# Suspiciousness in young minds: Convergent evidence from non-clinical, clinical and community twin samples Han-yu Zhoua, b, 1 Keri Ka-Yee Wong Li-juan Shia, d Xi-long Cui Yun Oian Wen-ging liang Ya-song Du Simon S.Y. Lui<sup>a, g</sup> Xue-rong Luo Zheng-hui Yif Eric F.C. Cheung Anna R. Docherty Raymond C.K. Chana, b, \* rckchan@psych.ac.cn <sup>a</sup>Neuropsychology and Applied Cognitive Neuroscience Laboratory, CAS Key Laboratory of Mental Health, Institute of Psychology, Beijing, China <sup>b</sup>Department of Psychology, University of Chinese Academy of Sciences, Beijing, China <sup>c</sup>Department of Psychology, University of Cambridge, Cambridgeshire, UK <sup>d</sup>School of Education, Hunan University of Science and Technology, Xiangtan, Hunan, China eMental Health Institute of the Second Xiangya Hospital, National Technology Institute of Psychiatry, Key Laboratory of Psychiatry and Mental Health of Hunan Province, Central South University, Changsha, China fShanghai Mental Health Centre, Shanghai Jiaotong University School of Medicine, Shanghai, China <sup>9</sup>Castle Peak Hospital, Hong Kong Special Administrative Region, China <sup>h</sup>Department of Psychiatry, University of Utah School of Medicine, Salt Lake City, <del>Utah</del>UT, USA <sup>i</sup>Virginia Institute for Psychiatric & Behavioral Genetics, Richmond, VA, USA \*Corresponding author at: Institute of Psychology, Chinese Academy of Sciences, 16 Lincui Road, Beijing 100101, China. <sup>1</sup>These authors contributed equally to the paper.

Abstract

### **Background**

We validated the Social Mistrust Scale (SMS) and utilized it to examine the structure, prevalence, and heritability of social mistrust in a large sample of Chinese children and adolescents.

#### Methods

In Study 1, a large sample of healthy twins (N=2094) aged 8 to 14 years (M=10.27 years, SD=2) completed the SMS. Structural equation modellingmodeling (SEM) was conducted to assess the structure of the SMS and to estimate the heritability of social mistrust in a sub-sample of twins (n=756 pairs). In Study 2, 32 adolescents with childhood-onset schizophrenia were compared with 34 healthy controls on levels of suspiciousness and clinical symptoms to examine the associations between the SMS and the Positive and Negative Syndrome Scale (PANSS).

### Results

We found a three-factor structure for social mistrust (home, school, and general mistrust). Social mistrust was found to be moderately - heritable (19%-40%), with mistrust at home most strongly influenced by genetic factors. Compared with 11.76% of the healthy controls, 56.25% of the adolescents with early-onset schizophrenia exhibited very high levels of social mistrust on all three subscales enof the SMS. The SMS exhibited good discriminant validity in distinguishing adolescents with childhood-onset schizophrenia from healthy controls, and showed associations with a broad range of symptoms assessed by the PANSS.

#### Conclusions

Social mistrust assessed by the SMS may be heritable. The SMS demonstrates good discriminant validity with clinical diagnoses of schizophrenia. However, it seems to be correlated with multiple aspects of psychopathology in the schizophrenia group, rather than being specific to delusional ideation/paranoia.

Keywords: Social mistrust; Suspiciousness; Heritability; Child; Schizophrenia

# **1.1** Introduction

Persecutory delusions are one of the most common symptoms in schizophrenia (Sartorius et al., 1986). There is growing evidence suggesting that such delusions exist on a continuum of severity in adults in the general population, with many individuals reporting a few paranoid thoughts and a few individuals (10%-15%) reporting many paranoid thoughts (Bebbington et al., 2013; Chan et al., 2011; Freeman, 2006; Van Os et al., 2009). In studies of adult patients, paranoia has received much research attention as it has been found to co-occur with a host of psychological problems (e.g., anxiety, insomnia, suicidal ideation and poor emotional and cognitive functioning) (Berry et al., 2015; Combs et al., 2006; Freeman et al., 2011). However, whether paranoia exists developmentally in non-clinical adolescents and children remains understudied and previous adult studies have predominantly been conducted in Western populations.

To date, only one study has examined paranoia in non-clinical adolescents and children in both non-Western and Western samples (Wong et al., 2014). This large cross-sectional survey of 8 to 14 year-olds (N=2498) from Hong Kong and the UK examined excessive suspiciousness, an attenuated form of paranoia, using the first dimensional measure of childhood suspiciousness: the *Social Mistrust Scale* (SMS). The study found that childhood suspiciousness was prevalent in 8 to 14 year-olds from both UK schools and Hong Kong international schools. Such suspiciousness was found to exist on a continuum of severity and was positively skewed: with many children being trusting and a few being mistrustful. Compared with trusting children, mistrustful children (defined as scoring 7 or above on the SMS) not only self-reported more internaliszing and externaliszing problem behaviours but also self-reported a greater level of mistrust in school rather than the home, which is also what we predict to be the case in our study.

Although Wong et al. (2014) found that there was no main effect of gender in either the UK or Hong Kong, there was a general age-related decline in levels of mistrust, with young children (8 to 10 years) reporting higher levels of mistrust than older adolescents (11 to 14 years). In the UK sample only, there was a gender x age interaction where mistrust was more common in boys than girls in younger children, but the pattern was reversed in children aged 10 and above. The authors suggested that these results were due to changes in school-related/education experiences (i.e. environmental influences) and brain maturation (i.e. genetic influences). With regard to environmental influences, as the children were from Hong Kong International schools and UK schools, the question of whether similar age and gender differences in levels of mistrust may be found in children with uniform educational experiences (such as mainland Chinese schoolchildren) has yet to be explored.

Another unanswered and important question pertains to the genetic and environmental influences of social mistrust. Twin studies of young adults in the general population have suggested moderate to high (about 50%) heritability estimates in paranoid ideation (Fagnani et al., 2011), with similar findings replicated in late adolescents (aged 16 years) (Shakoor et al., 2015a, 2015b, 2016). No sex difference in genetic and environmental influences on paranoia was evident (Shakoor et al., 2015a; Zavos et al., 2014). Paranoia, along with parent-rated negative symptoms, demonstrated the highest heritability (50%—54%) among all six kinds of psychotic experiences assessed by the Specific Psychotic Experiences Questionnaire (SPEQ) (Shakoor et al., 2015b, 2016; Zavos et al., 2014). Moreover, some studies have reported no difference in the heritability between the extreme group reporting the most severe and frequent psychotic experiences and the rest of the sample (Zavos et al., 2014). Together these results suggest that both paranoia in the general population and clinically diagnosed schizophrenia exist on the same continuum and may

share common genetic variants. Hence, heritability estimates of paranoia in younger populations, and its socio-cultural influences in non-Western children and adolescents, may help identify a developmental window for the early identification of schizophrenia which has yet to be examined.

Mistrustful children scoring high on the SMS (>7 points) have also been shown to exhibit more internaliszing and externaliszing problem behaviours compared with trusting children in Wong et al.'s (2014) study. However, whether the SMS has any clinical utility is unclear. Thus, examining the associations of the SMS with standardised measures of symptoms (e.g., Positive and Negative Syndrome Scale (PANSS)) in early onset-schizophrenia would help establish its usefulness.

To this end, we conducted two related studies to address the above gaps. In Study 1, our first aim was to assess the prevalence and structure of social mistrust using exploratory and confirmatory factor analysis, as this is the first study of the Chinese SMS in a large sample of healthy Chinese twins aged 8 to 14 years (N = 2094). We also conducted measurement invariance of the SMS across ages (younger vs. older children) and gender (female vs. male). Our second aim was to assess the heritability of mistrust in same-sex MZ and DZ twins (N = 756 pairs). In Study 2, our third aim was to test the convergent validity of the SMS with the Positive and Negative Syndrome Scale (PANSS) in a sample of adolescents with childhood-onset schizophrenia (n = 32) and healthy controls (n = 34).

In Study 1, we hypothesized that social mistrust would be prevalent amongstamong a few of the children, following a positively skewed distribution. Social mistrust assessed by the SMS would follow a 3-factor structure and would be heritable in Chinese twins. In Study 2, we hypothesized that the SMS would be positively correlated with the PANSS, specifically with the "suspiciousness/persecution" item.

### 2.2 Methods

### 2.1.2.1 Participants

### 2.1.1.2.1.1 Study 1

Healthy twins aged 8- to 14-years-old (M=[10.57 years, SD=[2.0, males]=[49.5%) from the Beijing Twin Study (BeTwiSt) (Chen et al., 2013) were recruited from Shenyang, China. This included monozygotic twins (MZ; n=[1311), dizygotic twins (DZ; n=[323) and opposite-gender twins (OG; n=[460). Zygosity was determined by DNA analysis and questionnaire (Chen et al., 2010). The age and gender distribution of this sample is detailed elsewhere (Supplementary Table 1). Informed parental consent was obtained before the start of the study and children completed questionnaires in groups. This study was approved by the Ethics Committee of the Institute of Psychology at the Chinese Academy of Sciences.

To examine the heritability of social mistrust, we included only same-gender twin pairs (and not opposite-gender twin pairs), resulting in 1512 twins (M=10.57 years, SD=2.01, males 49.34%) with complete data. The final sample consisted of 616 pairs of MZ twins (males 47.72%) and 140 pairs of DZ twins (males 47.72%) and 140 pairs of DZ twins (males 47.72%). We excluded opposite gender twin pairs in this subsample considering the following two reasons: (1) The influence of additive genetic factor and environmental factors on social mistrust (or the A, C, E parameters in the model) may vary in males and females (i.e., quantitative sex differences). (2) As for the opposite sex DZ twins, the correlations for the A factors ( $r_C$ ) may fall below the traditional value (i.e., 0.5 for  $r_A$ , 1 for  $r_C$ ) (i.e., qualitative sex differences).

# <del>2.1.2.</del>2.1.2 Study 2

Thirty-two adolescents with childhood-onset schizophrenia (males = 56.3%) recruited from Xiangya Hospital in Hunan, Shanghai Mental Health Centre, and Hong Kong (M = 13.91 years, SD = 1.57, range = 16 years). These participants were compared with 34 healthy adolescent controls (males = 61.8%) recruited from junior high schools in Hunan (M = 13.03 years, SD = 0.72, range 12 = 15 years). All patients were assessed by experienced psychiatrists (XLC, YQ, SSYL) using the PANSS (Kay et al., 1987). Patients met the DSM-IV-TR diagnostic criteria for schizophrenia (American Psychiatric Association, 1994) and were taking second-generation antipsychotic medication for not more than one year (mean chlorpromazine equivalence = 406.1 mg/day), with the exception of one 10-year-old drug-naïve patient. All healthy controls completed the 113-item behavioural problems section of the standardized Chinese version of the Child Behaviour Checklist (CBCL; parental version) (Su and Li, 1996) and had individual syndrome subscale scores and a total problem score falling within the range of normal behaviour. Adolescents with a history of any psychiatric illness, organic brain disorders, substance and/or alcohol abuse, and clinical evidence of mental retardation were excluded. Participants in the two groups did not differ in gender ratio but patients with schizophrenia were older (443] = 2.88, p < 0.01) and had significantly lower estimated IQ (450] = 0.09, p < 0.01) than healthy control adolescents (Supplementary Table 2).

All participants and their parents gave written informed consent before the commencement of the study. This study was approved by the Ethics Committees of the Institute of Psychology, the Chinese Academy of Sciences, the Xiangya Hospital in Hunan, the Shanghai Mental Health Centre and Castle Peak Hospital.

## 2.2.2.2 Measures

### 2.2.1.2.2.1 Social mistrust

Social Mistrust. The Social Mistrust Scale (SMS) is a 12-item dimensional measure of childhood mistrust rated on a No(0)/Sometimes(1)/Yes(2) scale (Wong et al., 2014). Summing all items produced a total mistrust score (out of 24) and three factors: home mistrust, school mistrust, and the *general mistrust* (reverse-scored). A higher score indicates a higher level of suspiciousness towards others. This scale has been shown to have good internal consistency in the current sample, a = 0.74 (total score), 0.58 (general), 0.64 (school), 0.63 (home). The SMS was translated into Chinese using a well-established four-step back translation procedure. First, a bilingual researcher translated the SMS from English to Chinese. Second, author 2 (who is bilingual) compared the Chinese and English versions for conceptual equivalence. Third, a psychologist who had not seen the English version translated the Chinese version back into English. Fourth, the two English versions were compared on conceptual equivalence by authors 1 and 2.

Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). This is a widely used semi-structured clinical interview that assesses positive symptoms (7 items), negative symptoms (7 items) and non-specific/general symptoms (16 items) of schizophrenia with a 7-point Likert scale. The scale had good internal reliability in this study (a = 0.91).

The Chinese version of the Child Behaviour Checklist (CBCL; parental version) (Su and Li, 1996) This is a 113-item standardized scale measuring adolescents emotional and behavioural problems on a Not True(0)/Somewhat, Sometimes True(1)/Very, Often True(2) scale. These were completed by their parents or guardians. The scale contains eight (for females) and nine (for males) individual syndrome scales for adolescents aged 12-16 years. The presence of one or more individual syndromes with scores higher than those of the Chinese normative cut-off scores indicated behavioural problems. The scale showed good internal consistency in our study ( $\alpha = 0.71$ ). The total and subscale problem scores of 34 healthy controls all fell within the normal range (range = 0-13 points, M = 3.10, SD = 3.18) (Supplementary Table 3).

### 2.3.2.3 Statistical analysis

Exploratory factor analysis (EFA) was first conducted using the principal component analysis in SPSS 18.0 on the older twins sample as this is the first administration of the Chinese version of the SMS. Next, a confirmatory factor analysis (CFA) was conducted in *Mplus 6* for Windows (Muthen and Muthén, 2010) on the younger twins to test the structural reliability of the SMS. Both samples did not differ in age and gender distribution (p) 0.05).

For the CFA, three measurement models of social mistrust were tested to ascertain its structure in this sample: a uni-dimensional model (a single mistrust latent factor); a two-factor model (mistrust (home & school) vs. general trust); and a three-factor model (home mistrust, school mistrust and general mistrust). Since the data were skewed, we used the weighted least square parameter estimator (WLSMV) to obtain robust standard errors and a mean- and variance-adjusted  $\chi^2$  statistic. Modification indices (MI) were included in the model only if it was a theoretically plausible modification that led to significant improvement in model fit indices. Taking the largest MI, the model was re-run after each modification and compared on the Akaike information Criterion (AIC; calculated by  $\chi^2$ -2 [degrees of freedom]), where the best-fitting model to the data had the lowest AIC (Brown, 2006). Additional measurement invariance models were constructed to determine the model fit for boys and girls, and younger (8-11 years) and older (12-14 years) children. We first examined configural invariance, followed by metric invariance (weak invariance) and scalar invariance (strong invariance) (Marsh et al., 2009). If the model fulfilled the strong invariance, the final step involved examining the latent mean invariance between different subgroups (i.e., boys vs girls; younger vs older children) (Marsh et al., 2009).

Mean scores and symptom distribution were reported. Univariate analysis of variance (ANOVA) was conducted to examine the effects of age, gender, and age x gender interaction on the SMS subscales.

For genetic modelling, variables were square-root transformed to satisfy the assumption of having a normal distribution due to the positively skewed SMS scores. Effects of age and gender were regressed out prior to the estimation of heritability of social mistrust and standardized residuals were used for subsequent analysis following standard practice (McGue and Bouchard, 1984). First, intra-class correlation coefficients (ICCs) of the MZ and DZ twins were calculated. To compare the strength of ICCs between MZ and DZ twins, we generated the Student's t-distribution for testing correlations against each other (Lenhard and Lenhard, 2014). Next, structural equation modellingmodeling (Neale et al., 1999) in OpenMx (Boker et al., 2011) was used to estimate the genetic and environmental parameters that best fit the observed covariance between twins in the total and subscale scores of the SMS. A univariate ACE model was used to test the effects of additive genetic factors (A), common environmental factors (C) and specific environmental factors that also includes measurement errors (E). We compared the full ACE model with the nested CE, AE models using the  $\chi^2$  difference test (Rijsdijk and Sham, 2002). A non-significant  $\chi^2$  of either the AE or the CE model compared with the full ACE model would indicate that the parsimonious AE or CE model was preferred. Otherwise, the full ACE model was reported. When there is a trend towards statistical significance (0.05|<|p\_i|<|0.1) where the ACE model is a better-fit to the data than the nested AE and CE models but the full ACE model had a lower AIC, we reported the full ACE model.

In Study 2, we examined group differences in levels of social mistrust (Wilcoxon signed-rank test) adjusting for non-normality. Although there were significant group differences in IQ and age, we did not find significant correlations between the SMS and age or IQ (ps|>|0.05) in each group. In addition, lower IQ might reflect an innate characteristic of schizophrenia patients. Thus, we did not control for the effects of IQ and age for subsequent group comparisons. Considering the skewness of the SMS scores, we calculated the Spearman correlations between the social mistrust scale (SMS) and clinical symptoms assessed by the PANSS to examine the convergent validity of the SMS. To assess the sensitivity of the SMS in differentiating clinical and non-clinical populations, we conducted Receiver Operating Characteristic Curve (ROC) analysis (Hanley and McNeil, 1982) with group membership as the dependent variable predicted by the SMS total score (independent variable). An AUC (area under the curve) value significantly larger than 0.5 suggests that the SMS is better than chance in predicting group membership of the

individual.

# 3.3 Results

# 3.1.3.1 Study 1

### **3.1.1.**3.1.1 Structure of the SMS

Our EFA results in older twin sample supported the two-factor structure where home and school mistrust belonged in one factor, and general mistrust was a separate factor (Supplementary Table 4). For the CFA models, the initial two-factor (mistrust (home & school) vs. general trust) and three-factor model (home mistrust, school mistrust and general mistrust) were both acceptable and almost equal in terms of good-of-fit indices. However, the three-factor model outperformed the two-factor model after several modifications. The two-factor model with modifications can be found in Supplementary Figure. 1. Table 1 documents all models tested and the final three-factor model (home mistrust, school mistrust, and general mistrust) with minor modifications that fitted the younger twin data best ( $\chi^2(df) = 109.72(47)$ , p < 0.001, CFI/TLI = 0.98/0.97, RMSEA = 0.036 (90% CI [0.027 0.045], p = 0.997, WRMR = 0.971) (Figure. 1). Measurement invariance models showed that the final three-factor model was structurally invariant (step 1) across younger and older children. However, means (step 2) were significantly higher on items 3,4,10 but significantly lower on items 1, 9 for younger children compared with older children. Measurement invariance models across genders established structural equivalence across genders, although mean levels of home mistrust was significantly higher for boys than for girls.

**Table 1** Confirmatory factor analysis models for the sSocial mMistrust Scale (SMS).

Model	$\chi^{2}(df)$	CFI	TLI	RMSEA 90% CI	p	WRMR	AIC (χ²-df)
Single factor (Mistrust)	527.40 (54)	0.832	0.795	0.092 (0.085 <u>-</u> 0.099)	0.000	2.272	419.40
Two factors Mistrust vs. trust)	247.62 (53)	0.931	0.914	0.059 (0.052 <del>-</del> _0.067)	0.018	1.547	141.62
Three factors Home, school and general mistrust)	246.77 (51)	0.931	0.910	0.061 (0.053- <u>_</u> 0.068)	0.010	1.523	144.77
Modification indices for two-factor model							
M1. SMS11 with SMS12	192.28 (52)	0.950	0.937	0.051 (0.043- <u>_</u> 0.059)	0.409	1.346	88.28
M2. SMS9 with SMS10	172.14 (51)	0.957	0.944	0.048 (0.040 <u>-</u> _0.056)	0.667	1.265	70.14
M3. SMS1 with SMS3	162.80 (50)	0.960	0.947	0.047 (0.039- <u></u> 0.055)	0.750	1.217	62.80
Modification indices for three-factor model							
11. MS11 with SMS12	175.35 (50)	0.956	0.941	0.049 (0.041 <u>-</u> 0.057)	0.562	1.263	75.35
42. SMS9 with SMS10	136.41 (49)	0.969	0.958	0.041 (0.033- <u>_</u> 0.050)	0.956	1.103	38.41
M3. SMS5 with SMS6	119.63 (48)	0.975	0.965	0.038 (0.029 <del></del> 0.046)	0.991	1.028	23.63
14. SMS1 with SMS3	109.72 (47)	0.978	0.969	0.036 (0.027 <del>-</del> 0.045)	0.997	0.971	15.72

Notes. CFI = comparative fix index; TLI = Tucker-Lewis index; RMSEA = root mean squared error of approximation; WRMR = weighted root mean square residual; AIC = Akaike s information criterion; M1 = modification indices model 1; SMS = Social Mistrust Scale. p < 0.01 for all  $\chi^2$  statistic. **The final model is in bold**.

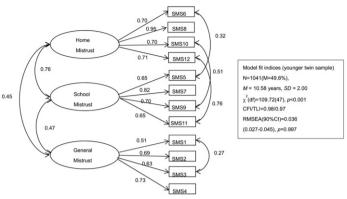


Figure 1 Fig. 1 Three-factor model of mistrust with minor modification in the younger twin subsample (N = 1041).

Notes. CFI = comparative fix index; TLI = Tucker-Lewis index; RMSEA = root mean squared error of approximation; WRMR = weighted root mean square residual; AIC = Akaike information criterion.

alt-text: Fig. 1

### 3.1.2.3.1.2 Prevalence of social mistrust

Total mistrust scores were positively skewed (M=2.82, SD=3.07) with more than two-thirds of the children reporting three points or less (69%) and a small group of 'mistrustful' children reporting high levels of suspiciousness (six points and above) (top 15%; 1 standard deviation above the mean) (Supplementary Figure, 2). As predicted, item endorsements were highest for school mistrust items (e.g., 9.6%; 'I worry too much about others trying to get at me at school' and 7.9%; 'being a target at school'), followed by a small percentage of children reporting home mistrust (2.5%-5.4%) and general (0.9%-3.7%) (Supplementary Table 5).

Males reported significantly higher levels of mistrust than females (F[1, 2080]=[6.53, p=[0.01; SMS total score:  $M_{\text{male}}$ =[2.99, SD=[3.14  $M_{\text{female}}$ ]=[2.65, SD=[2.99). However, this result should be interpreted with caution as the effect size of gender difference was quite small (Cohen-18 d = 0.11), indicating that this significance may be a result of our large sample size and deserves further investigation. Contrary to Wong et alet al. (2014), we did not find a significant main effect for age (p=[0.24) or interaction between age and gender (p=[0.67).

### 3.1.3.3.1.3 Heritability of social mistrust

ICCs of MZ and DZ twins are shown in Table 2. The ICCs of the total SMS score and its subscales were high and statistically significant in both MZ (r = 0.50 - 0.63, p < 0.01) and DZ (r = 0.46 - 0.52, p < 0.01) twins, demonstrating shared environmental effects. Except for the general mistrust subscale where ICCs for MZ and DZ twins were almost identical, the MZ twins had significant higher correlations than the DZ twins in both school mistrust (p = 0.04) and home mistrust (p = 0.01), indicating differential genetic effects for the subscales. For the total SMS score, the difference in ICCs demonstrated a trend towards statistical significance with the MZ twins having higher correlations than the DZ twins (p = 0.06).

**Table 2** ICCs and ACE models of social mistrust and its subscales in the twins sample (N = 1512).

alt-text: Table 2									
	ICC (MZ)	ICC (DZ)	A (95% CI)	C (95% CI)	E (95% CI)	Model	$\chi^2$ (df)	AIC	
SMS total	0.62**	0.52**	0.194 (0-0.45)	0.424 (0.17 <del>-</del> _0.62)	0.382 (0.34 <b>-</b> _0.43)	ACE	3946.04 (1508)	930.04	
General mistrust	0.50**	0.52**	=	0.504 (0.45- <u>-</u> 0.56)	0.496 (0.44 <del>-</del> _0.55)	CE	4066.19 (1509)	1048.19	
Home mistrust	0.63**	0.49**	0.402 (0.18- <u></u> 0.66)	0.242 (0 <del>-</del> _0.45)	0.356 (0.31 <del>-</del> _0.40)	ACE	3934.72 (1508)	918.72	

School mistrust	0.58**	0.46**	0.262 (0.03 <u>-</u> 0.54)	0.320 (0.05 <u>-</u> 0.54)	0.418 (0.37 <b>-</b> _0.47)	ACE	4002.14 (1508)	986.14

Notes. SMS = Social Mistrust Scale; ICC, intra-class correlation coefficients; MZ, monozygotic twins; DZ, dizygotic twins; A, additive genetic factors; C, shared environmental factors; E, specific environmental factors; AIC, Akaike<sup>1</sup>/<sub>2</sub>s information criterion.

\*\* *p* < 0.01.

As shown in Table 2, the ACE model best fit the measure of total mistrust, school mistrust and home mistrust ( $h^2 = 19.4\%$ , 26.2%, 40.2%, respectively). For the SMS total score, although additive genetic effects only showed a trend towards statistical significance (p = 0.07), the full ACE model had lower AIC (AIC = 930.04) compared to CE model (AIC = 931.29). Similarly for the home mistrust subscale, common environmental effects only reached marginal significance (p = 0.06) but the ACE model (AIC = 918.72) had lower AIC value than the AE model (AIC = 920.28). Thus we report the full ACE models in these two cases. For the general mistrust subscale, the CE model best fit the data with both the common and unique environment factors accounting for half of the total variance.

# 3.2.3.2 Study 2: eCorrelational analysis of the SMS

More than half of the patients with schizophrenia (n=18, 56.25%) scored six or above on the SMS (M=6.34, SD=4.73), the equivalent of scoring in 1 standard deviation above the mean (the top 15%) in community samples (Supplementary Figure, 3). Compared with healthy controls, adolescents with schizophrenia scored significantly higher on all three subscales of the SMS (ps<0.05) (Supplementary Table 6), specifically for three school mistrust items and a general mistrust item identified with an asterisk (ps<0.05, Supplementary Figure, 4).

ROC analysis revealed good discriminate validity for the social mistrust items (area under the curve (AUC) = 0.798, p < 0.01; 95% CI [0.689 - 0.906]), with 3.5 being the best cut-off point with the highest sensitivity (0.719) and specificity (0.824) (Supplementary Figure. 5).

The PANSS positive subscale scores showed trend significance in being positively correlated with the SMS total score (r/32/=0.32, p/=0.076). However, we did not find significant associations between the SMS and the suspiciousness/persecution item (P6) on the PANSS. We found that the SMS total and its subscale scores were significantly correlated with a broad range of clinical psychotic symptoms assessed by the PANSS, including the PANSS general subscale scores, total scores and some specific negative and general symptom items (e.g., social and emotional withdrawal, stereotyped thinking and unusual thought content) (range r/=0.36, r/=0.05), r/=0.05, r/=0.05) (Table 3).

**Table 3** Spearman correlations of clinical symptoms measured by the PANSS and the SMS (n=32)

alt-text: Table 3											
	Positive	Negative	General	-Total	Passive/apathetic social withdrawal (N4)	Stereotyped thinking (N7)	Anxiety (G2)	Unusual thought content (G9)	Poor attention (G11)	Lack of judgement and insight (G12)	Poor-impulse control (G14)
SMS total	0.32†	0.32†	0.44*	0.46**	₩	0.46**	==	0.47**		0.44*	=
School mistrust	==	==	0.36*	=	=	0.53**	0.39*	0.55**	=	E	=
Home mistrust	==	==	==		0.37*	=	=	=	0.40*	€	0.40*
General mistrust	==	==	=	=	=	=	=	=	=	0.40*	=

Notes. †0.05 | p | 0.01. \*p | 0.05. \*\*p | 0.01. Positive = Positive and Negative Syndrome Scale – positive symptoms; Negative = Positive and Negative Syndrome Scale – negative symptoms; General = Positive and Negative Syndrome Scale – symptoms; Total = Positive and Negative Syndrome Scale – total score; SMS = Social Mistrust Scale. To have a more comprehensive view of the relationship between the SMS and PANSS, we reported the correlations between SMS total scores and positive/negative subscales of PANSS although they only reached marginal significance. Other correlational estimates (e.g., correlations between PANSS items and SMS) only with a trend towards significance were not reported in the table.

# 4.4 Discussion

In the first large-scale twin study of Chinese children and adolescents, these two related but independent studies revealed three key insights into childhood suspicions: First, childhood social mistrust existed on a continuum of severity. Second, childhood suspicions demonstrated moderate heritability (total mistrust = 26%, home mistrust = 40%). Third, the Social Mistrust Scale (SMS) was found to have good discriminant validity in adolescents with childhood-onset schizophrenia versus healthy controls (AUC = 0.80), demonstrating moderate associations with multiple aspects of psychopathology in schizophrenia as assessed by the PANSS (rs = 0.32—0.55).

### 4.1.4.1 Structure and prevalence of social mistrust

The Chinese version of the SMS was psychometrically robust, with three inter-correlated factors best fitting the data. However, it should be noted that the two-factor model (mistrust [home & school] vs. general trust) was also a good fit in our Chinese sample. Given that this is the first study to assess the structure of the SMS, future research is needed to validate the structure of the SMS across cultures.

Replicating the findings from previous adult and community child studies, levels of social mistrust in 8- to 14-year-olds followed an exponential curve, with school mistrust being the most prevalent (Bebbington et al., 2013; Freeman, 2006; Wong et al., 2014). However, Chinese boys reported significantly higher levels of social mistrust than girls, contrary to Wong et al., set al. (2014) findings where no gender difference was found. A post-hoc analysis demonstrated that the absolute gender difference was small (M<sub>diff</sub> = 0.34; Cohen to the significant result may be due to our large sample size.

Our findings also suggest important cultural differences in levels of mistrust. In contrast to Wong et al.'s (2014) study where social mistrust showed age-related decline in the levels of mistrust, we did not find any developmental changes in Chinese children and adolescence. Overall, Chinese children reported much lower levels of home mistrust (2.5%-5.4%) compared with children from Hong Kong (4%-6%) and the UK (4%-10%) (Wong et al., 2014). It is possible that these lower rates reflect a culture-specific Confucian ideology in mainland China, where a secure and trusting family environment is highly valued. Alternatively, this contrast could also be due to children under-reporting in the home domain, as they may view mistrust as a 'private' matter not to be disclosed to outsiders. In both instances, replicating this study and conducting more detailed qualitative interviews with mistrustful and trusting children may help to clarify the nature of childhood suspiciousness in China.

### 4.2.4.2 Heritability of social mistrust

Findings from our twin study design demonstrated moderate heritability of childhood social mistrust (19%\_40%), with significant shared environmental effects on all levels of social mistrust (24%\_50%), and significant genetic effects influencing home mistrust in particular (40%). This contrasts findings from previous twin studies of older adolescents (aged 16 years and above) from the West, where shared environmental effects are negligible (Shakoor et al., 2015a, 2015b, 2016). This difference in findings may be due to age contrasts, as children in the current study were younger (aged 8\_14 years) and perhaps, more affected by the family environment (i.e., shared environment) in developing interpersonal relationships. It is possible that children in the current study have yet to experience the same level of unique environmental stressors (e.g., academic pressure and stressful life events) that older children in previous studies may have already endured, as stressful events are known to increase with age (Shakoor et al., 2016). Although the influence of the unique environment was less prominent in our younger sample, it still accounted for 38% of the variance in total social mistrust scores. This is consistent with previous findings suggesting that some environmental risk factors for psychotic disorders are individual-specific experiences, such as childhood trauma (Read et al., 2005) and cannabis use (Winkel and Kuepper, 2014).

## 4.3.4.3 Discriminant validity of the SMS

Compared with healthy controls, adolescent patients with childhood-onset schizophrenia reported significantly higher mean levels of social mistrust ( $M_{\text{diff}} = 4.11$ , p < 0.05). Patients reporting more suspicions also had more severe clinical symptoms. Social mistrust was moderately correlated with a broad range of psychotic symptoms; specifically, negative symptoms such as social and emotional withdrawal were positively correlated with social mistrust, suggesting that patients with excess suspiciousness of others may safeguard against malicious intents of others by avoiding social interactions altogether. It is also possible that patients who minimize social interactions are more likely to develop a more persistent form of paranoia, as they are less likely to be exposed to subsequent positive social interactions that may counter their past negative experiences. Patients reporting higher levels of mistrust at school also displayed higher levels of anxiety; meanwhile, patients with higher levels of home mistrust were more hostile and aggressive (p = 0.31, p = 0.08), perhaps suggesting the need of self-defence. This context-specific result was consistent with Wong et al. set al. (2014) study indicating school mistrust was more predictive of anxiety while home mistrust was more associated with aggression. The finding that the SMS is just as correlated to the general symptoms on the PANSS than only to the delusional ideation/paranoia item indicates that the SMS is linked to multiple aspects of psychopathology in the schizophrenia group. However, it may be the case that the SMS being a dimensional assessment tool with 12 items is indeed tapping into more dimensions of suspiciousness than the single-item on the PANSS is assessing.

### 4.4.4.4 Limitations

This study has several methodological limitations. First, in order to achieve a sufficiently powered sample, we relied on single informant child-report measures of behaviour, which might have inflated the observed relationships. Corroborating child reports with interviews and peer reports (not parent- or teacher-reports as previously found, Wong et al., 2014) may provide a better understanding of the causes of mistrust in future studies. Second, our twins

sample in study 1 was a convenience sample and may not be representative enough for children and adolescents in mainland China, however it does provide the first assessment of the heritability of childhood social mistrust. Third, adolescent patients with schizophrenia in Study 2 were older and had a significantly lower estimated IQ than healthy controls, which might have biased our results. However, post-hoc analysis showed no evidence of a direct relationship between social mistrust and IQ (p)>[0.05), suggesting that the SMS items were probably not confounded by IQ. Fourth, this study was cross-sectional in design and Future longitudinal studies should be conducted to help us understand the causes of childhood social mistrust.

### 4.5.4.5 Conclusions

To our knowledge, this is the first evidence of the prevalence, structure, and heritability of childhood social mistrust in two independent but related samples of mainland Chinese children and adolescents. We demonstrated for the first time that the Social Mistrust Scale (SMS) has good discriminate validity in identifying adolescents with childhood-onset schizophrenia from healthy controls and moderate associations with the PANSS, a standardized clinical measures of schizophrenia symptoms. The present findings documented that childhood social mistrust is also prevalent in non-Western children and adolescents, providing valuable cross-cultural evidence to the existing adult literature and theory of paranoia. Our findings support the use of the SMS in Chinese children.

# Acknowledgements

This study was supported by grants from the National Key Research and Development Programme (2016YFC0906402), the Beijing Training Project for the Leading Talents in S & T (Z151100000315020), the Beijing Municipal Science & Technology Commission Grant (Z161100000216138), and a grant from the CAS Key Laboratory of Mental Health, Institute of Psychology. Keri Wong is funded by the Betty Behrens Research Fellowship at Clare Hall College, University of Cambridge. The authors would like to thank for the staff from the Beijing Twin Study (BeTwiSt) of Institute of Psychology, Chinese Academy of Sciences to help liaise and collect the twins data.

## **Conflict of interest**

None

# **Contributors**

Han-yu Zhou analyzed and interpreted the data, and wrote up the first draft of the manuscript. Keri Wong analyzed and interpreted the data, and wrote up the first draft of the manuscript. Li-juan Shi, Xi-long Cui, Yun Qian, Wen-qing Jiang, Ya-song Du, Simon Lui, Xue-rong Luo collected the clinical data, making clinical diagnosis and rating for the childhood onset schizophrenia cases. Zheng-hui Yi and Eric Cheung commented significantly to the drafts of the manuscript. Anna Docherty interpreted the findings and contributed significantly to the paper writing. Raymond Chan designed the study, interpreted the findings, and contributed significantly to the writing up of the manuscript. All authors contributed to and have approved the final text.

# Role of **Ffunding Ssources**

The funding agents had no role in the study design, collection, analysis or interpretation of findings, and the decision to publish the findings.

# Appendix A. Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.03.027.

## References

American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 1994, American Psychiatry Association; Washington, DC.

Bebbington P.E., McBride O., Steel C., Kuipers E., Radovanovič M., Brugha T., Jenkins R., Meltzer H.I. and Freeman D., The structure of paranoia in the general population, Br. J. Psychiatry 202 (6), 2013, 419-427.

Berry K., Bucci S., Kinderman P., Emsley R. and Corcoran R., An investigation of attributional style, theory of mind and executive functioning in acute paranoia and remission, Psychiatry Res. 226 (1), 2015, 84-90.

Boker S., Neale M., Wilde M., Spiegel M., Brick T., Spies J., Estabrook R., Kenny S., Bates T., Mehta P. and Fox J., OpenMx: an open source extended structural equation modeling framework, *Psychometrika* **76**, 2011, 306–317.

Brown T.A., Confirmatory Factor Analysis for Applied Research, 2006, Guilford Publications.

- Chan R.C., Li X., Lai M.K., Li H., Wang Y., Cui J., Deng Y. and Raine A., Exploratory study on the base-rate of paranoid ideation in a non-clinical Chinese sample, Psychiatry Res. 185 (1), 2011, 254-260.
- Chen J., Li X., Chen Z., Yang X., Zhang J., Duan Q. and Ge X., Optimization of zygosity determination by questionnaire and DNA genotyping in Chinese adolescent twins, Twin Res. Hum. Genet. 13 (2), 2010, 194-200.
- Chen J., Li X., Zhang J., Natsuaki M.N., Leve L.D., Harold G.T., Chen Z., Yang X., Guo F., Zhang J. and Ge X., The Beijing Twin Study (BeTwiSt): Aa longitudinal study of child and adolescent development, Twin Res. Hum. Genet. 16 (1), 2013, 91-97.
- Combs D.R., Michael C.O. and Penn D.L., Paranoia and emotion perception across the continuum, Br. J. Clin. Psychol. 45 (1), 2006, 19-31.
- Fagnani C., Bellani M., Tansella M., Balestrieri M., Toccaceli V., Patriarca V., Stazi M.A. and Brambilla P., Investigation of shared genetic effects for psychotic and obsessive symptoms in young adult twins, *Psychiatry Res.* **188** (2), 2011, 276-282.
- Freeman DD., Delusions in the nonclinical population, Curr. Psychiatry Rep. 8 (3), 2006, 191-204.
- Freeman D., McManus S., Brugha T., Meltzer H., Jenkins R. and Bebbington P., Concomitants of paranoia in the general population, Psychol. Med. 41 (5), 2011, 923-936.
- Hanley J.A. and McNeil B.J., The meaning and use of the area under a receiver operating characteristic (ROC) curve, Radiology 143 (1), 1982, 29-36.
- Kay S.R., Fiszbein A. and Opfer L.A., The positive and negative syndrome scale (PANSS) for schizophrenia, Schizophr. Bull. 13 (2), 1987, 261.
- Lenhard W. and Lenhard A., Hypothesis Tests for Comparing Correlations, availablehttps://www.psychometrica.de/correlation.html 2014, Psychometrica; Bibergau (Germany).
- Marsh H.W., Muthén B.O., Asparouhov T., Lüdtke O., Robitzsch A., Morin A.J.S. and Trautwein U., Exploratory structural equation modeling, integrating CFA and EFA: application to students' evaluations of university teaching Struct. Equ. Model. 16 (3), 2009, 439-476.
- McGue M. and Bouchard T.J., Adjustment of twin data for the effects of age and sex, Behav. Genet. 14 (4), 1984, 325-343.
- Muthen L.K. and Muthén B.O., Mplus User S Guide, v. 6.1, 2010, Muthen and Muthén, UCLA; Los Angeles, CA.
- Neale M.C., Boker S.M., Xie G. and Maes H.M., Statistical Modeling, 1999, Department of Psychiatry, Virginia Commonwealth University; Richmond, VA.
- Read J., Van O.J., Morrison A.P. and Ross C.A., Childhood trauma, psychosis and schizophrenia: a literature review with theoretical and clinical implications, Acta Psychiatr. Scand. 112 (5), 2005, 330-350.
- Rijsdijk F.V. and Sham P.C., Analytic approaches to twin data using structural equation models, Brief Bioinform, Brief, Bioinform, 3 (2), 2002, 119-133.
- Sartorius N., Jablensky A., Korten A., Ernberg G., Anker M., Cooper J.E. and Day R., Early manifestations and first-contact incidence of schizophrenia in different cultures: Aa preliminary report on the initial evaluation phase of the WHO Collaborative Study on Determinants of Outcome of Severe Mental Disorders, *Psychol. Med.* 16 (4), 1986, 909-928.
- Shakoor S., McGuire P., Cardno A.G., Freeman D., Plomin R. and Ronald A., A shared genetic propensity underlies experiences of bullying victimization in late childhood and self-rated paranoid thinking in adolescence, *Schizophr. Bull.* 41 (3), 2015a, 754-763.
- Shakoor S., Zavos H.M., McGuire P., Cardno A.G., Freeman D. and Ronald A., Psychotic experiences are linked to cannabis use in adolescents in the community because of common underlying environmental risk factors, *Psychiatry Res.* **227** (2), 2015b, 144-151.
- Shakoor S., Zavos H.M., Haworth C.M., McGuire P., Cardno A.G., Freeman D. and Ronald A., Association between stressful life events and psychotic experiences in adolescence: evidence for gene-environment correlations, Br. J. Psychiatry 208 (6), 2016, 532-538.
- Su L. and Li X., Normalization of the Chinese version of Achenbach. S Child Behavioural Checklist in Hunan province, Chin. J. Clin. Psychol. 4 (1), 1996, 24-28, (in Chinese).
- Van Os J., Linscott R.-J.R.I., Myin-Germeys I., Delespaul P. and Krabbendam L., A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder, *Psychol. Med.* **39** (2), 2009, 179-195.
- Winkel R.V. and Kuepper R., Epidemiological, neurobiological, and genetic clues to the mechanisms linking cannabis use to risk for nonaffective psychosis, Annu. Rev. Clin. Psychol. 10 (1), 2014, 767-791.

Wong K.K., Freeman D. and Hughes C., Suspicious young minds: paranoia and mistrust in 8-to 14-year-olds in the UK and Hong Kong, Br. I. Psychiatry 205 (3), 2014, 221-229.

Zavos H.M., Freeman D., Haworth C.M., McGuire P., Plomin R., Cardno A.G. and Ronald A., Consistent etiology of severe, frequent psychotic experiences and milder, less frequent manifestations: a twin study of specific psychotic experiences in adolescence, JAMA Psychiatry 71 (9), 2014, 1049-1057.

# Appendix A. Appendix A. Supplementary data

Multimedia Component 1

Supplementary material

alt-text: Image 1

## **Queries and Answers**

### **Query:**

Please check the layout and presentation of Tables 1-3 if correct and amend as necessary.

Answer: Yes

**Query:** 

Your article is registered as a regular item and is being processed for inclusion in a regular issue of the journal. If this is NOT correct and your article belongs to a Special Issue/Collection please contact s.gudiseva@elsevier.com immediately prior to returning your corrections.

Answer: Yes

Query:

Please confirm that given names and surnames have been identified correctly and are presented in the desired order, and please carefully verify the spelling of all authors' names.

Answer: Yes

Query:

The author names have been tagged as given names and surnames (surnames are highlighted in teal color). Please confirm if they have been identified correctly.

Answer: Yes

Query:

Please check the hierarchy of the section headings and confirm if correct.

**Answer:** For the 2.2.Measures section, we don't need the heading of 2.2.1. Please just put "social mistrust" in the text.

Query:

Please provide the corresponding grant number(s) for the following grant sponsor(s): "CAS Key Laboratory of Mental Health, Institute of Psychology".

**Answer:** Sorry, but we don't have a grant number for the CAS Key Laboratory of Mental Health, Institute of Psychology.

Query:

Please check if grant sponsor names were captured correctly and amend as necessary.

**Answer:** Yes, they were captured correctly.

### Query:

Supplementary caption was not provided. Please check the suggested data if appropriate, and correct if necessary.

**Answer:** We have checked the supplementary materials. The data were correct and appropriately presented.