Stress across the life course and depression in a rapidly developing population: The Guangzhou Biobank Cohort Study

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Key points

- In a developing setting where specific childhood adversities are prevalent, childhood adversities and adulthood stressors were independently associated with depression among older adults.

- Adulthood stressors were more strongly associated with depressive symptoms among individuals with a history of childhood adversities, possibly providing evidence for stress sensitisation in the developing setting.

- Consistent findings of stress sensitisation for depression in settings with different social patterning suggest the relation between stress and depression is biologically mediated rather than contextually specific.

ABSTRACT

Objective: To examine the role of stress across the life course in the development of depression among older adults in a non-Western developing setting.

Methods: Multivariable linear and multinomial logistic regression were used in cross-sectional analyses of 9729 Chinese participants (mean age 60.2 years) from phase 3 of the Guangzhou Biobank Cohort Study (2006-8) to investigate the association of childhood adversities and adulthood stressors with depression.

Results: Childhood adversities were associated with mild depression (odds ratio (OR) 1.78, 95% CI 1.58-2.02) and moderate-to-severe depression (OR 2.30, 95% CI 1.68-3.15), adjusted for age, sex, education and childhood socio-economic status. Past-year adulthood stressors were also associated with mild depression (OR 1.96, 95% CI 1.54-2.02) and moderate-to-severe depression (OR 3.55, 95% CI 2.21-5.68), adjusting additionally for occupation and income. Adulthood stressors were more strongly associated with depressive symptoms among individuals with a history of childhood adversities.

Conclusions: Childhood adversities and adulthood stressors were independently associated with an increased risk of depression among older ambulatory adults, though adulthood stressors were more strongly associated with depression following exposure to childhood adversities. This is consistent with evidence from Western settings in which the social context of risk and protective factors for depression may differ, and implies that the role of stress in the aetiology of depression is not context-specific.

Introduction

Risk of depression may be established in childhood (Gilman, 2007) and depression often emerges by early adulthood (Zisook *et al.*, 2007). Factors associated with risk for depression include socioeconomic disadvantage (Ritsher *et al.*, 2001) and traumatic experiences during childhood (Widom *et al.*, 2007). Identifying modifiable environmental exposures early in life may facilitate prevention of depression later among older adults. Childhood adversity (CA) is a public health concern in developed countries (Gilbert *et al.*, 2009) and is of increasing concern in developing countries particularly because of the increasing numbers of "left-behind children", who live at home without one or both parents due to the rapid rise in domestic and international migrant workers. Left-behind children accounted for 25% of children in China (UNICEF and National Bureau of Statistics of China, 2013), whereas studies in the United States and the United Kingdom reported parental absence in 9.3% and 16.1% of children, respectively (Clark *et al.*, 2010; Kessler *et al.*, 1997).".

As in the West, CA may have strong adverse effects on mental health in China, yet the long term impact of childhood experiences are less clear in developing countries. CA may have less pronounced effects on mental health in China because of differences in the social and economic context. The social fabric of Chinese culture which values family harmony (Fang *et al.*, 2004; Xu *et al.*, 2007a) may mitigate the harms associated with CA, as family harmony was found to moderate the relationship between life stress and depressive symptoms among Chinese (Kavikondala *et al.*, 2015). While separation from a parent during childhood has been associated with depressive symptoms in adulthood in the West

(Kessler *et al.*, 1997; Pesonen *et al.*, 2007), such childhood adversities are emerging in developing countries due to increasing numbers of left-behind children.

The stress sensitisation hypothesis, based on the diathesis-stress model (Monroe and Simons, 1991) posits that adverse effects of stressful life events (SLE) in adulthood are potentiated among individuals with a history of CA (Hammen *et al.*, 2000). Stress sensitisation may operate across the life course by a number of mechanisms. CA may preclude the development of coping mechanisms such that life events are found more stressful. CA may also engender greater vulnerability through disruption of biological regulatory processes (Shonkoff *et al.*, 2009). Stress sensitisation effects for depression and other psychiatric disorders have been observed in Western developed settings (Gilman *et al.*, 2015; McLaughlin *et al.*, 2010), but data from low- and middle-income countries are limited (Norman *et al.*, 2012). This is consistent with the general under-representation of mental health research from developing countries (Patel and Kim, 2007). Despite rapid economic progress in Guangzhou, the provincial capital of Guangdong province in southern China, there has also been periods of significant hardships such as during the Japanese occupation in the 1940s, the Great Leap Forward in the late 1950s (MacFarquhar, 1983), and the Cultural Revolution in the 1960s. Most older adults in Guangzhou grew up in limited economic circumstances compared to older adults in developed settings. Thus, older residents of Guangzhou provide a unique opportunity to gain an early insight into the long-term effects of life course stress, where our findings will be relevant to other parts of China and to other parts of the world currently undergoing rapid economic development. To our knowledge, the stress sensitisation hypothesis for depression has not been tested in a non-Western developing setting.

A causal link between CA and depression, moderated by SLE, is plausible. However, CA, SLE and depression are associated with lower socio-economic status (SES) in Western populations (Gilman *et al.*, 2002; Hatch and Dohrenwend, 2007), making residual confounding in developed settings a possibility. By comparing associations in populations where confounding structures such as socioeconomic factors differ, we may improve causal inference (Au Yeung and Schooling, 2014). Moreover, testing theories developed in Western populations in a very different setting, i.e., a developing non-Western country, may clarify their relevance to the global population. Accordingly, we examined the association of CA and SLE with depression, and provide one of the first tests of the stress sensitisation hypothesis in a developing setting.

Methods

Study design and sample

The Guangzhou Biobank Cohort Study (GBCS) is a collaboration between Guangzhou No.12 Hospital and the Universities of Hong Kong and Birmingham, UK, as described in detail elsewhere (Jiang *et al.*, 2006). Recruitment of participants draws from the Guangzhou Health and Happiness Association for the Respectable Elders (GHHARE), a community social and welfare association unofficially aligned with the municipal government where membership is open to anyone 50 years of age or older for a monthly, nominal fee of 4 yuan (50 US cents). Approximately 7% of permanent Guangzhou residents aged 50 years or more are members of GHHARE, of which 33% enrolled in each of three phases of recruitment.

In phase 3 the questionnaire included the validated Chinese version of the 15-item Geriatric Depression Scale (GDS) (Lim *et al.*, 2000). Phase 3 participants were recruited

from September 2006 to January 2008. Members were included if they were capable of consenting, ambulatory, and not receiving treatment modalities that, if omitted, might result in immediate life-threatening risk, such as chemotherapy or radiotherapy for cancer or dialysis for renal failure. The Guangzhou Medical Ethics Committee of the Chinese Medical Association approved the study and all participants gave written, informed consent before participation.

Measures

Depression

Depressive symptoms were assessed using GDS, considered as a continuous score. Depressive symptoms were also categorised as mild "depression" (5 to 9 depressive symptoms), moderate-to-severe "depression" (≥ 10 depressive symptoms) or non-depressed (0 to 4 depressive symptoms) (Yesavage and Sheikh, 1986). As GDS is a screening instrument, "depression" corresponds to probable depression, requiring confirmation from diagnostic interviews. Various cut-off scores for the 15-item GDS have been reported in Chinese populations. We therefore applied different GDS cut-offs for depression: ≥4 (Lim *et al.*, 2000), and ≥8 (Cheng and Chan, 2004) in sensitivity analyses.

Childhood adversity

Participants completed a detailed questionnaire at the baseline examination, which included culturally sensitive questions to assess CA events before the age of 18 years: continuous separation from mother for more than a year, parents frequently quarrelling, sent away from home due to wrongdoing or an experience so frightening that it has been

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thought about years afterwards. CA was defined as at least one of the four adverse experiences during childhood.

Stressful life events

Participants were assessed on ten major life events in the past year including: separated or divorced, unemployed or retired, business bankruptcy, physically assaulted, major conflict within family, major injury or traffic accident, death of spouse, major illness or death of a close family member, major natural disaster (such as flood or drought), loss of all sources of income or living on debt. Respondents assessed the impact of each event using a five-point Likert-type scale: very positive, positive, neutral, negative or very negative impact. Past-year SLE was defined as at least one major life event in the last year with a perceived negative or very negative impact. However, SLE can also be considered as any major life event regardless of how it is perceived; as a sensitivity analysis we repeated the analysis using past year life event (LE), i.e., at least one major life event in the last year.

Childhood socio-economic status

Childhood SES, a potential confounder (Gilman *et al.*, 2002) between CA and depression was assessed in the GBCS, taking into account the cultural and historical context of mid-20th century southern China, from an index of parental possessions during childhood comprising a bicycle, a watch, and a sewing machine (Schooling *et al.*, 2008).

Statistical Analysis

We used chi-square tests to compare characteristics by CA and past-year SLE. We used multivariable linear and multinomial logistic regression to assess the adjusted associations of CA and past-year SLE with depressive symptom score and with different categories of GDS "depression", respectively. The association of CA with the outcomes was adjusted for age, sex, education and childhood SES as potential confounders, and then additionally for past-year SLE. The association of past-year SLE with the outcomes was adjusted for age, sex, childhood SES, education, occupation and personal income as potential confounders and then additionally for CA. To test the stress sensitisation hypothesis, we examined whether the association of CA with depressive symptoms or depression varied with the presence of past-year SLE from the heterogeneity across strata and from model fit using the Akaike Information Criterion (AIC) (Akaike, 1974), comparing a model including the relevant interaction term and any potentially confounding interactions with a model without the interaction term (Faraway, 2002). We tested the interaction of CA and past-year SLE with depressive symptoms on the additive scale. Interaction on the additive, rather than multiplicative scale, may give a better indication of mechanistic rather than statistical interaction (VanderWeele and Robins, 2007).

All analyses were performed in Stata release 12.1 (StataCorp, College Station, TX). A p-value of <0.05 (two-sided test) was considered statistically significant.

Results

Of the 10088 participants in GBCS phase 3, 9729 (96.4%) had complete data, and were included. Table 1 shows the socio-demographics of the study participants. The average age was 60.2 years, with men older (mean 63.1 years) than women (59.2 years).

Prevalence of Childhood adversity, Stressful life events and Depression

CA was reported by 37.1% of participants; 25.9% reported continuous separation from mother for more than a year, 10.2% had a frightening experience, 6.9% had parents frequently quarrelling and 2.3% had been sent away from home due to wrongdoing. Tetrachoric correlations between pairs of CAs were positive with a median value of 0.22 and an interquartile range of 0.10 to 0.30. 9.6% of participants reported a major life event in the past year, and 4.7% of participants had a past-year SLE (life event with a perceived negative impact). CA was associated with older age, lower childhood SES, less education, non-manual work and higher personal income (Table 1). CA was also more common among men, but this association was attenuated after adjustment for age. Past-year SLE was more common among women but was not associated with SES.

Average GDS score was 2.4 (standard deviation 2.3); 14.5% had depression with 12.8% having mild depression and 1.7% moderate-to-severe depression. Depression was associated with older age, less education, lower income and lower childhood SES (data not shown).

Childhood adversity and Depression

Composite CA and individual adversities was positively associated with depressive symptoms, adjusted for age, sex, education and childhood SES (Table 2, Table S1). Similarly adjusted, CA had a graded relation with mild and moderate-to-severe depression. These associations remained almost unchanged after additionally adjusting for past-year SLE

(Table 2), although CA was associated with past-year SLE (odds ratio (OR) 1.50, 95% confidence interval (CI) 1.24 to 1.82), adjusted for age, sex, childhood SES and education.

Stressful life events and Depression

Past-year SLE was positively associated with depressive symptoms, adjusted for age, sex, childhood SES, education, personal income, and occupation, which was unchanged after additionally adjusting for CA. Past-year SLE also had a graded relation with mild and moderate-to-severe depression, which again was almost unchanged after adjusting for CA (Table 2).

Stress sensitisation

The association of past-year SLE with depressive symptoms varied with exposure to CA. The AIC for a model including the interaction term was lower (44268.8) than for a model without (44270.0). Figure 1 shows the joint association of CA and past-year SLE with depressive symptoms, adjusted for age, sex, childhood SES, education, occupation and personal income. CA and past-year SLE together made a greater contribution to depressive symptoms than the sum of each of CA and past-year SLE.

Sensitivity analysis

Past-year LE (presence of any major life events regardless of perceived impact), was also positively associated with depressive symptoms and had a graded association with mild and moderate-to-severe depression (Table 3). CA was also associated with past-year LE (OR 1.36, 95% CI: 1.19, 1.57) adjusted for age, sex, childhood SES and education. However, the

association of CA with depressive symptoms and depression did not vary with past-year LE. Results were similar when different GDS cut-offs (≥ 4 and ≥8) were used for depression.

Discussion

In this sample of older ambulatory adults from an under-studied economically developing setting of southern China, CA was a common exposure. About 25% reported continuous separation from mother for more than a year during childhood (69.8% of all CAs reported). This may have resulted from the mass migration of workers from southern China to Hong Kong and other neighbouring regions during the period 1945-1955 (Vaughan and Dwyer, 1966), which corresponds to the childhood years of the sample. Consistent with previous findings from developed and developing countries (Chen *et al.*, 2008; Kendler *et al.*, 1999; Kessler and Magee, 1993; Lee *et al.*, 2011; Xu *et al.*, 2007b), both CA and past-year SLE were positively associated with depression in a non-Western developing population, adjusted for life course socio-economic status. However, CA and SLE may be less clearly associated with lower SES in a developing setting (Table 1) compared to the developed setting. Therefore if previously observed associations were due to confounding by SES, we would not expect to observe the same associations in a developing setting with a different confounding structure for CA and SLE (Batty *et al.*, 2009).

However, the association of CA with depression did not substantially change when additionally adjusting for SLE (Table 2), suggesting CA does not operate through SLE; rather, both CA and SLE may serve as independent triggers for the development of depression.

An alternative explanation for stress sensitisation is that exposure to childhood stressors generates a more negative perception of life events in adulthood. Negative perception of major life events (SLE) was more strongly associated with depression than any major life events (LE) (Table 2 compared with Table 3). However, our sample is not large enough to assess reliably whether CA contributed by generating less resilience to subsequent stressors and a more negative perception of life events, or whether environments where CA occurred tended to engender more traumatic life events. Consistent findings of stress sensitisation for depression in this study and in settings elsewhere, with a different confounding structure, suggest the relation between stress and depression is biologically mediated rather than contextually specific (Au Yeung and Schooling, 2014; Batty *et al.*, 2009). A possible biological mechanism for stress sensitisation is the enhanced expression of the FKBP5 gene among individuals with CA, which primes the dysregulation of the stress hormone system following SLE in adulthood (Klengel *et al.*, 2013).

The strengths of the study include a large population-based sample and the use of culturally sensitive assessments of CA, past-year SLE and childhood SES. This enabled an excellent response rate among older Chinese adults in a developing setting, where nearly all participants (>99%) responded to items on CA. Checklist inventories often include life events that may not be universally stressful (e.g. retirement), thus participants rated the impact of each major life event. Less than half the life events were perceived negatively reducing misclassification by only including life events with a perceived negative impact. Childhood SES was assessed by an index of parental possessions during childhood. This provided a novel proxy for childhood environment in the developing setting for adjustment

of childhood SES in the analysis. We also assessed interaction on an additive scale because it may represent a mechanistic effect (VanderWeele and Robins, 2007), Moreover, there has been general consensus in the epidemiological community that interactions of public health importance are additive interactions (Knol and VanderWeele, 2012; Rothman *et al.*, 2008; Saracci, 1980), which provide evidence for targeting subpopulations where interventions would be most effective (Greenland, 2009).

The findings are also subject to some limitations. First, CAs were retrospectively reported and susceptible to recall bias, and could be affected by current psychopathology. However, a reappraisal of retrospective reports suggested that current psychopathology does not reduce reliability or validity of recall of CA (Brewin *et al.*, 1993), and CAs ascertained from retrospective self-reports or from child protection services records give similar associations (Gilbert *et al.*, 2009). Moreover, CA is predominantly under-reported and over-reporting of CA is rare (Hardt and Rutter, 2004). Second, past-year SLE could either precede depression or be a consequence of depression i.e., the stress generation effect (Hammen, 1991), and the cross-sectional sample would not be able to distinguish this . However, CA by definition occurred before the age of 18 years, and thus precedes the occurrence of past-year SLE or current depression as these were assessed in participants aged 50 years or older. Cohorts spanning the life course with longitudinal measurements of CA, SLE and depressive symptoms in older people are rare in developed settings. The historical socio-economic context of developing countries precludes the existence of such long-running and resource-intensive prospective cohort studies. Third, family history of depression is a potential confounder of the association of CA and past-year SLE with depression (Weissman *et al.*, 2005) and was not available in the GBCS. Fourth, GBCS was

not designed to be population representative and participants may be more socially active and health conscious than the underlying population, which means estimates of prevalence may not be generalisable, although prevalence of diabetes and hypertension is similar to nationally representative samples of urban Chinese (Jiang *et al.*, 2006). However, internal estimates of associations, as studied here, are more likely to be generalisable, because associations are more likely to be consistent across groups. Fifth, CA was assessed from only four questions and may not be precisely measured compared to specific questions on abuse, however such questions were not thought to be socially acceptable for some of our older participants. Given that we only used two categories for CA this would again bias towards the null. Sixth, depression was assessed using a screening instrument (GDS) as diagnostic interviews could not be carried out in this large sample. In addition, post-traumatic stress disorder (PTSD) was not assessed in the GBCS. However, as the prevalence of PTSD in a large community sample in China was very low (Phillips *et al.*, 2009), the inclusion of participants with PTSD would therefore unlikely affect our findings. Concerns have also been raised regarding the use of diagnostic interviews in a developing setting (Guo *et al.*, 2009) and the poor correlation of DSM-5 diagnostic categories with the neurobiology of psychiatric illness (Casey *et al.*, 2013; Cuthbert and Insel, 2013).

Our results support that CA, which is predominantly composed of maternal separation in our sample, has a strong association with depression despite differences in cultural norms and socioeconomic context. In a developing setting where parental absence during childhood is prevalent, such early life experiences may also have an adverse role in mental health. Studies are therefore needed to examine if the more than 60 million left-

behind children currently in China (UNICEF and National Bureau of Statistics of China, 2013) may potentially be at higher risk for depression.

Our findings have public health and clinical implications. CA occurs during a developmental period and is correlated with subsequent stressors in adulthood, thus interventions at both early and later stages of the life course to reduce the impact of stress on mental health may be required (Shonkoff *et al.*, 2009). Although stress induces structural and functional changes in the brain, particularly in the hippocampus, amygdala and prefrontal cortex (Popoli *et al.*, 2012) - interventions designed to decrease stress may also produce specific plasticity-related alterations in brain function and structure (Davidson and McEwen, 2012). For example, a proposed mechanism for the enduring effects of cognitive therapy in depression is via enhanced prefrontal activation, which thereby inhibits amygdala activation (DeRubeis *et al.*, 2008).

In addition to preventive strategies for CA, a therapeutic approach could modify the behavioural response to CA from sensitisation to "steeling". Steeling refers to the successful resolution of early stress that thereby increases resilience to stressful events later in the life course (Tronick, 2006). Individual variation in resilience to stress may be partly determined by the success or failure in coping with stressors during childhood (Tronick, 2003). Consistent with the steeling phenomenon, exposure to moderate stressors during childhood contributed to an attenuated depressive response to subsequent life events (Shapero *et al.*, 2015). Steeling may operate by the development of self-efficacy (Dienstbier, 1989) and adaptive coping strategies in response to CA such as utilisation of social support and positive cognitive appraisals (Compas *et al.*, 2001). This is consistent with our findings that only past-year SLE potentiated the relation of CA with depressive symptoms, whereas

life events that were perceived positively did not act synergistically. Thus, interventions

that enhance resilience could result in a more positive perception of life events, and

perhaps prevent the accumulation of stress across the life course (Southwick *et al.*, 2005).

However, further studies are needed to evaluate the potential benefits of interventions

(Meichenbaum, 1996) to induce steeling in response to CA and avoid cascades of stress

sensitisation. Such interventions could in theory have beneficial effects due to the plasticity

of the brain (Davidson and McEwen, 2012) with CA and SLE as potential targets for the

prevention of depression.

Previous presentation

Parts of this study were presented in oral form at the World Psychiatric Association Regional Congress, Hong Kong, 12-14 December 2014.
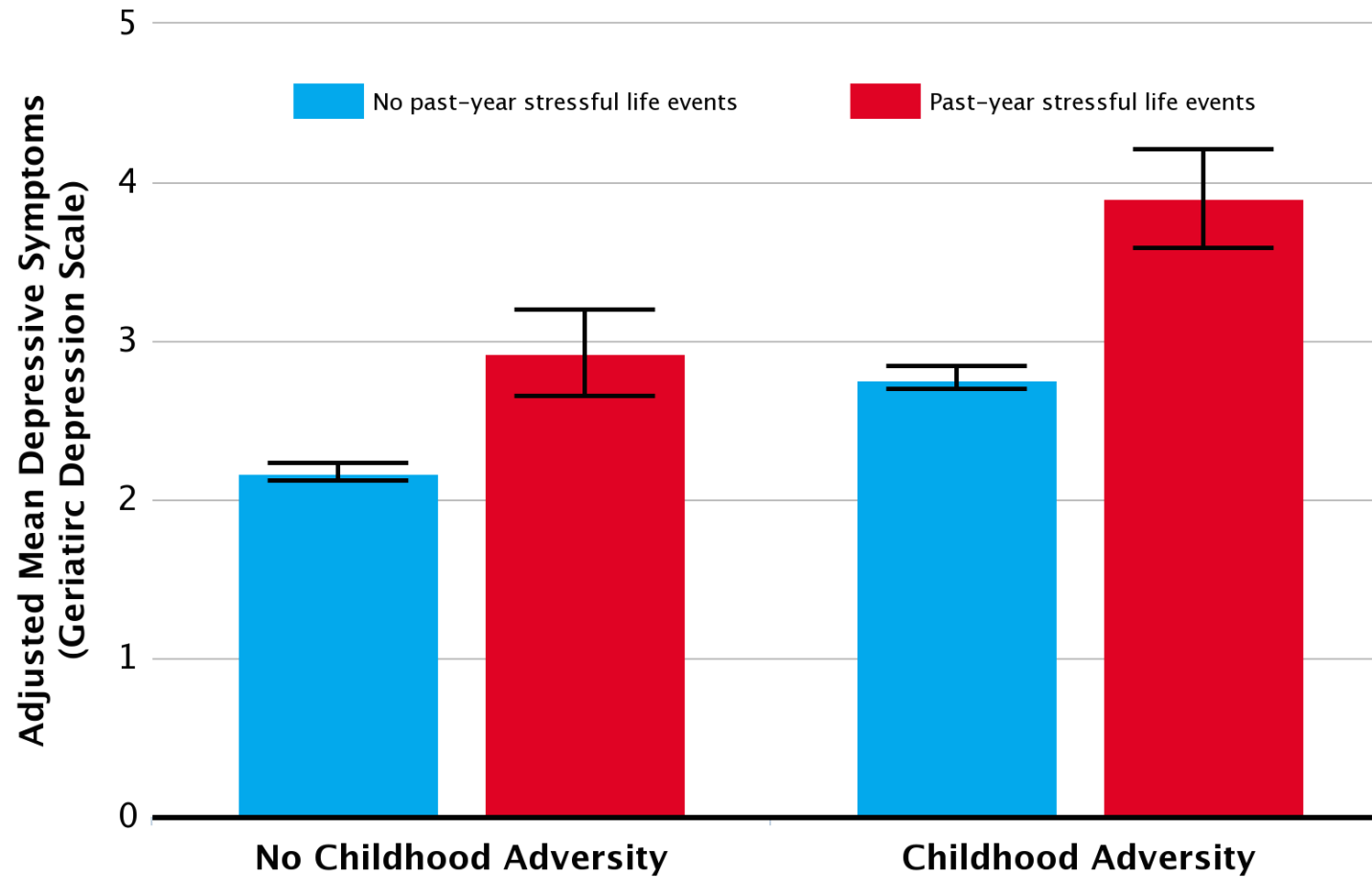
Conflict of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Figure 1 Adjusted Mean Depressive Symptoms and 95% Confidence Intervals by Childhood Adversity and Past-year Stressful Life Events, GBCS 2006-2008

Adjusted for age, sex, childhood socioeconomic status, education, personal income and occupation

Table 1 Characteristics by childhood adversity (CA) and past-year stressful life events (SLE) in phase 3 of the Guangzhou Biobank Cohort Study (GBCS)

	All	CA None	CA ≥ 1	P value	SLE None	SLE ≥ 1	P value
N	9729	6123	3606		9268	461	
Sex	%			<0.001			0.05
Men	25.6	23.3	29.6		25.8	21.7	
Women	74.4	76.7	70.4		74.2	78.3	
Age (years)				<0.001			0.46
50-54	29.9	33.7	23.5		29.7	33.8	
55-59	24.8	25.2	24.2		24.9	23.6	
60-64	17.4	17.7	16.9		17.4	17.8	
65-69	13.1	11.6	15.6		13.1	11.9	
70-74	9.6	8.0	12.2		9.6	8.0	
75-79	5.2	3.8	7.6		5.2	4.8	
Education				<0.001			0.12
Less than primary	8.7	7.4	10.9		8.8	6.7	
Primary	29.2	28.9	29.7		29.3	28.0	
Junior middle	27.7	28.2	26.8		27.8	26.7	
Senior middle	26.0	27.6	23.3		25.7	31.5	
Junior college	5.9	5.9	5.9		6.0	4.3	
College	2.5	1.9	3.5		2.5	2.8	
Longest held occupation[a]				0.01			0.56
Manual	68.0	68.5	67.3		68.0	68.8	
Non-manual	20.3	19.3	21.8		20.2	21.0	
Others	11.7	12.2	10.9		11.8	10.2	
Personal income[b]				<0.001			0.75
<10 000	26.8	26.8	26.8		26.8	26.7	
10-15 000	45.3	45.7	44.7		45.2	46.6	
>15 000	23.0	22.0	24.7		23.0	22.8	
Unknown	4.9	5.5	3.9		5.0	3.9	
Parental possessions[c]				<0.001			0.50
None	59.3	56.7	63.6		59.4	57.9	
1 item	10.3	10.8	9.5		10.4	8.9	
2 items	7.5	7.7	7.2		7.5	8.0	
3 items	22.9	24.8	19.7		22.8	25.2	
CA							
None	62.9	-	-		63.3	55.1	<0.001
≥ 1	37.1	-	-		36.7	44.9	

[a] Manual occupations are: agricultural worker, factory worker, sales and service. Non-manual occupations are: administrator/manager, military/disciplined and professional/technical

[b] 1 USD = 6.1 yuan

[c] Parental possessions during childhood (bicycle, watch and sewing machine) as a proxy for childhood socioeconomic status

Table 2 Association of childhood adversity and past-year stressful life events with depressive symptoms and depression (Geriatric Depression Scale) in 9729 participants, GBCS 2006-2008

		Depressive symptoms		Depression					
				None (reference)	Mild		Moderate-to-severe		
	Model	β	95% CI	OR	OR	95% CI	OR	95% CI
Childhood adversity	a	0.61	0.52, 0.70	1	1.78	1.58, 2.02	2.30	1.68, 3.15
	b	0.59	0.50, 0.68	1	1.77	1.57, 2.00	2.24	1.63, 3.06
Stressful life events	c	0.96	0.75, 1.17	1	2.01	1.58, 2.55	3.71	2.33, 5.93
	d	0.90	0.70, 1.11	1	1.96	1.54, 2.49	3.48	2.18, 5.67

[a] Adjusted for age, sex, education, childhood socioeconomic status
[b] Adjusted for age, sex, education, childhood socioeconomic status, stressful life events
[c] Adjusted for age, sex, childhood socioeconomic status, education, personal income, occupation
[d] Adjusted for age, sex, childhood adversity, childhood socioeconomic status, education, personal income, occupation

Table 3 Association of past-year life events with depressive symptoms and depression (Geriatric Depression Scale) in 9729 participants, GBCS 2006-2008

		Depressive symptoms		Depression					
				None (reference)	Mild		Moderate-to-severe		
	Model	β	95% CI	OR	OR	95% CI	OR	95% CI
Life events	c	0.66	0.51, 0.81	1	1.73	1.44, 2.07	2.57	1.72, 3.84
	d	0.62	0.47, 0.77	1	1.67	1.39, 2.00	2.43	1.62, 3.64

[c] Adjusted for age, sex, childhood socioeconomic status, education, personal income, occupation
[d] Adjusted for age, sex, childhood adversity, childhood socioeconomic status, education, personal income, occupation

Table S1. Association of individual childhood adversities with depressive symptoms and depression (Geriatric Depression Scale) in 9729 participants, GBCS 2006-2008

	Depressive symptoms		Depression					
			None (ref)	Mild			Moderate-to-severe	
	β	95% CI	OR	OR	95% CI		OR	95% CI
Maternal separation	0.38	0.28, 0.48	1	1.38	1.20, 1.56		1.77	1.28, 2.47
Parents frequently quarrelling	0.88	0.70, 1.05	1	2.07	1.70, 2.51		3.14	2.06, 4.79
Sent away from home	0.90	0.60, 1.20	1	1.74	1.25, 2.45		3.89	2.09, 7.24
Frightening experience	0.94	0.78, 1.08	1	2.12	1.79, 2.50		3.57	2.49, 5.12

[a] Adjusted for age, sex, education, childhood socioeconomic status

References

Akaike H. 1974. A new look at the statistical model identification. *IEEE T Automat Contr* **19**: 716-723.

Au Yeung SL, Schooling CM. 2014. More ways to distinguish real from artefactual associations in observational studies. *Int J Epidemiol* **43**: 1665-1666.

Batty GD, Victoria C, Lawlor DA 2009 Family based life course studies in low- and middle-income countries. In *Family Matters: Using Family Based Studies to Determine the Mechanisms Underlying Early Life Determinants of Adult Chronic Diseases*, pp 129-150. Eds DA Lawlor & G Mishra. Oxford: Oxford University Press.

Brewin CR, Andrews B, Gotlib IH. 1993. Psychopathology and early experience: a reappraisal of retrospective reports. *Psychol Bull* **113**: 82-98.

Casey BJ, Craddock N, Cuthbert BN*, et al.* 2013. DSM-5 and RDoC: progress in psychiatry research? *Nat Rev Neurosci* **14**: 810-814.

Chen J, Zhang J, Zhang W, Feng J. 2008. The relationship between childhood abuse and clinical features of depressive patients [in Chinese]. *Journal of Psychiatry* **21**: 258-260.

Cheng ST, Chan AC. 2004. A brief version of the geriatric depression scale for the chinese. *Psychol Assessment* **16**: 182-186.

Clark C, Caldwell T, Power C, Stansfeld SA. 2010. Does the Influence of Childhood Adversity on Psychopathology Persist Across the Lifecourse? A 45-Year Prospective Epidemiologic Study. *Ann Epidemiol* **20**: 385-394.

Compas BE, Connor-Smith JK, Saltzman H, Thomsen AH, Wadsworth ME. 2001. Coping with stress during childhood and adolescence: Problems, progress, and potential in theory and research. *Psychol Bull* **127**: 87-127.

Cuthbert B, Insel T. 2013. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. *BMC Med* **11**: 126.

Davidson RJ, McEwen BS. 2012. Social influences on neuroplasticity: stress and interventions to promote well-being. *Nat Neurosci* **15**: 689-695.

DeRubeis RJ, Siegle GJ, Hollon SD. 2008. Cognitive therapy versus medication for depression: treatment outcomes and neural mechanisms. *Nat Rev Neurosci* **9**: 788-796.

Dienstbier RA. 1989. Arousal and physiological toughness: Implications for mental and physical health. *Psychol Rev* **96**: 84-100.

Fang X, Xu J, Sun L, Zhang J. 2004. Family Functioning: Theory, Influencing Factores, and Its Relationship with Adolescent Social Adjustment [in Chinese]. *Advances in Psychological Science* **12**: 544-553.

Faraway JJ. 2002 Practical regression and ANOVA using R. Available at http://cran.r-project.org/doc/contrib/Faraway-PRA.pdf. Last assessed on June 9, 2015.

Ferguson N. 2011 *Civilization: the West and the Rest*: Penguin, London.

Gilbert R, Widom CS, Browne K*, et al.* 2009. Burden and consequences of child maltreatment in high-income countries. *Lancet* **373**: 68-81.

Gilman SE. 2007. Invited Commentary: The Life Course Epidemiology of Depression. *Am J Epidemiol* **166**: 1134-1137.

Gilman SE, Kawachi I, Fitzmaurice GM, Buka SL. 2002. Socioeconomic status in childhood and the lifetime risk of major depression. *Int J Epidemiol* **31**: 359-367.

Gilman SE, Ni MY, Dunn EC*, et al.* 2015. Contributions of the social environment to first-onset and recurrent mania. *Mol Psychiatr* **20**: 329-336.

Greenland S. 2009. Interactions in epidemiology: relevance, identification, and estimation. *Epidemiology* **20**: 14-17.

Guo WJ, Hu CY, Zhao XD. 2009. Mental illness in China. *Lancet* **374**: 1064-1065.

Hammen C. 1991. Generation of stress in the course of unipolar depression. *J Abnorm Psychol* **100**: 555-561.

Hammen C, Henry R, Daley SE. 2000. Depression and sensitization to stressors among young women as a function of childhood adversity. *J Consult Clin Psych* **68**: 782-787.

Hardt J, Rutter M. 2004. Validity of adult retrospective reports of adverse childhood experiences: review of the evidence. *J Child Psychol Psyc* **45**: 260-273.

Hatch SL, Dohrenwend BP. 2007. Distribution of traumatic and other stressful life events by race/ethnicity, gender, SES and age: a review of the research. *Am J Commun Psychol* **40**: 313-332.

Jiang C, Thomas GN, Lam TH*, et al.* 2006. Cohort profile: The Guangzhou Biobank Cohort Study, a Guangzhou-Hong Kong-Birmingham collaboration. *Int J Epidemiol* **35**: 844-852.

Kavikondala S, Stewart SM, Ni MY*, et al.* 2015. Structure and validity of Family Harmony Scale: an instrument for measuring harmony (in press). *Psychol Assessment*.

Kendler KS, Karkowski LM, Prescott CA. 1999. Causal relationship between stressful life events and the onset of major depression. *Am J Psychiat* **156**: 837-841.

Kessler RC, Abelson J, Demler O, *et al.* 2004. Clinical calibration of DSM-IV diagnoses in the World Mental Health (WMH) version of the World Health Organization (WHO) Composite International Diagnostic Interview (WMHCIDI). *Int J Method Psych* **13**: 122-139.

Kessler RC, Davis CG, Kendler KS. 1997. Childhood adversity and adult psychiatric disorder in the US National Comorbidity Survey. *Psychol Med* **27**: 1101-1119.

Kessler RC, Magee WJ. 1993. Childhood adversities and adult depression: basic patterns of association in a US national survey. *Psychol Med* **23**: 679-690.

Klengel T, Mehta D, Anacker C, *et al.* 2013. Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. *Nat Neurosci* **16**: 33-41.

Knol MJ, VanderWeele TJ. 2012. Recommendations for presenting analyses of effect modification and interaction. *Int J Epidemiol* **41**: 514-520.

Kuh D, Ben-Shlomo Y, Lynch J, Hallqvist J, Power C. 2003. Life course epidemiology. *J Epidemiol Commun H* **57**: 778-783.

Lee S, Guo WJ, Tsang A, *et al.* 2011. The prevalence of family childhood adversities and their association with first onset of DSM-IV disorders in metropolitan China. *Psychol Med* **41**: 85-96.

Lim PP, Ng LL, Chiam PC, *et al.* 2000. Validation and comparison of three brief depression scales in an elderly Chinese population. *Int J Geriatr Psych* **15**: 824-830.

MacFarquhar R. 1983 *Origins of the Cultural Revolution: Great Leap Forward 1958–60*. New York: Columbia University Press.

McEwen BS. 2012. Brain on stress: How the social environment gets under the skin. *P Natl Acad Sci* **109**: 17180-17185.

McGowan PO, Sasaki A, D'Alessio AC, *et al.* 2009. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat Neurosci* **12**: 342-348.

McLaughlin KA, Conron KJ, Koenen KC, Gilman SE. 2010. Childhood adversity, adult stressful life events, and risk of past-year psychiatric disorder: a test of the stress sensitization hypothesis in a population-based sample of adults. *Psychol Med* **40**: 1647-1658.

Meichenbaum D. 1996. Stress Inoculation Training for Coping with Stressors. *The Clinical Psychologist* **49**: 4-7.

Monroe SM, Simons AD. 1991. Diathesis-stress theories in the context of life stress research: implications for the depressive disorders. *Psychol Bull* **110**: 406-425.

Norman RE, Byambaa M, De R, *et al.* 2012. The long-term health consequences of child physical abuse, emotional abuse, and neglect: a systematic review and meta-analysis. *PLoS Medicine* **9**: e1001349.

Patel V, Kim YR. 2007. Contribution of low- and middle-income countries to research published in leading general psychiatry journals, 2002–2004. *Brit J Psychiat* **190**: 77-78.

Pesonen A-K, Räikkönen K, Heinonen K, *et al.* 2007. Depressive Symptoms in Adults Separated from Their Parents as Children: A Natural Experiment during World War II. *Am J Epidemiol* **166**: 1126-1133.

Phillips MR, Zhang J, Shi Q, *et al.* 2009. Prevalence, treatment, and associated disability of mental disorders in four provinces in China during 2001–05: an epidemiological survey. *The Lancet* **373**: 2041-2053.

Popoli M, Yan Z, McEwen BS, Sanacora G. 2012. The stressed synapse: the impact of stress and glucocorticoids on glutamate transmission. *Nat Rev Neurosci* **13**: 22-37.

Ritsher JEB, Warner V, Johnson JG, Dohrenwend BP. 2001. Inter-generational longitudinal study of social class and depression: a test of social causation and social selection models. *Br J Psychiatry* **178**: s84-s90.

Rothman KJ, Greenland S, Lash TL. 2008 *Modern Epidemiology*. New York: Wolters Kluwer Health.

Saracci R. 1980. Interaction and synergism. *Am J Epidemiol* **112**: 465-466.

Schooling CM, Jiang CQ, Lam TH, *et al.* 2008. Life-course origins of social inequalities in metabolic risk in the population of a developing country. *Am J Epidemiol* **167**: 419-428.

Shapero B, Hamilton J, Stange J, *et al.* 2015. Moderate Childhood Stress Buffers Against Depressive Response to Proximal Stressors: A Multi-Wave Prospective Study of Early Adolescents. *J Abnorm Child Psychol* 1-11.

Shonkoff JP, Boyce WT, McEwen BS. 2009. Neuroscience, molecular biology, and the childhood roots of health disparities: building a new framework for health promotion and disease prevention. *JAMA* **301**: 2252-2259.

Southwick SM, Vythilingam M, Charney DS. 2005. The Psychobiology of Depression and Resilience to Stress: Implications for Prevention and Treatment. *Annu Rev Clin Psychol* **1**: 255-291.

Tronick E. 2006. The inherent stress of normal daily life and social interaction leads to the development of coping and resilience, and variation in resilience in infants and young children: comments on the papers of Suomi and Klebanov & Brooks-Gunn. *Ann N Y Acad Sci* **1094**: 83-104.

Tronick EZ. 2003. "Of Course All Relationships Are Unique": How Co-creative Processes Generate Unique Mother–Infant and Patient–Therapist Relationships and Change Other Relationships. *Psychoanal Inq* **23**: 473-491.

UNICEF, National Bureau of Statistics of China. 2013 What Census Data Can Tell Us About Children in China: Facts and Figures. Available at http://www.unicef.cn/en/uploadfile/2013/1216/20131216111141945.pdf. Last assessed on February 10, 2014.

VanderWeele TJ, Robins JM. 2007. The identification of synergism in the sufficient-component-cause framework. *Epidemiology* **18**: 329-339.

Vaughan TD, Dwyer DJ. 1966. Some Aspects of Postwar Population Growth in Hong Kong. *Econ Geogr* **42**: 37-51.

Wachs TD, Georgieff M, Cusick S, McEwen BS. 2014. Issues in the timing of integrated early interventions: contributions from nutrition, neuroscience, and psychological research. *Ann NY Acad Sci* **1308**: 89-106.

Weissman MM, Wickramaratne P, Nomura Y, *et al.* 2005. Families at high and low risk for depression: a 3-generation study. *Arch Gen Psychiat* **62**: 29-36.

Widom CS, DuMont K, Czaja SJ. 2007. A prospective investigation of major depressive disorder and comorbidity in abused and neglected children grown up. *Arch Gen Psychiatry* **64**: 49-56.

Xu A, Xie X, Liu W, Xia Y, Liu D. 2007a. Chinese Family Strengths and Resiliency. *Marriage Fam Rev* **41**: 143-164.

Xu CG, Jiao ZA, Cao WS, Yu HH. 2007b. Relationship of depressive disorder and childhood maltreated experiences [in Chinese]. *Journal of Psychiatry* **20**: 147-149.

Yesavage JA, Sheikh JI. 1986. Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version. *Clin Gerontologist* **5**: 165-173.

Zisook S, Lesser I, Stewart JW, *et al.* 2007. Effect of age at onset on the course of major depressive disorder. *Am J Psychiat* **164**: 1539-1546.