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

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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, Shaoqian, 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 (e.g. 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?

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.
Additive interaction was assessed using the method of Rothman[30].

Evaluation by multiplicative and additive models. We tested for multiplicative interaction by including the product term in multivariate logistic regression.

Subgroups with or without stressful events. The logistic regression model included the following potential confounders: age, sex, education, body mass index 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), 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).

**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].

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 manager 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 allergic 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).

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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 (\( P > 0.05 \)).

| Variable               | participants without self-reported illness or injury\# | \( P \) | participants with self-reported illness or injury\# | \( P \) |
|------------------------|-------------------------------------------------------|-------|--------------------------------------------------|-------|
| Age(year\(\text{mean±SD}\)) |                                                       |       |                                                 |       |
|                        | 28.25±9.46                                            | 0.658 | 26.9±8.14                                        | 0.104 |
| Gender                 |                                                       |       |                                                 |       |
| Male                   | 509(46.0)                                             | 0.528 | 92(39.3)                                         | 0.165 |
| Female                 | 597(54.0)                                             |       | 142(60.7)                                        |       |
| Education              |                                                       |       |                                                 |       |
| Compulsory school      | 597(30.8)                                             | 0.829 | 754(30.5)                                        | 0.953 |
| High school graduate   | 341(30.8)                                             |       | 1542(62.4)                                      |       |
| University/college degree| 692(62.6)                                             |       | 167(71.4)                                        |       |
| BMI(kg/m\(^2\))        |                                                       |       |                                                 |       |
| \( <18.5 \)            | 187(16.9)                                             | 0.062 | 52(22.2)                                         | 0.895 |
| \( 18.5-23.9 \)        | 734(66.4)                                             |       | 151(64.5)                                        |       |
| \( \geq 24 \)          | 185(16.7)                                             |       | 31(13.2)                                         |       |
| Smoking status         |                                                       | 0.113 |                                                 | 0.626 |
| Never                  | 945(85.4)                                             |       | 207(88.5)                                        |       |
| Current/Former         | 161(14.6)                                             |       | 27(11.5)                                         |       |
| Alcohol intake         |                                                       | 0.145 |                                                 | 0.096 |
| Never                  | 324(29.3)                                             |       | 53(22.6)                                         |       |
| Sometimes              | 757(68.4)                                             |       | 174(74.4)                                        |       |
| Often/always           | 25(2.3)                                               |       | 7(3.0)                                           |       |
| Physical activity*     |                                                       | 0.000 |                                                 | 0.185 |
| Rarely/never           | 275(24.9)                                             |       | 58(24.8)                                         |       |
| Sometimes              | 483(43.7)                                             |       | 96(41.0)                                         |       |
| Often/always           | 348(31.5)                                             |       | 80(34.2)                                         |       |

#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.

| Variable               | participants without self-reported illness or injury\# | \( P \) | participants with self-reported illness or injury\# | \( P \) |
|------------------------|-------------------------------------------------------|-------|--------------------------------------------------|-------|
| Age(year\(\text{mean±SD}\)) |                                                       |       |                                                 |       |
| Stressful life events  |                                                       |       |                                                 |       |
| Death of a family member or close friend | 48(10.9)                                             |       | 48(10.9)                                        |       |
| Career change          | 62(14.7)                                              |       | 62(14.7)                                        |       |
| Life change            | 126(30.5)                                             |       | 126(30.5)                                      |       |
| Other events           | 206(50.8)                                             |       | 206(50.8)                                      |       |

Table 2 Stressful life events for 4002 southern Chinese people
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

| Self-reported events                                      | Case participants (n = 1340) | Control participants (n = 2662) | All participants (n = 25,938)† |
|----------------------------------------------------------|-----------------------------|--------------------------------|--------------------------------|
| Disease or death (mean (SD))*                            | 0.3 (0.5)                   | 0.1 (0.4)                      | 0.000                          |
| Personal injury or illness (%)                           | 234 (17.5)                  | 189 (7.1)                      | 0.000                          |
| Severe disease of family member or close friend (%)      | 82 (6.1)                    | 83 (3.1)                       | 0.000                          |
| Death of family member or close friend (%)               | 68 (5.1)                    | 106 (4.0)                      | 0.110                          |
| Any disease or death (%)                                 | 328 (24.5)                  | 346 (13.0)                     | 0.000                          |
| Conflicts in personal relationships, (mean (SD))*        |                             |                                |                                |
| Interpersonal disharmony (%)                            | 150 (11.2)                  | 176 (6.6)                      | 0.000                          |
| Family discord (%)                                       | 59 (4.4)                    | 72 (2.7)                       | 0.004                          |
| Marital disruption (%)                                   | 30 (2.2)                    | 32 (1.2)                       | 0.012                          |
| Trouble from children (%)                               | 91 (6.8)                    | 116 (4.4)                      | 0.001                          |
| Split up from boyfriend or girlfriend (%)               | 212 (15.8)                  | 290 (10.9)                     | 0.000                          |
| Any conflicts event (%)                                  | 396 (29.6)                  | 533 (20.0)                     | 0.000                          |
| Life changes or other events (mean (SD))*                |                             |                                |                                |
| Overwork (%)                                             | 561 (41.9)                  | 814 (30.6)                     | 0.000                          |
| Economic plight (%)                                      | 288 (21.5)                  | 464 (17.4)                     | 0.002                          |
| Career change (%)                                        | 46 (3.4)                    | 63 (2.4)                       | 0.051                          |
| Living environment change (%)                            | 221 (16.5)                  | 365 (13.7)                     | 0.019                          |
| Lifestyle change (%)                                     | 191 (14.3)                  | 306 (11.5)                     | 0.013                          |
| Suffer a criminal or civil penalty (%)                   | 3 (0.2)                     | 0 (0.0)                        | 0.015                          |
| Any other temporal events (%)                            | 832 (62.1)                  | 1343 (50.0)                    | 0.000                          |
| Total stressful events (mean (SD))*                      |                             |                                |                                |
| Any stressful event (%)                                  | 1000 (74.6)                 | 1595 (59.9)                    | 0.000                          |
| Number of stressful events (%)*                          |                             |                                | 0.000                          |

* 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.
### Table 4

| 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**
| Variable                              | All participants | Participants with stressful life events | Participants without stressful life events |
|---------------------------------------|------------------|-----------------------------------------|------------------------------------------|
|                                       | Case participants (1340) | Control participants (2662) | Adjusted odds† | Case participants (1000) | Control participants (1595) | Adjusted odds† | Case participants (340) | Control participants (1067) | Adjusted odds† |
|                                       | 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                                    |
### 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                                      | P 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 allele 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-c (IFN-c); 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;
PTSD: post-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.

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Authors’ contributions
Study concept and design: XSZ YYL RL; acquisition of data: JRC FL YGL JYC XMS 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.

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