Association of Stress Management Skills and Stressful Life Events With Allergy Risk: a Case-control Study in Southern China

Jingru Cheng

Zhengzhou University

Fei Li

Southern Medical University

Yigui Lai

People's Hospital of Yangjiang

Jieyu Chen

Southern Medical University

Xiaomin Sun

Southern Medical University

Lei Xiang

Southern Medical University

Pingping Jiang

Southern Medical University

Shengwei Wu

Southern Medical University

Ya Xiao

Southern Medical University

Lin Zhou

Southern Medical University

Ren Luo

Southern Medical University

Xiaoshan Zhao (✉ zhaoxs0609@163.com)

Southern Medical University <https://orcid.org/0000-0003-3081-0103>

Yanyan Liu

Southern Medical University

Research article

Keywords: stress management skills, stressful life events, allergies

Posted Date: August 18th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-48082/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background: Psychosocial stress and stressful life events are known to aggravate atopic diseases. Less is known about the impact of stress management skills on allergies. Here we sought to determine whether stress management skills are associated with the allergies and to assess the combined effects of stress management skills and stressful events on allergy risk.

Methods: A survey on risk factors for self-reported allergic diseases was carried out among 28,144 southern Chinese people; 14 stressful life events and 8 stress management skills were retrospectively recorded in a case-control setting with multivariate logistic regression analysis. Multiplicative and additive interactions between stressful events and stress management skills were evaluated.

Results: Stressful events significantly increased allergy risk. The odds ratio (OR) for allergies was 1.65 (95% confidence interval CI, 1.41–1.93) for those reporting one or two stressful events and 3.10 (95% CI, 2.55–3.79) for those reporting more than two stressful events. Stress management skills were adversely associated with allergic risk for people experiencing stressful events (OR, 0.71; 95% CI, 0.53–0.97) when adjusted demographically, particularly “concentrate on pleasant thoughts at bedtime” (OR, 0.67; 95% CI, 0.51–0.89), “pace myself to prevent tiredness” (OR, 0.67; 95% CI, 0.54–0.83), “get enough sleep” (OR, 0.48; 95% CI, 0.32–0.72) and “take some time for relaxation each day” (OR, 0.55; 95% CI, 0.37–0.80). There was a significant linear trend for allergy risk from good stress management skills with no stressful events to poor stress management skills with stressful events ($P < 0.000$), with significant interaction in additive models ($P = 0.006$).

Conclusions: There are independent and antagonistic combined associations of stressful life events and stress management skills with allergy risk. This supports the use of stress management skills in managing allergic disease.

Background

Many studies have demonstrated an increased prevalence of asthma and allergic conditions in various regions[1–3]. Genetics[4], environment[5], female sex[6] and lifestyle factors[7] are common risk factors for allergic disease. However, psychosocial stress[8,9] is becoming more important as a significant risk factor for allergic sensitization and a possible cause of its increased prevalence.

Stress has been described as ‘a constellation of events, comprised of a stimulus (stressor) that precipitates a reaction in the brain’[10]. Critical events, such as disease or the death of a parent or friend, conflicts in personal relationships, or changes in living environment, are stressors in life[11]. They demand psychological readjustment and may have a greater influence on susceptibility to illness or its course[12]. The association between stressful events and onset of asthma was suggested in an early study[13]. Several retrospective studies[12, 14–16] and at least one prospective study[17] have reported a positive association between stressful events and the incidence of allergic disease among adolescents and adults. Liu *et al.*[18] provide excellent evidence that stressful events can enhance allergic inflammatory responses.

It follows that managing stress could be expected to have salutary effects on the occurrence of allergic diseases and underlying disease course. Stress-reducing interventions aim at modifying stress appraisal and decreasing subjective anxiety; stress management skills are lifestyle behaviors that help people to prevent stressful events from occurring and manage their responses to those stressful events. There are indications that stress management interventions might affect basal autonomic or endocrine responses[19]. Walker *et al.*[20] found that patients who received relaxation training and guided imagery prior to chemotherapy reported a better quality of life and less emotional distress than patients who did not. In a systematic review, Huntley *et al.* [21] found that relaxation therapy had a positive effect on asthma outcomes. However, the specific relationship between stress management skills and the occurrence of allergic diseases, and its combined effect with stressful events on allergies, has largely been unexplored.

This case-control study sought to examine the link between stress management skills and allergies in a southern Chinese population, as well as interactional effects with stressful events on allergic diseases. It was hypothesized that better stress management skills would be associated with fewer allergies and would moderate the negative influence of stressful events on allergy risk.

Methods

Study design and subjects

A survey on possible risk factors for the development of asthma and allergies was undertaken between April 2012 and January 2013 in six cities randomly selected in Guangdong province, southern China (Guangzhou, Huizhou, Shaoguan, Jiangmen, Zhanjiang and Heyuan). We selected one or two convenient areas (e.g. schools, companies, government agencies or factories) in each city for cluster sampling. Original questionnaire data were obtained from 28,144 persons. Of these, 13,491 (47.94%) were men and 14,653 (52.06%) women. A matched case-control study was conducted to investigate the relationship between life events, stress management skills and allergic diseases. Case and control participants were selected from these 28,144 respondents. The case participants were willing to participate and met the following inclusion criteria: (i) 18 years of age or older; (ii) with one or more self-reported allergic diseases (asthma or bronchitis, allergic rhinitis, atopic dermatitis); (iii) not pregnant or lactating, and (iv) no critical illness (eg. depression/anxiety, DM, hypertension, cardiovascular or renal diseases, et al.) or intake of medication in the previous 2 weeks.

Self-reported allergic diseases were selected by positive answers to any of the following questions:

- Asthma: Have you ever had asthma? If so, has a doctor diagnosed the disease?

- Allergic rhinitis: Have you ever had 'hay fever' or other allergic nasal symptoms (sneezing, nasal itching, blocked nose or runny nose) in the absence of a cold or flu, g. from pollen or animals? A doctor's diagnosis for the disorder was required.
- Atopic dermatitis: Have you ever had symptoms of itchy rash called atopic eczema or eczema localized to flexural regions (such as folds of the elbows, behind the knees), facial, or generalized to the body? In addition, a doctor's diagnosis was asked about.

For each case participant, we validate the allergic diseases by asking "has a doctor diagnosed the disease" or by evaluating their medical histories getting from each unit managers (at least one year medical examination report between 2012 and 2013 for each participant). Only include cases with the "yes" response or with the "allergic disease" medical record. And two matched control participants were randomly selected from the respondents who had reported no symptoms suggestive of asthma or atopic disease during their lifetime, and were incidence-density matched to the case participants by departments of the selected area, sex and age (± 3 years). Eligible control participants were 18 years or older, not pregnant or lactating, and had no history of any other serious chronic disease. As is standard in incidence-density matching, a control participant could serve as a control for more than one case participant[22]. A total of 1340 participants with allergies and 2662 healthy control participants were recruited.

Questions on stressful life events

We asked if the respondent had ever experienced various specific potentially stressful life events. The events were based on a commonly used life event scale[23]. The original list included 14 items, and subjects were asked to respond either "yes (scored 1)" or "no (scored 0)". Based on preliminary data analysis, and knowledge of life events generally regarded as stressful, the events were divided into three groups: disease or death of family members or close friends; conflicts in personal relationships (including relationships with family members, spouses, colleagues or friends); life changes or other events (e.g. economic, career, lifestyle, living environment). Indicators used in the analyses included a total stressful life event score (range from 0 to 14) obtained by summing all 14 items as well as subscale scores related to particular domains (Table 2).

Assessment of stress management skills

The Health-Promoting Lifestyle Profile II (HPLP-II) was used to measure stress management skills. The scale was developed by Walker and colleagues in 1987[24] and later revised as the HPLP-II[25]. The Chinese version of HPLP-II was developed by Lee and Loke, who established validity and credibility with an internal consistency coefficient (Cronbach's alpha) of 0.91[26]. It measures six dimensions of self-reported health-promoting behaviours, including spiritual growth (nine items), health responsibility (nine items), physical activity (eight items), nutrition (nine items), interpersonal relations (nine items) and stress management (eight items). Each subgroup can be used independently[27]. In this study, we only used the stress management subscale, the Cronbach's alpha of which was reported in Hong Kong as 0.75[28]. It includes eight items (Table S1), covers most approaches of managing or reducing stress. Participants were asked to rate the frequency of stress management behaviours using the four-point Likert scale as 1 (never or rarely), 2 (sometimes), 3 (often), 4 (routinely). The total stress management skill score are all 8 items score combined, ranges from 8 to 32, higher scores represent more engagement in stress management behaviour. For descriptive scores and logistic regression analysis, the total stress management skill ratings were trichotomized as good (25–32), moderate (17–24) or poor (8–16).

Data collection and other exposure

To increase participation and ensure the completeness and truthfulness of each questionnaire, recruitment was conducted in conference halls of different selected units by trained investigators in cooperation with the administrators. The self-administered questionnaire included an introduction detailing the objectives of the study and guaranteeing anonymity and confidentiality of data. Further questions on demographic factors (age, sex, height, body weight and education), active and passive smoking history, alcohol drinking habits, physical activity, history of allergic disease, stressful life events and stress management skills were surveyed.

Educational level was categorized into three groups: (i) junior high school education (compulsory schooling), (ii) high school education, and (iii) any university, college or higher education by reported highest academic background at baseline. Body mass index was calculated as weight in kilograms divided by the square of height in metres. We categorized body mass index as <18.5 (malnourished), 18.5–23.9 (normal weight), or ≥ 24 (overweight), which differs from the World Health Organization classification[28] but is suitable for Chinese adult populations[29]. Information on smoking was based on questions regarding never smoking, currently smoking and ever having smoked. Participants were asked to state how often they drank alcohol and engaged in physical activity (never, sometimes, often, always) through the questions, "Do you normally drink alcohol more than three times per week?" and "Do you exercise vigorously for 20 min or more at least three times a week (such as brisk walking, bicycling, aerobic dancing, using a stair climber)?"

Statistical analysis

For demographic and exposure variables, differences in means or proportions between participants with and without allergic diseases were evaluated using Student's *t* or chi-squared tests, as appropriate. The risks of allergies with exposure to stressful events and stress management skills were analyzed using conditional logistic regression models. The number of stressful events was used as a continuous variable to predict allergies outcomes; in addition, the total number of life events was categorized as 0, 1–2 and >3. For stress management skills, stratified analyses were conducted among subgroups with or without stressful events. The logistic regression model included the following potential confounders: age, sex, education, body mass index, smoking status, alcohol intake and physical activity. The interaction effect between stressful events and stress-management skills was further evaluated by multiplicative and additive models. We tested for multiplicative interaction by including the product term in multivariate logistic regression. Additive interaction was assessed using the method of Rothman[30].

The 95% confidence intervals (95% CI) for the odds ratios (ORs) were calculated; $P < 0.05$ was considered to be statistically significant. All statistical analyses were performed using SPSS 13.0 and SAS 9.3.

Results

Demographic characteristics, smoking status, alcohol intake and physical activity are presented in Table 1. Among participants without self-reported illness or injury group, cases were likely to take less vigorous exercise ($P = 0.000$). Alcohol intake, educational level, body mass index and smoking status didn't effect significantly for allergic diseases either in participants with or without self-reported illness or injury ($P > 0.05$).

Table 1 Basic characteristics of 1340 cases and 2662 controls in southern China						
Variable	participants without self-reported illness or injury [#]		P	participants with self-reported illness or injury [#]		P
	Cases N(%)	Controls N(%)		Cases N(%)	Controls N(%)	
Age(year mean±SD)	28.25±9.46	28.10±9.26	0.658	26.90±8.14	25.63±7.80	0.104
Gender			0.528			0.165
Male	509(46.0)	1110(44.9)		92(39.3)	87(46.0)	
Female	597(54.0)	1363(55.1)		142(60.7)	102(54.0)	
Education			0.829			0.953
Compulsory school	73(6.6)	177(7.2)		10(4.3)	7(4.2)	
High school graduate	341(30.8)	754(30.5)		57(24.4)	47(24.9)	
University/college degree	692(62.6)	1542(62.4)		167(71.4)	135(71.4)	
BMI(kg/m ²)			0.062			0.895
≤18.5	187(16.9)	486(19.7)		52(22.2)	40(21.2)	
18.5-23.9	734(66.4)	1628(65.8)		151(64.5)	126(66.7)	
≥24	185(16.7)	359(14.5)		31(13.2)	23(12.2)	
Smoking status			0.113			0.626
Never	945(85.4)	2161(87.4)		207(88.5)	170(89.9)	
Current/Former	161(14.6)	312(12.6)		27(11.5)	19(10.1)	
Alcohol intake			0.145			0.096
Never	324(29.3)	804(32.5)		53(22.6)	53(28.0)	
Sometimes	757(68.4)	1621(65.5)		174(74.4)	135(43.7)	
Often/always	25(2.3)	48(1.9)		7(3.0)	1(0.5)	
Physical activity*			0.000			0.185
Rarely/never	275(24.9)	454(18.4)		58(24.8)	33(17.5)	
Sometimes	483(43.7)	1049(42.4)		96(41.0)	87(46.0)	
Often/always	348(31.5)	970(39.2)		80(34.2)	69(36.5)	
#Self-reported illness or injury: personal injury or illness as one kind of life event, but not serious because people with serious or chronic diseases are excluded at the beginning of the research.*Vigorous physical activity in leisure-time exercise. Values of P for age were calculated using the independent-samples t test; and others using the chi-squared test. Significant differences are highlighted in bold.						

Stressful life events

The percentage of subjects who had experienced stressful events is shown in Table 2. Overall, 65.8% of participants reported one or more stressful events during their lifetime. People with allergies were significantly more likely to report a wide variety of stressful life events ($P < 0.05$), except for "death of a family member or close friend" and "career change". Life changes or other events, e.g. overload, economic plight, career change, or living environment change, were reported by 62.2% of adults and were more prevalent than disease or death or conflicts, which were reported by 22.3% and 29.3% of participants, respectively.

Table 2 Stressful life events for 4002 southern Chinese people

Self-reported events	Case participants (n = 1340)	Control participants (n = 2662)	P	All participants (n = 25,938)†
Disease or death (mean (SD))*	0.3 (0.5)	0.1 (0.4)	0.000	0.2 (0.5)
Personal injury or illness (%)	234 (17.5)	189 (7.1)	0.000	2590 (10.0)
Severe disease of family member or close friend (%)	82 (6.1)	83 (3.1)	0.000	1133 (4.4)
Death of family member or close friend (%)	68 (5.1)	106 (4.0)	0.110	953 (3.7)
Any disease or death (%)	328 (24.5)	346 (13.0)	0.000	5786 (22.3)
Conflicts in personal relationships, (mean (SD))*	0.4 (0.7)	0.3 (0.6)	0.000	0.3 (0.6)
Interpersonal disharmony (%)	150 (11.2)	176 (6.6)	0.000	2039 (7.9)
Family discord (%)	59 (4.4)	72 (2.7)	0.004	771 (3.0)
Marital disruption (%)	30 (2.2)	32 (1.2)	0.012	378 (1.5)
Trouble from children (%)	91 (6.8)	116 (4.4)	0.001	1400 (5.4)
Split up from boyfriend or girlfriend (%)	212 (15.8)	290 (10.9)	0.000	3040 (11.7)
Any conflicts event (%)	396 (29.6)	533 (20.0)	0.000	7587 (29.3)
Life changes or other events (mean (SD))*	1.0 (1.0)	0.8 (0.9)	0.689	0.9 (1.0)
Overwork (%)	561 (41.9)	814 (30.6)	0.000	8672 (33.4)
Economic plight (%)	288 (21.5)	464 (17.4)	0.002	5554 (21.4)
Career change (%)	46 (3.4)	63 (2.4)	0.051	1030 (4.0)
Living environment change (%)	221 (16.5)	365 (13.7)	0.019	3990 (15.4)
Lifestyle change (%)	191 (14.3)	306 (11.5)	0.013	3444 (13.3)
Suffer a criminal or civil penalty (%)	3 (0.2)	0 (0.0)	0.015	17 (0.1)
Any other temporal events (%)	832 (62.1)	1343 (50.0)	0.000	16136 (62.2)
Total stressful events (mean (SD))*	1.7 (1.6)	1.2 (1.3)	0.000	1.3 (1.4)
Any stressful event (%)	1000(74.6)	1595(59.9)	0.000	17075(65.8)
Number of stressful events (%)*			0.000	
0	340 (25.4)	1067 (40.1)		8863 (34.2)
1 or 2	663 (49.5)	1251 (47.0)		12498 (48.2)
>2	337 (25.1)	344 (12.9)		4577 (17.6)

* Values of *P* for comparison of people with and without allergies were calculated using the Student's *t* test; and others using the chi-squared test. Significant differences are highlighted in bold. †Subjects over 18 years old.

The relationship between stressful events and allergies was studied in 4002 southern Chinese people (1340 case participants and 2662 control participants). Allergies were significantly associated with the number of total stress events, disease or death events, conflicts and life changes or other events. These associations were only slightly attenuated after adjustment for age, sex, education, body mass index, smoking status, alcohol intake and physical activity (Table 3). A dose–response relationship was found between allergies and increasing total stressful events, the data showed that the risk of allergies was significantly increased 2.5–3.7-fold by two or more preceding or concomitant stressful events (Table 3). Adjusting for age, sex, education, body mass index, smoking status, alcohol intake and physical activity did not modify the effect of stressful events on allergies.

Table 3 Associations of allergies with stressful life events in 4002 Chinese people

Exposure	Odds of allergies (odds ratio, 95% confidence interval) [†]	
	Crude	Adjusted [‡]
Categorical variable		
0 total stressful events	1.00	1.00
1 or 2 total stressful events	1.66 (1.43–1.94) ^{***}	1.65 (1.41–1.93) ^{***}
total stressful events	3.07 (2.54–3.73) ^{***}	3.10 (2.55–3.79) ^{***}
Continuous variable		
Total number of stressful events	1.27 (1.21–1.33) ^{***}	1.27 (1.21–1.33) ^{***}
Number of disease or death events	1.96 (1.70–2.26) ^{***}	1.95 (1.69–2.25) ^{***}
Number of conflict events	1.41 (1.28–1.56) ^{***}	1.39 (1.26–1.54) ^{***}
Number of life changing or other events	1.27 (1.19–1.36) ^{***}	1.27 (1.19–1.37) ^{***}

*** $P < 0.001$, indicate significant odds ratios compared with reference. [†]For models with continuous variable, odds ratios are the odds of asthma with increase in one stressful event. [‡]Adjusted for age, sex, education, body mass index, smoking status, alcohol intake and physical activity.

Stress management skills

Table 4 presents the independent associations between total stress management skills and eight specific aspects and allergy risk in the study population. For all participants, data showed that the total stress management skills was significant negatively associated with allergies (OR, 0.74; 95% CI, 0.57–0.95), even after adjusting for age, sex, education, body mass index, smoking status, alcohol intake and physical activity. Significant decreased allergic risks were also observed among individuals who answered sometimes or often for “concentrate on pleasant thoughts at bedtime”, “pace myself to prevent tiredness”, “get enough sleep”, “take some time for relaxation each day” and “Balance time between work and play” (adjusted ORs ranged from 0.54 to 0.81, Table 4). No significant associations with allergic risk were found for “accept those things in my life that I cannot change”, “use specific methods to control my stress” and “practise relaxation or meditation for 15-20 min daily”, despite a tendency towards a reduced allergic risk (ORs of good or moderate management skills are all negative compared with poor skills).

Results from the stratified analyses are presented in Table 4, too. Like the results for all participants, using one or more stress management skills was significantly or borderline significantly associated with decreased allergic risk among people with stressful events. It is worth noting that among people without stressful events, no significant associations was observed between stress management skills and allergic risk.

Table 4 Adjusted odds ratios and 95% confidence intervals for stress management skills in all participants and in subjects stratified by stressful life events

	All participants			Participants with stressful life events			Participants without stressful life events		
Variable	Case participants (1340)	Control participants (2662)	Adjusted oddst	Case participants (1000)	Control participants (1595)	Adjusted oddst	Case participants (340)	Control participants (1067)	Adjusted oddst
	N (%)	N (%)	(odds ratio, 95% confidence interval)	N (%)	N (%)	(odds ratio, 95% confidence interval)	N (%)	N (%)	(odds ratio, 95% confidence interval)
Total stress management skills									
Poor	217 (16.2)	351 (13.2)	1	181 (18.1)	239 (15.0)	1	36 (10.6)	112 (10.5)	1
Moderate	926 (69.1)	1796 (67.5)	0.92 (0.76–1.12)	690 (69.0)	1079 (67.6)	0.92 (0.74–1.16)	236 (69.4)	717 (67.2)	1.17 (0.76–1.78)
Good	197 (14.7)	515 (19.3)	0.74 (0.57–0.95)*	129 (12.9)	277 (17.4)	0.71 (0.53–0.97)*	68 (20.0)	238 (22.3)	1.18 (0.72–1.96)
Stress management skill items:									
Accept those things in my life that I cannot change									
Rarely or never	72 (5.4)	123 (4.6)	1	58 (5.8)	72 (4.5)	1	14 (4.1)	51 (4.8)	1
Sometimes	350 (26.1)	814 (30.6)	0.74 (0.54–1.03)	279 (27.9)	496 (31.1)	0.70 (0.47–1.02)	71 (20.9)	318 (29.8)	0.90 (0.46–1.74)
Often or always	918 (68.5)	1725 (64.8)	0.95 (0.69–1.30)	663 (66.3)	1027 (64.4)	0.82 (0.56–1.19)	255 (75.0)	698 (65.4)	1.61 (0.85–3.04)
Use specific methods to control stress									
Rarely or never	56 (4.2)	91 (3.4)	1	45 (4.5)	55 (3.4)	1	11 (3.2)	36 (3.4)	1
Sometimes	452 (33.7)	861 (32.3)	0.93 (0.65–1.33)	346 (34.6)	550 (34.5)	0.82 (0.54–1.26)	106 (31.2)	311 (29.1)	1.24 (0.60–2.60)
Often or always	832 (62.1)	1710 (64.2)	0.92 (0.64–1.31)	609 (60.9)	990 (62.1)	0.84 (0.56–1.28)	223 (65.6)	720 (67.5)	1.26 (0.61–2.60)
Concentrate on pleasant thoughts at bedtime									
Rarely or never	179 (13.4)	239 (9.0)	1	140 (14.0)	159 (10.0)	1	39 (11.5)	80 (7.5)	1
Sometimes	741 (55.3)	1461 (54.9)	0.73 (0.58–0.90)**	569 (56.9)	883 (55.4)	0.78 (0.60–1.01)	172 (50.6)	578 (54.2)	0.66 (0.43–1.02)
Often or always	420 (31.3)	962 (36.1)	0.67 (0.53–0.85)**	291 (29.1)	553 (34.7)	0.67 (0.51–0.89)**	129 (37.9)	409 (38.3)	0.79 (0.50–1.25)
Pace myself to prevent tiredness									
Rarely or never	342 (25.5)	521 (19.6)	1	275 (27.5)	320 (20.1)	1	67 (19.7)	201 (18.8)	1
Sometimes	506 (37.8)	1011 (38.0)	0.80	380 (38.0)	611 (38.3)	0.75	126 (37.1)	400 (37.5)	0.97

			(0.67–0.96)*			(0.61–0.93)**			(0.68–1.37)
Often or always	492 (36.7)	1130 (42.4)	0.76 (0.63–0.91)**	345 (34.5)	664 (41.6)	0.67 (0.54–0.83)***	147 (43.2)	466 (43.7)	1.14 (0.80–1.62)
Get enough sleep									
Rarely or never	68 (5.1)	80 (3.0)	1	58 (5.8)	49 (3.1)	1	10 (2.9)	31 (2.9)	1
Sometimes	555 (41.4)	858 (32.2)	0.81 (0.57–1.14)	439 (43.9)	608 (38.1)	0.63 (0.42–0.94)*	116 (34.1)	250 (23.4)	1.55 (0.72–3.33)
Often or always	717 (53.5)	1724 (64.8)	0.54 (0.39–0.77)***	503 (50.3)	938 (58.8)	0.48 (0.32–0.72)***	214 (62.9)	786 (73.7)	0.97 (0.46–2.05)
Take some time for relaxation each day									
Rarely or never	87 (6.5)	95 (3.6)	1	71 (7.1)	58 (3.6)	1	16 (4.7)	37 (3.5)	1
Sometimes	558 (41.6)	1064 (40.0)	0.63 (0.46–0.86)**	422 (42.2)	684 (42.9)	0.53 (0.37–0.78)**	136 (40.0)	380 (35.6)	0.95 (0.50–1.79)
Often or always	695 (51.9)	1503 (56.5)	0.59 (0.43–0.82)**	507 (50.7)	853 (53.5)	0.55 (0.37–0.80)**	188 (55.3)	650 (60.9)	0.87 (0.46–1.64)
Balance time between work and play									
Rarely or never	84 (6.3)	122 (4.6)	1	72 (7.2)	86 (5.4)	1	12 (3.5)	36 (3.4)	1
Sometimes	632 (47.2)	1034 (38.8)	0.95 (0.71–1.29)	491 (49.1)	662 (41.5)	0.93 (0.66–1.31)	141 (41.5)	372 (34.9)	1.24 (0.61–2.50)
Often or always	624 (46.6)	1506 (56.6)	0.69 (0.51–0.94)*	437 (43.7)	847 (53.1)	0.68 (0.48–0.96)*	187 (55.0)	659 (61.8)	1.03 (0.51–2.08)
Practise relaxation or meditation for 15-20 min daily									
Rarely or never	146 (10.9)	223 (8.4)	1	116 (11.6)	142 (8.9)	1	30 (8.8)	81 (7.6)	1
Sometimes	578 (43.1)	1099 (41.3)	0.87 (0.68–1.10)	433 (43.3)	667 (41.8)	0.84 (0.64–1.11)	145 (42.6)	432 (40.5)	0.99 (0.62–1.60)
Often or always	616 (46.0)	1340 (50.3)	0.81 (0.64–1.03)	451 (45.1)	786 (49.3)	0.79 (0.59–1.05)	165 (48.5)	554 (51.9)	0.99 (0.61–1.59)

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, indicate significant odds ratios compared with reference. †Adjusted for age, sex, education, body mass index, smoking status, alcohol intake and physical activity.

Combined effect of stressful life events and stress management skills

We further analyzed the combined effects of stressful events and stress management skills on the risk of allergic diseases (Table 5). There was a significant linear trend for the risk of allergies from good stress management skills with no stressful events to poor stress management skills with stressful events ($P < 0.000$, Table S1). Although an interaction in the multiplicative model was not observed, significant additive interactions were found between stressful events and total stress management skills ($P = 0.255$ and 0.006 , respectively). The results for “concentrate on pleasant thoughts at bedtime” and “balance time between work and play” were similar to those for total stress management skills (Table 5). Interaction was significant in both multiplicative and additive models for “pace myself to prevent tiredness” ($P = 0.023$ and 0.000 , respectively).

Table 5 Interaction between stressful life events and stress management skills in southern Chinese allergy study

Stress management skills	<i>P</i> for interaction	
	Multiplicative	Additive
Total stress management skills	0.255	0.006
Accept those things in my life that I cannot change	0.019	0.113
Use specific methods to control stress	0.936	0.685
Concentrate on pleasant thoughts at bedtime	0.286	0.006
Pace myself to prevent tiredness	0.023	0.000
Get enough sleep	0.802	0.193
Take some time for relaxation each day	0.812	0.517
Balance time between work and play	0.489	0.008
Practise relaxation or meditation for 15–20 min daily	0.699	0.170

Significant differences are highlighted in bold.

Discussion

Associations of allergy risk with stressful life events and stress management skills alone and in combination were examined in a case-control study in 1340 case participants and 2662 control participants. In general, stressful events were positively associated with allergic risk while stress management skills were negatively associated. We found antagonistic effects of stressful events and stress management skills among people experiencing stressful events. Moreover, alcohol intake and less vigorous exercise were associated with increased allergy risk.

This positive association between allergic diseases and stressful events is consistent with results from other investigations. A prospective study showed that the illness of a family member, marital problems, divorce or separation, and conflicts with a supervisor were associated with the onset of asthma[17]. A cross-sectional study of 15-year-old Norwegian adolescents found asthma to be associated with exposure to violence and stressful events[32]. It is known that diseases or bereavements and conflicts in personal or parental relationships are common stress events[12,16,17]. Our results found lifestyle changes, such as overloading the individual, economic plight, living environment change, a criminal or civil penalty and other events were also associated with allergic episodes. This was confirmed by another report that among children who had lived abroad for a year, sensitization was more common in case children than in control children, suggesting that stress related to living environment change could enhance the development of atopy[33]. However, a cross-sectional design did not allow assessment of the causality or directionality of relationships. Diagnosed allergies might also lead to increased stress and stress events. A temporal relationship of personal or parental conflict with asthma diagnosis was found in a retrospective study of Finnish university students, which at the same time found that the diagnosis of asthma was related to and increased the number of subsequent stressful events[12]. More prospective studies are warranted on stressful events and allergies.

Stress reduction and elimination would be the most desirable intervention but is often difficult to achieve in our fast-paced, high-pressure societies. A growing number of studies have considered coping strategies and management support issues[10]. Several popular approaches were used[34], such as enhancing cognitive awareness of stressors and coping, relaxation techniques, anger management and anxiety reduction techniques, incorporating healthy eating and regular physical activity, managing time, et al. There were few profile can access these factors comprehensively. One scale measurement of Current Status (MOCS) was used to assess perceived stress management skill (ability to respond to the demands of daily life), but it is only with respect to coping confidence, relaxation, assertiveness and tension awareness by questions such as “When problems arise, I know how to cope with them” (response range from 1=cannot do this at all to 5=can do this extremely well)[35]. Coping inventories such as the Coping Inventory for Stressful Situations assess not coping skills but coping styles habitually used in stress situations, independently of whether the respective coping style successfully helps manage stress[36], while the Inventory for Assessment of Stress management skills assesses perceived stress management skills rather than objective lifestyle behaviours[36]. We chose the HPLP-II, which assesses daily stress management lifestyle behaviours and establishes the individuals’ ability to acknowledge sources of stress and control mechanisms, helps people to prevent stressful events from occurring and manage their responses to those stressful events.

Of the many studies on stress management interventions, few concentrate on the impact of stress management skills on atopic disorders. This study of southern Chinese people indicates that people with allergic diseases are likely to have worse stress management skills, especially in the areas of “concentrate on pleasant thoughts at bedtime”, “pace myself to prevent tiredness”, “get enough sleep”, “take some time for relaxation each day” and “balance time between work and play”, which are skills that relax and reduce fatigue. As we know, relaxation techniques have been shown to acutely decrease activity of stress-responsive systems and thus prepare for either active stress management or regeneration[20,37]. Further stratified analyses showing that stress management skills were significantly associated with decreased allergy risk only among participants who experienced stressful events, similar results were not observed among people who did not. This suggests that stress management skills are likely to be needed when stressful

events are being experienced, but could be omitted when there are no stressful events. This has not been reported hitherto. Our finding gives suggestive guidance for the timing of stress management skills training.

To our knowledge, this study is the first attempt to characterize the effect of the relationship between stressful events and stress management skills on allergic diseases. The results suggest that the combination of stressful events and stress management skills significantly decreased the risk of allergies compared with stressful events only. There might be a linear dose–response relationship between stressful events and allergic diseases with a degree of stress management skills exposure. Although interaction in multiplicative models did not reach statistical significance, additive interactions were observed for total stress management skills. These observations suggest that stress management skills can significantly moderate the effects of stressful events on allergy risk, especially “concentrate on pleasant thoughts at bedtime”, “pace myself to prevent tiredness”, “balance time between work and play” and “balance time between work and play”.

Hypersensitivity reactions to alcoholic drinks are common, as reviewed recently [38,39]. There is increasing evidence that alcohol intake might play a role in promoting the development of immunoglobulin-E (IgE)-mediated hypersensitivity to different allergens[40,41]. But our findings in this case-control study didn't get the same results. We found that relatively vigorous exercise, such as brisk walking, bicycling or aerobic dancing, for 20 min or longer at least three times a week, can significantly decrease the incidence of allergic disease. Another study reported that an exercise training program is well tolerated in children with mild-to-moderate asthma and can improve both aerobic and anaerobic fitness[42].

Research on the mechanisms of stress inducing allergic diseases (or with comorbidities) has been reported. Neuroendocrine and autonomic nervous system (ANS) responses, the activity of the hypothalamic-pituitary-adrenocortical (HPA) axis and the immune system are common research directs. The role of allelic variation in genes that regulate stress responses, as well as stress-induced changes in DNA methylation patterns and gene expression are also been related mechanisms[43].

In a study of more than 1200 (predominantly African American) adults exposed to traumatic events, Ressler et al.[44] implicated the pituitary adenylate cyclase–activating peptide (PACAP)–PAC1 receptor pathway on the pathogenesis of post-traumatic stress disorder (PTSD). In this study both PACAP38 (PACAP peptide containing 38 residues) blood levels and the C allele of a functional single nucleotide polymorphism (SNP; rs2267735) in an estrogen-receptor element of the gene for the PAC1 receptor (ADCYAP1R1) were significantly associated with PTSD or more PTSD symptoms in female.

Several studies have reported a relationship between stressful life events and the immune function. After death of a spouse, T lymphocyte responses to mitogens in bereaved subjects were found to be significantly lower than in controls[45]. Under psychological stress the risk of viral infections is greater[46] and could be associated with airway inflammation and promote the onset of asthma[47].

Psychoneuroimmunology also provides a plausible biological pathway through which stress may affect asthma morbidity, primarily through dysregulation of the hypothalamic-pituitary-adrenal axis[48]. And in the autonomic nervous system of atopic subjects cholinergic activity seems to predominate over adrenergic activity [49,50]. Adolescents with asthma who experienced more stress have been shown to have higher levels of interleukin 5 (IL-5) and interferon- γ (IFN- γ); cytokines associated with type 2 and type 1 immune responses, respectively[51]. In animals, chronic stress elevates glucocorticoid levels for long periods, leading to an increased cholinergic system function[52]. These alterations of adrenal function and subsequent cytokine profiles may thus interconnect chronic stress with immunity changes favouring atopy. There is also evidence that immune changes under stress are affected by control of stress[53].

Furthermore, stress induces specific IgE production in the lungs of sensitized rats, suggesting linkage between allergic reaction and stress[54]. Evidence suggests that stress management interventions result in the restoration of a more normal TH₁/TH₂ and immune function balance. However, further research is warranted to prove a direct link between clinical improvement and immune change following psychological interventions in allergic diseases.

Limitations

We relied on questionnaire in the study, which is prone to several sources of bias [55–57]. But our study included large population-based sample and high participation rates. And as we know, self-reports of questionnaire is a pragmatic and efficient option of data collection for large epidemiological studies. And self-reported data are relatively low cost to collect and do not involve complicated field logistics or invasive procedures such as blood sampling. This is the common method used in the epidemiological research. And we have taken steps to avoid the bias for accuracy data.

First, the selection of life events is based on well-known life event scales, and represent severe life-events[23,58]. Study participants indicated (yes/no) their experience of 14 major events that had happened in their life, these events concerns about disease or death of family members or close friends; conflicts in personal relationships or life changes. They have a strong impact on emotions, one would expect to be remembered reliably, and are likely to be recalled more accurately than other events[59]. Therefore, reporting bias as regard the events is unlikely to be different among cases and controls.

Second, the recall biases in our manuscript are mainly on the allergic disease and the stressful life events. However, enterprises/factories or government unit would hold routine health examinations for employees every year. We evaluated these medical histories getting from each unit managers (at least one year medical examination report between 2012 and 2013 for each participant) to minimize the diseases recall bias. What's more, the events studied (mourning, divorce and loss of the job) have a strong impact on emotions and are likely to be recalled more accurately than other events[58]. And exclusion of cases who completed questionnaires after five-year post diagnosis was done to minimize recall bias and reverse. Thus, recall bias could have influenced our estimates only to a minor extent.

Third, epidemiological studies can be affected by selection bias. In this study, we included six cities randomly selected in Guangdong province, and then selected one or two convenient areas (e.g. schools, companies, government agencies or factories) in each city for cluster sampling. The sample size was reasonably large, and the response rate was relatively high (83.01%). Thus, a selection bias is fairly unlikely. Furthermore, matching the controls for age and gender diminishes bias in reporting of the disease[60], and bias caused by gender differences in the prevalence of the disease.

Conclusion

We confirmed a strong positive association between stressful life events and allergies, and found a significantly inverse relationship between stress management skills and allergies among people who experienced stressful events. We also observed some antagonism effects of stress management skills with stressful events on allergy risk. This is conducive to assessing and addressing the effects of stress management skills in managing allergic disease. Further studies are warranted to characterize the exact preventative role of stress management skills in the etiology or progression of allergies.

Abbreviations

OR:odds ratio; CI:Confidence interval; DM:diabetic mellitus;

HPLP-II: Health- Promoting Lifestyle Profile II;

MOCS:One scale measurement of Current Status;

IgE: immunoglobulin-E; ANS:autonomic nervous system;

HPA: hypothalamic-pituitary- adrenocortical;

PACAP:pituitary adenylate cyclase-activating peptide;

PTSDpost- traumatic stress disorder;

SNP:single nucleotide polymorphism;IL-5:interleukin 5; IFN-c:interferon-c.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Nanfang Hospital in Guangzhou, China (2012) LunShenZi (No.035). Verbal consent was obtained at the onset of the interview after the interviewer fully explaining the purpose of the study, participants who agreed to take part in were asked to fill out the questionnaire and provide written informed consent to share his/her information with investigators for data statistics. The participants were free to withdraw at any time without giving any reason. Strict confidentiality was maintained throughout the process of data collection and analysis.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that there is no conflict of interests.

Funding

This work was supported by the Key Project of National Natural Science Foundation of China (No. 81830117), the NSFC-Guangdong joint fund (No. U1132001), the National Science Foundation of China (No. 81760821, 81703952), the Natural Science Foundation of Guangdong Province, China (No.2017A030313722, 2018A0303130320), and the Science & Technical Plan of Guangzhou, Guangdong, China (No. 201903010069). The funders had no input to the study design, analysis, interpretation of data, production of this manuscript.

Authors' contributions

Study concept and design: XSZ YYL RL; acquisition of data: JRC FL YGL JYC XMS LX PPJ SWW YX; analysis and interpretation of data: JRC FL YGL; drafting of the manuscript: JRC FL YGL; critical revision of the manuscript for important intellectual content: XSZ YYL RL LZ; study supervision: XSZ YYL RL. All authors were involved in the formulation of the research questions.

Acknowledgements

We thank our study participants. We also thank administrators of selected units for their contribution to the data collection and case ascertainment.

Author details

¹ Department of Nephrology, the First Affiliated Hospital of Zhengzhou University, Zhengzhou, 450052, China. ² School of Traditional Chinese Medicine, Southern Medical University, Guangzhou, Guangdong, 510515, China. ³ Department of Traditional Chinese Medicine, People's Hospital of Yangjiang, Yangjiang, Guangdong, 529500, China. ⁴ Endocrinology Department, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, 510515, China.

References

1. von Mutius E. The rising trends in asthma and allergic disease. *Clin Exp Allergy*. 1998;28(Suppl. 5):45-9; discussion 50-
2. Kusunoki T, Morimoto T, Nishikomori R, Yasumi T, Heike T, Fujii T, et al. Changing prevalence and severity of childhood allergic diseases in Kyoto, Japan, from 1996 to 2006. *Allergol Int*. 2009;58:543-
3. Wong GW, Leung TF, Ko FW. Changing prevalence of allergic diseases in the Asia-Pacific region. *Allergy Asthma Immunol Res*. 2013;5:251-
4. Ono SJ. Molecular genetics of allergic diseases. *Annu Rev Immunol*. 2000;18: 347-
5. Azalim S, Camargos P, Alves AL, Senna MI, Sakurai E, Schwabe Keller W. Exposure to environmental factors and relationship to allergic rhinitis and/or asthma. *Ann Agric Environ Med*. 2014;21:59-
6. Akkurt I, Sümer H, Özşahin SL, Gönülgür U, Özdemir L, Doğan O, et al. Prevalence of asthma and related symptoms in Sivas, Central Anatolia. *J Asthma*. 2003;40:551-6.
7. Marshall GD. Internal and external environmental influences in allergic diseases. *J Am Osteopath Assoc*. 2004;104 (5 Suppl. 5):S1-S
8. Dave ND, Xiang L, Rehm KE, Marshall GD. Stress and allergic diseases. *Immunol Allergy Clin North Am*. 2011;31:55-
9. Lee MR, Son BS, Park YR, Kim HM, Moon JY, Lee YJ, et al. The relationship between psychosocial stress and allergic disease among children and adolescents in Gwangyang Bay, Korea. *J Prev Med Public Health*. 2012;45:374-
10. Dhabhar FS. Stress-induced augmentation of immune function – the role of stress hormones, leukocyte trafficking, and cytokines. *Brain Behav Immun*. 2002;16: 785-
11. Rutters F, Pilz S, Koopman AD, Rauh SP, Te Velde SJ, Stehouwer CD, et al. The association between psychosocial stress and mortality is mediated by lifestyle and chronic diseases: the Hoorn Study. *Soc Sci Med*. 2014;118:166-
12. Kilpeläinen M, Koskenvuo M, Helenius H, Terho EO. Stressful life events promote the manifestation of asthma and atopic diseases. *Clin Exp Allergy*. 2002; 32:256-
13. Teiramaa E. Psychosocial and psychic factors and age at onset of asthma. *J Psychosom Res*. 1979;23:27-
14. Levitan H. Onset of asthma during intense mourning. *Psychosomatics*. 1985;26:939-41.
15. Turyk ME, Hernandez E, Wright RJ, Freels S, Slezak J, Contreras A, et al. Stressful life events and asthma in adolescents. *Pediatr Allergy Immunol*. 2008; 19:255-
16. Loerbroks A, Apfelbacher CJ, Thayer JF, Debling D, Stürmer T. Neuroticism, extraversion, stressful life events and asthma: a cohort study of middle-aged adults. *Allergy*. 2009; 64:1444-50.
17. Lietzén R, Virtanen P, Kivimäki M, Sillanmäki L, Vahtera J, Koskenvuo M. Stressful life events and the onset of asthma. *Eur Respir J*. 2011;37:1360-
18. Liu LY, Coe CL, Swenson CA, Kelly EA, Kita H, Busse WW. School examinations enhance airway inflammation to antigen challenge. *Am J Respir Crit Care Med*. 2002;165:1062-
19. de Brouwer SJ, Kraaijaat FW, Sweep FC, Donders RT, Eijsbouts A, van Koulil S, et al. Psychophysiological responses to stress after stress management training in patients with rheumatoid arthritis. *PLoS ONE*. 2011;6:
20. Walker LG, Walker MB, Ogston K, Heys SD, Ah-See AK, Miller ID, et al. Psychological, clinical, and pathological effects of relaxation training and guided imagery during primary chemotherapy. *Br J Cancer*. 1999;80:262-8.
21. Huntley A, White AR, Ernst E. Relaxation therapies for asthma: a systematic review. *Thorax*. 2002;57:127-31.
22. Rothman KJ, Greenland S. Case-control studies. In: Rothman KJ, Greenland S, editors. *Modern epidemiology*. USA: Lippincott Williams & Wilkins; 2008. 93-114.
23. Holmes TH, Rahe RH. The social readjustment rating scale. *J Psychosom Res*. 1967;11:213-8.
24. Walker SN, Sechrist KR, Pender NJ. The Health-Promoting Lifestyle Profile: development and psychometric characteristics. *Nurs Res*. 1987;36:76-

25. Walker SN, Sechrist KR, Pender NJ. The Health-Promoting Lifestyle Profile II. University of Nebraska Medical Center, College Of Nursing. <https://www.unmc.edu/nursing/faculty/health-promoting-lifestyle-profile-II.html>. Accessed 1995.
26. Lee RL, Loke AJ. Health-promoting behaviors and psychosocial well-being of university students in Hong Kong. *Public Health Nurs.* 2005;22:209-
27. Sonmezer H, Cetinkaya F, Nacar M. Healthy life-style promoting behaviour in Turkish women aged 18–64. *Asian Pac J Cancer Prev.* 2012;13:1241-
28. Leung SS, Chiang VC, Chui YY, Mak YW, Wong DF. A brief cognitive-behavioral stress management program for secondary school teachers. *J Occup Health.* 2011;53:23-
29. World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO Consultation. *World Health Organ Tech Rep Ser.* 2000; 894:i-xii,1-253.
30. Chen C, Lu FC, Department of Disease Control Ministry of Health, PR China. The guidelines for prevention and control of overweight and obesity in Chinese adults. *Biomed Environ* 2004;17 (Supp I):1-36.
31. Rothman KJ. The estimation of synergy or antagonism. *Am J Epidemiol.* 1976;103:506-11.
32. Haavet OR, Straand J, Saugstad OD, Grünfeld B. Illness and exposure to negative life experiences in adolescence: two sides of the same coin? A study of 15-year-olds in Oslo, Norway. *Acta Paediatr.* 2004; 93, 405-11.
33. Anderzén I, Arnetz BB, Söderström T, Söderman E. Stress and sensitization in children: a controlled prospective psychophysiological study of children exposed to internal relocation. *J Psychosom Res.* 1997;43:259-69.
34. Sharma M. Yoga as an Alternative and Complementary Approach for Stress Management: A Systematic Review. *J Evid Based Complementary Altern Med.* 2014;19:59-67.
35. Faul LA, Jim HS, Williams C, Loftus L, Jacobsen PB. Relationship of stress management skill to psychological distress and quality of life in adults with cancer. *Psychooncology.* 2010;19:102-9.
36. Wirtz PH, Thomas L, Domes G, Penedo FJ, Ehler U, Nussbeck FW. Psychoendocrine validation of a short measure for assessment of perceived stress management skills in different non-clinical populations. *Psychoneuroendocrinology.* 2013;38:572-86.
37. Pawlow LA, Jones GE. The impact of abbreviated progressive muscle relaxation on salivary cortisol and salivary immunoglobulin A (sIgA). *Appl Psychophysiol Biofeedback.* 2005;30:375-87.
38. Vally H, Thompson PJ. Allergic and asthmatic reactions to alcoholic drinks. *Addict Biol.* 2003;8:3-11.
39. Vally H, Thompson PJ. Alcoholic drinks and asthma. *Clin Exp Allergy.* 2002;32:186-91.
40. Gonzalez-Quintela A, Vidal C, Gude F. Alcohol, IgE and allergy. *Addict Biol.* 2004;9:195-204.
41. Linneberg A, Petersen J, Nielsen NH, Madsen F, Frølund L, Dirksen A, et al. The relationship of alcohol consumption to total immunoglobulin E and the development of immunoglobulin E sensitization: the Copenhagen Allergy Study. *Clin Exp Allergy.* 2003;33:192-8.
42. Counil FP, Varray A, Matecki S, Beurey A, Marchal P, Voisin, M, et al. Training of aerobic and anaerobic fitness in children with asthma. *J Pediatr.* 2003;142:179-84.
43. Rosenberg SL, Miller GE, Brehm JM, Celedón JC. Stress and asthma: novel insights on genetic, epigenetic, and immunologic mechanisms. *J Allergy Clin Immunol.* 2014;134:1009-15.
44. Ressler KJ, Mercer KB, Bradley B, Jovanovic T, Mahan A, Kerley K, et al. Post-traumatic stress disorder is associated with PACAP and the PAC1 receptor. *Nature.* 2011;470:492-7.
45. Schleifer SJ, Keller SE, Camerino M, Thornton JC, Stein M. Suppression of lymphocyte stimulation following bereavement. *JAMA.* 1983;250:374-7.
46. Cohen S, Tyrrell DA, Smith AP. Psychological stress and susceptibility to the common cold. *N Engl J Med.* 1991;325:606-12.
47. Wright RJ, Rodriguez M, Cohen S. Review of psychosocial stress and asthma: an integrated biopsychosocial approach. *Thorax.* 1998; 53:1066-74.
48. Wright RJ, Cohen RT, Cohen S. The impact of stress on the development and expression of atopy. *Curr Opin Allergy Clin Immunol.* 2005;5:23-9.
49. Miller BD, Wood B. Psychophysiological reactivity in asthmatic children: a cholinergically mediated confluence of pathways. *J Am Acad Child Adolesc Psychiatry.* 1994;33:1236-45.
50. Marshall PS. Allergy and depression: a neurochemical threshold model of the relation between the illnesses. *Psychol Bull.* 1993;113:23-43.
51. Chen E, Fisher EB, Bacharier LB, Strunk RC. Socioeconomic status, stress, and immune markers in adolescents with asthma. *Psychosom Med.* 2003;65:984-92.
52. Marshall PS. Allergy and depression: a neurochemical threshold model of the relation between the illnesses. *Psychol Bull.* 1993;113:23-43.
53. Brosschot JF, Benschop RJ, Godaert GL, Olff M, De Smet M, Heijnen CJ, et al. Influence of life stress on immunological reactivity to mild psychological stress. *Psychosom Med.* 1994;56:216-24.
54. Persoons JH, Berkenbosch F, Schornagel K, Thepen T, Kraal G. Increased specific IgE production in lungs after the induction of acute stress in rats. *J Allergy Clin Immunol.* 1995;95:765-70.
55. Garber MC, Nau DP, Erickson SR, Aikens JE, Lawrence JB. The concordance of self-report with other measures of medication adherence: a summary of the literature. *Med Care.* 2004; 42:649–52.
56. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med.* 2005;353:487–97.
57. Bruxvoort K, Goodman C, Kachur SP, Schellenberg D. How patients take malaria treatment: a systematic review of the literature on adherence to antimalarial drugs. *PLoS ONE.* 2014;9:

58. Miller MA, Rahe RH. Life changes scaling for the 1990s. *J Psychosom Res.* 1997;43:279-92.
59. Ferree NK, Cahill L. Post-event spontaneous intrusive recollections and strength of memory for emotional events in men and women. *Conscious Cogn.* 2009;18: 126–34.
60. Rothman KJ. Biases in study design. In: Rothman KJ. *Epidemiology: An introduction*; USA:Oxford University Press; 2012. p. 124-47.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Questionnaire.docx](#)
- [TableS2.docx](#)
- [TableS1.docx](#)