takes to complete the questionnaire  $\leq 100$  s (n = 52,054) were excluded.

The study protocol was approved by the Ethics Committee of the Zhengzhou University (ZZUIRB2021–118). Students were advised to get their parents' permission before completing the questionnaire. All study participants consented for participation in this study.

## 2.2. Data collection

This research used an online questionnaire to collect their sociodemographic data including age, gender grade, residential location (city, rural and country-level city), mental state (worry, and fear levels), attitudes toward COVID-19 vaccines, and depressive symptoms. The degree of worried and fear levels was divided into five levels: "extremely" "very" "somewhat" "not so" and "not at all", and each response is scored on 5-point Likert scale [17]. Worried and fear score of 1-2 was classified as low or none level, 3 was classified as moderate level, 4-5 was classified as high level respectively. Questions about attitudes toward COVID-19 vaccines was measured with five questions [18]: (1) Are you worried about contracting COVID-19? (No/Fair/Very much); (2) Have you heard of the COVID-19 vaccine? (No/Yes) (3) Do you think COVID-19 infection can be prevented by vaccines? (No/Unclear/Yes); (4) What do you think of the safety of the COVID-19 vaccine? (They are not safe with obvious side effects /Unclear /They are safe with no side effects); (5) If widespread vaccination, are you willing to COVID-19 vaccine inoculation? (No/Unclear/Yes).

The Chinese version of the Children Depression Inventory (CDI) was used to evaluate depressive symptoms. CDI is a simple and efficient selfevaluation tool for children's depressive symptom level (Cronbach's alpha coefficient 0.82) [19]. CDI is applicable to children aged 7–17 years old [20]. The scale contains 27 items in total and participants were asked how often they had been troubled by these symptoms in the past two weeks, the scores of 0, 1, and 2 are used to indicate "occasionally", "often", and "always" respectively, indicating the frequency of the appearance of symptoms. CDI divided into 5 subscales: anhedonia, negative mood, negative self-esteem, ineffectiveness, interpersonal problem [21]. Higher scores indicate greater depressive symptoms. The score rang is 0–54, the cut-off point for screening for depressive symptoms is set at 19 points [22,23].

#### 2.3. Statistical analysis

Regarding descriptive statistics, continuous variables represented as average (Mean)  $\pm$  standard deviation (SD), and categorical variables were presented as frequencies (n) and percentages (%). Difference between groups was tested by the chi-squared test for categorical variables, and students *t*-test for continuous variables. Logistic regression models were constructed to estimate attitudes toward COVID-19 vaccines and depressive symptoms in different grades. Multivariable adjustment models were performed in this study. In adjusted model, we use potential confounding factors with large statistical differences between the without depression group and the depression group to control our analysis. These confounding factors include age, gender, residential location, worried level, and fear level. The SPSS software, version 21.0 (SPSS Inc., Chicago) was used for all data analysis, and the two-sided level of significance was set 0.05.

## 3. Results

## 3.1. Characteristics of the participants

A total of 386,924 primary school students aged 6-12 years old (median = 9.59) were completed the online survey. The sociodemographic characteristics and their relationship with depressive symptoms are presented in Table 1. The overall prevalence of depressive symptoms was 6.20% among elementary school students during the normalization of the COVID-19 epidemic in China. The prevalence of depressive symptoms was observed higher in females compared to males (6.04% vs. 5.67%), and the prevalence was higher in fifth and sixth grade students than third and fourth grade students and first and second grades (10.22% vs. 6.07% vs. 3.04%). Prevalence of self-reported depressive symptoms was 7.27% in students lived in rural regions, 5.02% in students lived in country-level city, and 5.21% found in students lived in city. In addition, our results showed that students with depressive symptoms were different from the proportion of gender, grade, residential location, worried level, fear level and attitudes toward COVID-19 vaccines compared to participants without depressive symptoms (all P < 0.05).

## 3.2. The rate of different severities of depressive symptoms

Table 2 demonstrates the proportion of students with depressive symptoms in different grades. In first and second grades, the rate of depressive symptoms was 3.04%, in third and fourth grades, the rate of depressive symptoms was 6.07%, and in fifth and sixth grades, the rate of depressive symptoms was 10.22%. On the CDI subscale anhedonia, the mean scores for first and second grades students were 1.66, the mean for third and fourth grades students was 2.01, and the mean for fifth and sixth graders students was 2.38. Of note, with the increase of grade, the scores of the five subscales (including anhedonia, negative mood, negative self-esteem, ineffectiveness, interpersonal problem) also increased respectively (all P < 0.001).

#### 3.3. Attitudes toward COVID-19 vaccines at different grade levels

In Table 3, the highest proportion of students who are very worry to be infected with COVID-19 was 32.03% found in the fifth and sixth grades compared to first and second grades (29.21%) and third and fourth grades (30.49%). The vast majority of students heard about COVID-19 vaccine previously. However, many students still have unclear perceptions about the protection and safety of vaccines. Among elementary school students, 20.79% of students do not know whether the vaccine can protect him from the COVID-19 infection, and 40.60% of students do not know whether the COVID-19 vaccine is safe. Although there are unclear about the protection and safety of the COVID-19 vaccine, 92.97% of the people are willing to be vaccinated.

## Table 1

Characteristics of the study participants by depression.

Characteristics	All participants (N = 386,924)	No- depression (N = 364,322)	Depression ( <i>N</i> = 22,602)	p value
Age (years)	9.59 ± 1.61	9.54 ± 1.60	$10.35\pm1.53$	< 0.001
Gender (%)	9.09 ± 1.01	9.01 ± 1.00	10.00 ± 1.00	< 0.001
	205,967	194,298	11,669	
Male	(53.23)	(53.33)	(51.63)	
. 1	180,957	170,024	10,933	
Female Grade (%)	(46.77)	(46.67)	(48.37)	< 0.001
First and second	158,516	153,704		<0.001
grades	(40.97)	(42.19)	4812(21.29)	
Third and fourth	134,302	126,137		
grades	(34.71)	(34.62)	8165(36.13)	
Fifth and sixth		84,481		
grades	94,106(24.32)	(23.19)	9625(42.58)	
Residential location (%)				< 0.001
iocation (70)	203,506	192,896	10,610	<0.001
City	(52.60)	(52.95)	(46.94)	
2	123,909	114,904	. ,	
Rural	(32.02)	(31.54)	9005(39.84)	
		56,522		
Country-level city	59,509(15.38)	(15.51)	2987(13.22)	
Worried level (%)	246 022	220 120	16 000	< 0.001
High	246,932 (63.82)	230,130 (63.17)	16,802 (74.34)	
riigii	(03.82)	79,227	(74.34)	
Moderate	83,110(21.48)	(21.75) 54,965	3883(17.18)	
Low/none	56,882(14.70)	(15.09)	1917(8.48)	
Fear level (%)				< 0.001
	166,584	153,207	13,377	
High	(43.05)	(42.05)	(59.19)	
Moderate	138,280 (35.74)	132,129 (36.27) 78,986	6151(27.21)	
Low/none	82,060(21.21)	(21.68)	3074(13.60)	
Worry to be infected with	02,000(21:21)	(21:00)		
COVID-19 (%)				< 0.001
		70,764		
No	70,764(19.42)	(19.42)	2497(11.05) 10,333	
Fair	196,262 (50.72)	185,929 (51.03)	(45.72)	
i un	117,401	107,629	(10.72)	
Very much	(30.34)	(29.54)	9772(43.24)	
Heard about COVID-19 vaccine				
previously (%)				< 0.001
No	5109(1.32)	3991(1.10)	1118(4.95)	
	381,815	360,331	21,484	
Yes Feel vaccine could keep you free of	(98.68)	(98.90)	(95.05)	
COVID-19 (%) No	20,166(5.21)	17,777(4.88)	2389(10.57)	< 0.001
Unclear	80,453(20.79)	72,974 (20.03)	7479(33.09)	
Yes	286,305 (74.00)	273,571 (75.09)	12,734 (56.34)	
Feel vaccine safe (%) Not safe with				< 0.001
obvious side effects	13,803(3.57)	11,327(3.11)	2476(10.95)	
CIICCO	157,088	145,983	11,105	
Unclear	(40.60)	(40.07)	(49.13)	
Safe with no				
obvious side	216,033	207,012		
effects	(55.83)	(56.82)	9021(39.91)	

Table 1 (continued)

Characteristics	All participants (N = 386,924)	No- depression ( <i>N</i> = 364,322)	Depression ( <i>N</i> = 22,602)	p value
Are you willing to get the COVID- 19 vaccine (%)				
No	6330(1.64)	5153(1.41)	1177(5.21)	< 0.001
Unclear	20,856(5.39)	17,825(4.89)	3031(13.41)	
	359,738	341,344	18,394	
Yes	(92.97)	(93.69)	(81.38)	

Data were presented as mean (SD) normal distribution continuous variables and numbers (percentages) for categorical variables; *P* values calculated using student's t-test and chi-square.

Compared with No-depression, P < 0.05.

## Table 2

Prevalence of depressive symptoms and scores of five subscale among students of different grades.

Variables	First ar second grades			Third and fourth grades		Fifth and sixth grades	
	N = 15	8,516	N = 134,302		N = 94,106		
Depressive symptoms	4812	3.04	8165	6.07	9625	10.22	<0.001
Scale score							
Total score	6.78	4.69	8.09	5.68	9.26	6.863	< 0.001
Anhedonia score	1.66	1.84	2.01	2.14	2.38	2.47	< 0.001
Negative Mood score	0.98	1.49	1.28	1.83	1.63	2.25	< 0.001
Negative Self- Esteem score	1.16	0.84	1.37	1.04	1.6	1.26	< 0.001
Ineffectiveness score	2.11	1.23	2.41	1.36	2.51	1.43	< 0.001
Interpersonal Problem score	0.87	0.93	1.02	1.04	1.15	1.15	<0.001

Depressive symptoms were presented as numbers and percentages, and scale score were presented as mean and SD. Comparison of three groups, P < 0.05.

# 3.4. Association between attitudes toward COVID-19 vaccines and depression in different grades

Table 4 presents the results of multivariable logistic regression analysis. In terms of COVID-19 vaccine protection, compared with students who feel vaccine could not keep themselves free of COVID-19 among first and second grade students, the adjusted model showed that students who feel vaccine could keep themselves free of COVID-19 were at lower risk of depression (aOR = 0.322 (95%CI: 0.293-0.354). Among third and fourth grade students and fifth and sixth grade students, compared with students who didn't worry to be infected, students who very worry to be infected with COVID-19 were at higher risk of depression (aOR = 0.391 (95%CI: 0.361-0.422) and (aOR = 0.413(95% CI: 0.382-0.446).

In terms of vaccine safety, compared with students who feel vaccine not safe with obvious side effects among first and second grade students, students who feel vaccine safe with no obvious side effects were at lower risk of depression (aOR = 0.175 (95%CI: 0.158-0.194). Among third and fourth grade students and fifth and sixth grade students, compared with students who feel vaccine not safe with obvious side effects, students who feel vaccine safe with no obvious side effects were at lower risk of depression (aOR = 0.236 (95%CI: 0.218-0.256) and (aOR = 0.282(95%CI: 0.260-0.305).

In terms of willingness to vaccinate, compared with students who are unwilling to receive future COVID-19 vaccination among first and second grade students, students who are willing to receive future COVID-19

#### Table 3

Attitudes toward COVID-19 vaccines at different grade levels.

Questions	Attitudes toward COVID-19 vaccines	All participants		First and second grades		Third and fourth grades		Fifth and sixth grades	
		n	%	n	%	n	%	n	%
	Worry to be infected with COVID-19 (%)								
01	No	73,261	18.93	31,777	20.05	24,944	18.57	16,540	17.58
Q1	Fair	196,262	50.72	80,434	50.74	68,407	50.94	47,421	50.39
	Very much	117,401	30.34	46,305	29.21	40,951	30.49	30,145	32.03
	Heard about COVID-19 vaccine previously (%)								
Q2	No	5109	1.32	1571	0.99	1911	1.42	1627	1.73
-	Yes	381,815	98.68	156,945	99.01	132,391	98.58	92,479	98.27
Q3	Feel vaccine could keep you free of COVID-19 (%)								
	No	20,166	5.21	7932	5.00	7217	5.37	5017	5.33
	Unclear	80,453	20.79	31,737	20.02	27,945	20.81	20,771	22.07
	Yes	286,305	74.00	118,847	74.97	99,140	73.82	68,318	72.60
	Feel vaccine safe (%)								
~ .	Not safe with obvious side effects	13,803	3.57	4749	3.00	5108	3.80	3946	4.19
Q4	Unclear	157,088	40.60	65,303	41.20	54,281	40.42	37,504	39.85
	Safe with no obvious side effects	216,033	55.83	88,464	55.81	74,913	55.78	52,656	55.95
~-	Are you willing to get the COVID-19 vaccine (%)								
	No	6330	1.64	2076	1.31	2401	1.79	1853	1.97
Q5	Unclear	20,856	5.39	6948	4.38	7312	5.44	6596	7.01
	Yes	359,738	92.97	149,492	94.31	124,589	92.77	85,657	91.02

#### Table 4

Association between attitudes toward COVID-19 vaccines and depressive symptoms in different grades.

Attitudes toward COVID-19 vaccines	First and second gr	ades	Third and fourth grades		Fifth and sixth grades		
	cOR (95%CI)	aOR (95%CI)	cOR (95%CI)	aOR (95%CI)	cOR (95%CI)	aOR (95%CI)	
Feel vaccine could keep you free of COV	ID-19						
No	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	
	0.680	0.687	0.773	0.787	0.788	0.797	
Unclear	(0.617-0.750)	(0.622-0.758)	(0.712-0.838)	(0.725-0.854)	(0.727-0.854)	(0.734-0.864)	
	0.280	0.322	0.353	0.391	0.388	0.413	
Yes	(0.256–0.308)	(0.293–0.354)	(0.327–0.381)	(0.361–0.422)	(0.359–0.418)	(0.382–0.446)	
Feel vaccine safe							
Not safe with obvious side effects	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	
	0.298	0.340	0.344	0.391	0.436	0.470	
Unclear	(0.271-0.329)	(0.308-0.375)	(0.318-0.372)	(0.361-0.423)	(0.403-0.472)	(0.434-0.509)	
	0.144	0.175	0.202	0.236	0.257	0.282	
Safe with no obvious side effects	(0.131–0.159)	(0.158–0.194)	(0.187–0.219)	(0.218–0.256)	(0.237–0.278)	(0.260–0.305)	
Are you willing to get the COVID-19 vac	cine						
No	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	1.00(ref)	
	0.624	0.647	0.723	0.750	0.809	0.802	
Unclear	(0.534-0.730)	(0.552-0.758)	(0.640-0.816)	(0.663-0.849)	(0.717-0.912)	(0.711-0.906)	
	0.195		0.245	0.265	0.291	0.298	
Yes	(0.171 - 0.223)	0.212(0.18-0.243)	(0.221 - 0.273)	(0.239 - 0.295)	(0.261 - 0.324)	(0.268-0.332)	

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; cOR, crude odds ratio.

cOR: Unadjusted.

aOR: Adjusted for age, gender, residential location, worried level and fear level.



Fig. 1. Abbreviations: OR, odds ratio; CI, confidence interval; N & N, No & Not safe with obvious side effects; N & U, No & Unclear; N & Y, No & Safe with no obvious side effects; U & N, Unclear & Not safe with obvious side effects; U & U, Unclear & Unclear; U & Y, Unclear & Safe with no obvious side effects; Y & N, Yes & Not safe with obvious side effects; Y & N, Yes & Not safe with obvious side effects; Y & U, Yes & Unclear; Y & Y, Yes & Safe with no obvious side effects; Y & U, Yes & Unclear; Y & Y, Yes & Safe with no obvious side effects; ref., reference. Adjusted for age, gender, grade, residential location, worried level and fear level.

vaccination were at lower risk of depression (aOR = 0.212 (95%CI: 0.180–0.243). Among third and fourth grade students and fifth and sixth grade students, compared with students who are unwilling to receive future COVID-19 vaccination, students who are willing to receive future COVID-19 vaccination were at lower risk of depression (aOR = 0.265 (95%CI: 0.239–0.295) and (aOR = 0.298 95%CI: 0.268–0.332).

We found that a significant association between students with positive attitudes toward vaccine were less likely to have symptoms of depression compared to students with negative attitudes among elementary school students (aOR = 0.151; 95%CI: 0.140–0.164). Detailed information was showed in Fig. 1.

## 4. Discussion

In the current large-scale cross-sectional research involved 386,924 primary school students, the prevalence of depressive symptoms was higher in higher grades. The prevalence was higher in fifth and sixth grade students than third and fourth grade students and first and second grades (10.22% vs. 6.07% vs. 3.04%). Meanwhile, we also observed many students still have unclear perceptions about the protection and safety of vaccines, and vaccination willingness has a downward trend as the grade level rises. Although the protection and safety of the COVID-19 vaccine for most people are not yet clear, 92.97% of people are willing to vaccinate. In terms of attitudes toward COVID-19 vaccines, students with more positive attitudes have a lower risk of depressive symptoms.

Our current study indicated that the prevalence of depressive symptoms was higher in higher grades. The prevalence of depressive symptoms was 10.22% in fifth and sixth grade students, 6.07% in third and fourth grade students, and 3.04% found in first and second grades. It suggested that a higher prevalence of depressive symptoms in highergrade students than lower-grades students. The higher-grade students face greater academic pressure, especially the sixth-grade students who need to take the primary graduation exam. The COVID-19 epidemic disrupted their daily learning rhythm; from this, it may be inferred that that the epidemic put academic pressure on students [24]. In addition, students were also asked to complete their daily health status check-in and restrict their trip, which can result in depressive symptoms. Previous studies have pointed out that external environmental factors are believed to be related to the occurrence of depression, especially stressful life events [25,26]. As a sensitive group, the psychological condition of primary school students is particularly worthy of attention.

Moreover, our study showed that many students still have unclear perceptions about the protection and safety of vaccines and vaccination willingness has a downward trend as the grade level rises. However, many studies have shown that age and education are positively correlated with receiving vaccines [27–29]. This may be due to the lower grade students have relatively little knowledge of vaccines and generally believe that vaccines can protect themselves. In contrast, the understanding of vaccines in upper grade students may be affected by the Internet and other channels, resulting in mixed praise and criticism of vaccines. A previous study showed that in developing countries, people are most susceptible to false information spread through Internet software [30]. This suggests that guidelines can be formulated in terms of network information to curb the spread of vaccine-related misinformation.

Of note, in terms of vaccine protection, safety, and willingness to vaccinate, students with more positive attitudes have a lower risk of depressive symptoms. Previous studies have shown that vaccine acceptance is related to anxiety and depression [27]. Meanwhile, there is a lot of evidence that mental health was negatively affected by the COVID-19 [31,32], thus, we think students who have a positive attitude toward vaccine will also have more confidence in the situation of the epidemic. Therefore, while the government educates children about vaccines, it is also beneficial to children's mental health.

As far as we know, the large numbers of participants and the high completeness of the data are major strengths of our study. Secondly, since Henan is the province with the most educated population in China, it can represent the depressive symptoms of students during COVID-19 pandemic to some extent. Thirdly, we used the Chinese version of the CDI, which is a simple and time efficient self-reporting tool to evaluate children's depression levels (Cronbach's alpha coefficient 0.82).

Nevertheless, there are a few potential limitations in our study. First, we adjusted for various potential risk factors in the outcome analysis, however, the possibility of residual confounding persists. Second, since this is a cross-sectional design, it lacks temporality and cannot be determined whether it is a causal association. Third, the study participants were primary students, which may affect the extension of our study results to other grade students. Fourth, retrospective design increases recall bias, and self-selection bias may be caused by the selfreported property of the research. Fifth, the presence of depressive symptoms was determined by Chinese version of the Children Depression Inventory (CDI), which is a simple and highly effective selfassessment tool for depressive symptoms. However, a single screening tool does not guarantee the reliability and validity of the study.

In summary, we found that the prevalence of depressive symptoms was higher in higher grades, and the prevalence of higher-grade students reached 10.22%. Meanwhile, many students still have unclear perceptions about the protection and safety of vaccines, and students with more positive attitudes have a lower risk of depressive symptoms. Based on these findings, it is necessary for the government and schools to promote vaccine safety and reliability information in a timely manner to increase the vaccination rates.

## **Ethics** approval

Approval for the study was obtained from the Ethics Committee of Zhengzhou University (ZZUIRB2021-118). All the participants consented for participation in this study.

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## Data sharing statement

All relevant data that support the findings of this study are available on request from Mrs. Cuiping Wu (wucuiping@zzu.edu.cn).

## Author statement

Qingqing Xu and Cuiping Wu designed research; Zhenxing Mao, Keliang Fan, Hualiang Lin, Xian Wang, Xiaomin Lou, Chongjian Wang, Dandan Wei and Juan Wang collected the data; Qingqing Xu analyzed the data and drafted the manuscript; Zhenxing Mao, Cuiping Wu, and Keliang Fan revised the manuscript. Cuiping Wu had primary responsibility for final content. All authors read and approved the final manuscript.

## **Declaration of Competing Interest**

The authors declare that they have no conflict of interest.

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