

## RESEARCH SUBMISSION

# Resilience and vulnerability in adolescents with primary headaches: A cross-sectional population-based study

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## Abstract

**Background:** A scarcity of studies on the role of resilience resources (RRs) and vulnerability risk (VR) in children and adolescents with primary headache hampers the development of a risk-resilience model for pediatric headaches.

**Objective:** To examine the extent to which headache frequency and diagnosis are associated with RRs and VR and explore possible predictors of low RRs and high VR in a cross-sectional population-based study in adolescents.

**Methods:** This is a cross-sectional population study conducted in a small city in Brazil (Delfinópolis). Consents and analyzable data were obtained from 339/378 adolescents (89.7%). RRs and VR were assessed using the validated Brazilian version of the Resiliency Scales for Children and Adolescents, completed by the adolescents. Parents filled a structured questionnaire assessing sociodemographic and headache characteristics, as well as the Brazilian-validated version of the Strengths and Difficulties Questionnaire added to the impact supplement to evaluate the adolescent's psychosocial adjustment skills. Teachers completed a structured questionnaire about the students' school performance.

**Results:** A higher frequency of headache was associated with lower RRs ( $F_{3,335} = 2.99$ ,  $p = 0.031$ ) and higher VR ( $F_{3,335} = 4.05$ ,  $p = 0.007$ ). Headache diagnosis did not significantly influence the risk of having lower RRs or higher VR. In the exploratory analyses, females (OR 3.07; 95% CI: 1.16–9.3) and individuals with psychosocial adjustment problems (OR 7.5; 95% CI: 2.51–22.4) were predictors of low RRs, and prenatal exposure to tobacco (OR 5.6; 95% CI: 1.57–20.9) was a predictor of high VR in adolescents with primary headache.

**Conclusions:** The risk of low RRs and high VR was associated with a higher headache frequency, but not with headache diagnosis. These findings may contribute to the development of a risk-resilience model of headaches in the pediatric population and help identify novel targets and develop effective resources for successful interventions.

## KEYWORDS

headache, migraine, pain, resilience, vulnerability

**Abbreviations:** ACEs, adverse childhood experiences; ER, emotional reactivity; HFH, high-frequency headaches; IFEH, intermediate-frequency episodic headaches; LFEH, low-frequency episodic headaches; RI, resource index; RRs, resilience resources; RSCA, Resiliency Scales for Children and Adolescents; SDQ, Strengths and Difficulties Questionnaire; VI, vulnerability index; VR, vulnerability risk; SM, sense of mastery; SR, sense of relatedness; SES, socioeconomic status.

## INTRODUCTION

Childhood resilience is a dynamic developmental process that reflects positive adaptation despite significant life adversities.<sup>1-3</sup> Rather than a personality trait or an individual attribute, resilience can be conceived as a two-dimensional construct that involves exposure to adversity and positive adjustment outcomes.<sup>4</sup> Childhood adversity refers to negative life circumstances that are faced by the child, such as familial adversities (e.g., abuse, parental psychopathology, and divorce), sociodemographic exposure (e.g., poverty, violence, and perceived discrimination), and chronic diseases, including chronic pain.<sup>1,4</sup> Positive adaptation reflects the absence of emotional or behavioral maladjustment in response to adversity or, more strictly, as behaviorally manifested social competence.<sup>4</sup>

Vulnerability is defined as the susceptibility to a specified negative outcome in the context of risk or adversity.<sup>5</sup> Resilience counterbalances vulnerability in a manner that higher resilience resources (RRs) are associated with a lower degree of vulnerability, or, conversely, lower RRs are associated with higher vulnerability risk (VR).<sup>2</sup> The following personal characteristics of RR have been reported in the literature: optimism,<sup>6</sup> sense of self-efficacy,<sup>7</sup> adaptability,<sup>8</sup> sense of trust,<sup>9</sup> perceived access to support,<sup>10</sup> comfort with others,<sup>2,11</sup> and tolerance of differences.<sup>12</sup> On the other hand, among the characteristics of high VR: a low threshold and high intensity of emotional response (sensitivity), few recovery skills and a significant impairment in response to strong emotional reactions.<sup>5,12</sup> In addition to resilience, numerous protective factors can reduce vulnerability, including intellectual ability, easy-going temperament, autonomy, self-reliance, communication competency, sociability, and effective coping skills.<sup>13</sup>

Resilience has been considered a reliable predictor of better health and quality of life among adolescents with chronic illnesses, such as type 1 diabetes,<sup>14</sup> cancer,<sup>15,16</sup> inflammatory bowel disease,<sup>17</sup> asthma,<sup>18</sup> and chronic pain.<sup>19</sup> Thus, resilience may be a promising target of intervention in these groups of patients to buffer the negative impact of serious illnesses.<sup>20</sup> A better understanding of drivers of resilience in children and adolescents who are exposed to medical conditions should translate into successful preventive and rehabilitative interventions and social policies to promote healthy development in vulnerable groups.<sup>2</sup> According to a recent meta-analysis, school-based intervention programs focused on resilience, particularly those based on cognitive-behavioral therapy, are effective in reducing depressive and anxiety symptoms in children and adolescents aged 5–18 years.<sup>21</sup>

Although resilience and coping have been often used indistinguishably, they are conceptually distinct constructs.<sup>22</sup> Resilience consists of how an event is appraised and influences the selection of a positive coping strategy, whereas coping strictly refers to the strategies or behaviors, positive (e.g., pain acceptance, pain self-efficacy) or negative (e.g., pain catastrophizing, fear of pain), employed following the appraisal of a stressful circumstance.<sup>22-24</sup>

Resilience models for pediatric chronic illnesses are multidimensional and account for individual, family, social, and cultural factors.

A narrower approach is often observed in pediatric chronic pain and headache studies focusing mainly on factors that are associated with maladaptive pain coping strategies or behaviors, such as pain catastrophizing,<sup>25</sup> fear of pain,<sup>26</sup> and anxiety.<sup>27</sup> Two clinical studies with children and adolescents with primary headaches suggested that pain self-efficacy and pain acceptance were associated with less fear of pain and disability, better school functioning, and fewer depressive symptoms.<sup>24,28</sup> One of these studies,<sup>28</sup> however, did not find a significant association between pain self-efficacy and headache severity.

Population-based studies have shown evidence on the comorbidity between migraine and/or high-frequency headaches (HFH) and psychiatric symptoms<sup>29-31</sup> and/or psychosocial adjustment problems.<sup>32</sup> Moreover, low RRs and high vulnerability are reported in children and adolescents with mental health problems.<sup>2,11,12</sup> Therefore, it is plausible to speculate an association between psychosocial adjustment problems, RRs, VR, and primary headaches.

The scarcity of studies of the role of RRs and VR in children and adolescents with primary headaches has hampered the development of risk-resilience models for pediatric headaches and represent a barrier to developing novel beneficial interventions for this vulnerable group. Furthermore, to our knowledge, no population-based studies have investigated resilience and vulnerability in children and adolescents with primary headaches.

Accordingly, we took advantage of a population sample of adolescents to examine the extent to which headache frequency and diagnosis are associated with RRs and VR and to explore possible predictors of low RRs and high VR in adolescents with primary headaches. Based on the higher risk of psychiatric comorbidity and maladaptive pain coping strategies or behaviors observed in children and adolescents with chronic migraine and chronic daily headache, we hypothesize that adolescents with high-frequency headache and/or migraine exhibit lower RRs and a higher VR compared to non-headache controls.

## METHODS

### Sample

The present study utilized a cross-sectional population design in a small city in Minas Gerais state (Delfinópolis), Brazil. No formal statistical power calculation was conducted before the collection of data and we relied on primary data. According to the most recent official demographic census, this region covers an area with approximately 6,830 inhabitants, 70.9% of whom live in the urban area. The Human Development Index (HDI) in this city is 0.740, with a life expectancy of 77.3 years and fecundity rate of 2.3. The HDI is a composite index using geometric mean of normalized indices for health, education, and living dimensions. The health dimension is assessed by life expectancy at birth; the education dimension is measured by mean of years of schooling for adults and expected years of schooling for children at school entry; and the living dimension is measured by gross national income per capita.

The target sample was composed of all adolescents from 10 to 18 years of age living in the city according to the last population census. All of them attended the only school in the city. The adolescents, their parents, and teachers were asked to complete structured and validated self-reported questionnaires. The study was conducted in 2016. Adolescents from urban and rural areas were assessed as long as they were enrolled in the school system, which is required by Brazilian law. According to the municipal education commission, the target sample ( $n = 378$ ) corresponded to 96.2% of the adolescents who lived in the city in 2016. Of the target sample, informed consent was obtained from 371 adolescents (98.1%). A total of 32 adolescents (8.6%) were excluded for the following reasons: (1) lack of completed questionnaires from the parents ( $n = 6$ ), teachers ( $n = 2$ ), or the students themselves ( $n = 2$ ), (2) more than 10% of missing responses ( $n = 13$ ), and (3) because of intellectual disability ( $n = 9$ ), resulting in a final sample of 339 adolescents.

## Procedure

Parents were invited to attend a school meeting, where the study was explained in detail. Parents who agreed to participate in the study completed the questionnaires, which was supervised by the teachers and one of the authors (M.A.A.). Teachers have been previously trained on how to complete the questionnaires and supervise the parents and the adolescents. In the following 2 weeks, the adolescents also completed the questionnaire while being supervised by the teachers in the classroom.

## Measures

Supervised by the teacher and one of the authors (M.A.A.), parents completed a standardized and validated questionnaire with 102 questions that assessed the adolescents' sociodemographic characteristics, developmental milestones, past medical history, mental health, and headaches. Also supervised by the teachers, adolescents completed a validated scale with 64 items assessing resilience and vulnerability profiles. Teachers completed a standardized and validated questionnaire with 20 questions assessing the students' school performance.

### Headache ascertainment

The headache questionnaire consisted of 14 questions that assessed distinguishing features that are required for a headache diagnosis according to the International Classification of Headache Disorders, 3rd edition (ICHD-3).<sup>33</sup> The questionnaire is the validated Brazilian Portuguese version of the questionnaire that was used in the American Migraine Studies<sup>34</sup> and was jointly completed by the adolescents and their parents. Based on the average headache frequency, the adolescents were categorized as (1) no headaches (no lifetime report of

headaches), (2) low-frequency episodic headaches (LFEH; headaches in the past year and less than 5 days of headaches per month in the last 3 months), (3) intermediate-frequency episodic headaches (IFEH; 5–9 days of headaches per month in the last 3 months), and (4) HFH ( $\geq 10$  days of headaches per month in the last 3 months).

### Psychosocial adjustment

The parents completed the validated Brazilian version of the Strengths and Difficulties Questionnaire (SDQ) added to the impact supplement.<sup>35,36</sup> The SDQ is a 25-item instrument that was developed to evaluate psychosocial adjustment from the perspective of parents and/or teachers. The SDQ consists of five scales, each with five items assessing emotional symptoms, conduct problems, hyperactivity/inattention, peer problems, and prosocial behavior problems. The parents completed the parental version of the SDQ and the impact supplement that was related to any adjustment symptoms in terms of chronicity, resultant distress, social impairment, and burden to others.<sup>13</sup> The Cronbach's alpha of this questionnaire was 0.8 (95% CI: 0.77–0.83).

### School performance

Before supervising the parents and adolescents to complete the questionnaires, the teachers were asked to provide structured information about the students' school performance, with measurements of overall achievement for the school year that was derived from competencies in language, mathematics, science, and social studies. Adolescents were ranked as being below expectations (i.e., failed to achieve a minimal number of established milestones for the year), matching expectations, or exceeding expectations (i.e., achieved milestones that are only expected to be achieved in the following school year) for the grade in accordance with education board standards.

### Resilience and vulnerability profiles

Resilience and vulnerability profiles were assessed using the validated Brazilian version of the Resiliency Scales for Children and Adolescents (RSCA) completed by the adolescents.<sup>13,37</sup> The RSCA is a self-report questionnaire designed for a third-grade reading level to be applied in children and adolescents from 9 to 18 years of age (extra information is at <https://prince-embury.socialpsychology.org/files>). The objective of the RSCA is to identify and quantify core personal features of resilience in youths, expressed in their own words and about their own experiences.<sup>12</sup> The RSCA draws from three core measurable constructs of resilience: Sense of mastery (SM), sense of relatedness (SR), and emotional reactivity (ER). In all of the scales, the items' response options were on a 5-point Likert-type scale: 0 (never), 1 (rarely), 2 (sometimes), 3 (often), and 4 (almost always).<sup>13</sup>

The SM scale is a 20-item self-report questionnaire and distinguishes three conceptually related domains or subscales: optimism, self-efficacy, and adaptability. Optimism consists of positive attitudes about world/life and one's own life; self-efficacy refers to developing problem-solving attitudes and strategies; and adaptability is expressed by the ability to be receptive to criticism and to learn from one's mistakes.<sup>13</sup> The Cronbach's alpha of this scale was 0.87 (95% CI: 0.85–0.89).

The SR scale is a 24-item self-report questionnaire comprised by four subscales: sense of trust, support, comfort, and tolerance. The sense of trust is defined as the degree to what each other is perceived as reliable; support refers to the individual's belief that he or she can count on others when dealing with adversities; comfort is the degree to which an individual can be in the presence of others without distress or anxiety; and tolerance is the individual's belief that he or she can safely express differences within a relationship.<sup>13</sup> The Cronbach's alpha of this scale was 0.9 (95% CI: 0.89–0.92).

Finally, the ER scale is a 20-item self-report questionnaire constituted by three subscales: sensitivity, recovery, and impairment. Respectively, it refers to the threshold and intensity of emotional responses, recovery skills, and the impairment determined by strong emotional reactions.<sup>13</sup> Contrary to the SM and SR scales, low ER scores indicate higher levels of resilience, and high scores indicate higher levels of vulnerability.<sup>13</sup> The Cronbach's alpha of this scale was 0.9 (95% CI: 0.89–0.92).

Scores on the three scales are used to derive two indexes: Resource index (RI) and vulnerability index (VI). The RI express the RRs and is computed as the average of SM and SR scale scores, and its results estimate the youth's personal strength or resources.<sup>13</sup> The VI expresses the VR and is computed as the difference between the ER raw score and the RI.<sup>13</sup> Because of the lack of Brazilian normative data for these indexes, raw scores were used in this study.

## Analytical plan

To ensure consistency of the analyses, the data were subjected to exhaustive quality checks through visual inspection and tabular analyses. Missing cases were not replaced, and no outlier was suppressed. Race was divided into two categories: white and non-white. The five income classes were defined according to the Brazilian Economic Classification Criteria, based on total family income, and do not reflect quintiles. They are determined based on the buying power for a basket of products and services that is defined by the institute and that is related to socioeconomic characteristics. Economic classes A and B represent the upper economic classes, whereas D and E describe different levels of poverty, and C is the middle class.

Categorical data (e.g., sex and level of education) are reported as frequencies and percentages. Continuous data (e.g., age) are reported as means (M)  $\pm$  standard deviation (SD). Prevalence and odds ratios (ORs) of headache frequency according to demographic characteristics were computed individually by median-unbiased estimation and exact confidence interval using the mid-p method.<sup>38</sup>

To check the effect of headache frequency on the RSCA indexes and scales, a linear model was fitted to the data. However, because the residual normality and homoscedasticity assumptions were violated, a robust one-way analysis of variance (ANOVA) between groups was performed. The MM-estimator was then defined, as recommended by the literature. This estimator is an extension of the maximum likelihood method and is a robust estimation that deals with outliers and other influential points.<sup>39,40</sup> The bootstrap method was used to compute all estimates, fixing 1,000 resamples from the data. This method produced all estimates and its related *p* values of the comparison between the no headache group (reference) to the other conditions.

To further explore possible predictors of the association between primary headaches, low RRs, and/or high VR, a binary logistic regression was modeled, and two contrasting groups were formed. In the Brazilian version of the RSCA, there is no default score for setting its cutoffs. We used results that fall 1.5 standard deviations from the mean as criteria to detect the early signs of children at risk of high vulnerability or low RRs. This specific threshold was inspired by DSM-5 recommendation for specific learning disorder<sup>41</sup> and studies in which the same cutoff was implemented for developmental disorders.<sup>42,43</sup> Therefore, the low-RR group consisted of children with primary headaches and Z-scores  $\leq 1.5$  SD in the resilience index. Conversely, the high-VR group was formed of those children with Z-scores  $\geq 1.5$  SD in the VI.

The following variables were defined as independent in the models: age, race, gender, socioeconomic status (SES), prenatal exposure to tobacco or alcohol, prematurity, low birthweight, psychosocial adjustment difficulties (abnormal SDQ total index with clinically significant daily life impact), and sleep problems. The variance inflation factor (VIF) was calculated to determine the degree of multicollinearity in the data. When VIF was  $\geq 5$ , collinearity was suspected; thus, the variable was suppressed, and the models were rebuilt. A regression model was modeled as a post hoc sensitivity analysis to ensure the reliability of the results obtained through the logistic analysis. In this analysis, we regressed the non-dichotomized output variable on the selected predictors and checked their significance through the Pillai's trace statistic.

The data were analyzed using R 4.0 software with the tidyverse, psych, jtools, car, and MASS packages. The significance level was set at 5% (two-sided). The data and R scripts were deposited in an open-access repository, freely available at <https://osf.io/wmxc9/>.

## RESULTS

Of the 378 adolescents in the target sample, parental consent was obtained from 371 adolescents (98.1%), and analyzable data (i.e., complete information) were obtained from 339 adolescents (89.7% and 91.4% of the target and consented samples, respectively). The adolescents ranged from 10 to 18 years old, and 53.4% were girls (Table 1).

Table 2 shows the prevalence and OR of the headache frequency groups according to the adolescents' demographic characteristics.

TABLE 1 Target sample, consented and analyzed sample according to demographic features

Characteristic	Target sample	Consented		Final sample		Response rates (%)	
	<i>n</i>	<i>n</i>	%	<i>n</i>	%	Target sample	Consented
<i>Age group</i>							
10–12	102	101	99.0	99	29.2	97.1	98.0
13–15	170	168	98.8	160	47.2	94.1	95.2
16–18	106	102	96.2	80	23.6	75.5	78.4
<i>Gender</i>							
Female	201	198	98.5	181	53.4	90.0	91.4
Male	177	173	97.7	158	46.6	89.3	91.3
<i>Race</i>							
White	–	255	–	239	70.5	–	93.7
Non-white	–	102	–	90	26.6	–	88.2
Non-respondents	–	14	–	10	2.9	–	71.4
<i>Income class<sup>a</sup></i>							
A and B	–	99	–	93	27.4	–	93.9
C	–	217	–	203	59.9	–	93.5
D and E	–	55	–	43	12.7	–	78.2
Total	378	371	98.1	339	100.0	89.7	91.4

<sup>a</sup>Income classes defined according to the Brazilian Economic Classification Criteria. Classes A and B represent the upper economic classes, D and E describe different levels of poverty, and C is the middle class.

Among the participating adolescents, 40 (11.8%) did not report lifetime headaches, 254 (74.9%) reported LFEH, 28 (8.3%) reported IFEH, and 17 (5.0%) reported HFH. The prevalence of no lifetime headaches was significantly higher in boys (OR 4.6; 95% CI: 2.18–10.6). Episodic migraine was diagnosed in 23 adolescents (6.8%), chronic migraine was diagnosed in seven adolescents (2.1%), probable migraine was diagnosed in 98 adolescents (28.9%), episodic tension-type headache was diagnosed in 20 adolescents (5.9%), probable tension-type headache was diagnosed in 87 adolescents (25.7%), and headache unspecified was diagnosed in 64 adolescents (18.9%).

The average scores and SDs of the RSCA indexes, scales, and subscales in the total sample and headache frequency groups are shown in Table 3 and Figure 1. The effects of headache frequency on SM score ( $F_{3,335} = 3.13$ ,  $p = 0.025$ ) and ER score ( $F_{3,335} = 3.04$ ,  $p = 0.029$ ) were significant. The slopes' comparisons revealed that adolescents with IFEH ( $\Delta$ : –6.5, 95% CI: –11.9 to –1.2) and HFH ( $\Delta$ : –8.4, 95% CI: –15.0 to –1.4) had significantly lower SM scores compared with non-headache controls. Adolescents with HFH had higher ER score ( $\Delta$ : 11.1, 95% CI: 2.4–20.1) than non-headache controls (Table 4, Figure 1). No significant effect of headache frequency on SR score was found ( $F_{3,335} = 2.04$ ,  $p = 0.108$ ). The effects of headache frequency on the RI ( $F_{3,335} = 2.99$ ,  $p = 0.031$ ) and VI ( $F_{3,335} = 4.05$ ,  $p = 0.007$ ) were also significant. Adolescents with HFH ( $\Delta$ : –9.4, 95% CI: –14.9 to –4.2) had significantly lower RI score compared with non-headache controls. These results were partially similar to the VI, whereas adolescents with IFEH ( $\Delta$ : 11.0, 95% CI:

0.4–21.7) and HFH ( $\Delta$ : 18.34, 95% CI: 7.3–29.8) had higher scores than controls without headache (Table 4, Figure 1).

Headache diagnosis did not significantly influence the RSCA indexes, scales, or subscales. No significant effects of headache diagnosis on SM score ( $F_{6,332} = 1.68$ ,  $p = 0.125$ ), SR score ( $F_{6,332} = 1.92$ ,  $p = 0.077$ ), ER score ( $F_{6,332} = 0.45$ ,  $p = 0.840$ ), the RI ( $F_{6,332} = 2.07$ ,  $p = 0.056$ ), or the VI ( $F_{6,332} = 1.25$ ,  $p = 0.282$ ) were found.

The logistic regression (LR) analysis explored the predictors of low RRs, as well as high vulnerability. These two constructs partially overlap, and 19% ( $n = 5$ ) of the participants were assigned into both groups. The following predictors were included: age ( $M = 13.9$ ,  $SD = 2.1$ ), race (white = 239, 72.6%), gender (female = 181, 53.4%), socioeconomic status (High SES = 93, 27.4%), sleep problems (yes,  $n = 11$ , 3.3%), prematurity (yes,  $n = 40$ , 12%), prenatal exposure to tobacco (yes,  $n = 74$ , 22%), prenatal exposure to alcohol yes, ( $n = 35$ , 10.4%), and psychosocial adjustment difficulties (yes,  $n = 33$ , 9.7%). According to the LR analysis, the female gender (OR 3.07; 95% CI: 1.16–9.3) and the presence of psychosocial adjustment problems (OR 7.5; 95% CI: 2.51–22.4) were identified as predictors of low RRs. Prenatal exposure to tobacco (OR 5.6; 95% CI: 1.57–20.9) was the only predictor of high VR in adolescents with primary headache (Table 5). A linear regression was modeled as post hoc sensitivity analysis with partially convergent results. This analysis concluded that female gender ( $F = 6.58$ ,  $p < 0.0001$ ) predicts low RRs, and psychosocial adjustment problems predict both low RRs ( $F = 9.81$ ,  $p < 0.001$ ) and also high vulnerability ( $F = 10.25$ ,  $p < 0.001$ ).

TABLE 2 Prevalence and adjusted odds ratios of headache frequency according to demographic features

	No headache			LFEH			IFEH			HFH		
	n	%	OR (95% CI)	n	%	OR (95% CI)	n	%	OR (95% CI)	n	%	OR (95% CI)
<i>Age group</i>												
10-12	10	10.1	Reference	79	79.8	Reference	7	7.1	Reference	3	3.0	Reference
13-15	19	11.9	1.19 (0.53-2.79)	117	73.1	1.44 (0.80-2.69)	13	8.1	0.87 (0.312-2.23)	11	6.9	0.44 (0.093-1.48)
16-18	11	13.8	1.41 (0.56-3.6)	58	72.5	1.49 (0.74-3.02)	8	10.0	0.69 (0.227-2.04)	3	3.8	0.80 (0.135-4.8)
<i>Gender</i>												
Female	9	5.0	Reference	141	77.9	Reference	19	10.5	Reference	12	6.6	Reference
Male	31	19.6	4.6 (2.18-10.6)*	113	71.5	1.41 (0.86-2.30)	9	5.7	1.92 (0.86-4.6)	5	3.2	2.13 (0.76-7.0)
<i>Race</i>												
White	28	11.7	Reference	177	74.1	Reference	20	8.4	Reference	14	5.9	Reference
Non-white	10	11.1	0.95 (0.41-2.00)	72	80.0	0.71 (0.387-1.28)	5	5.6	1.51 (0.59-4.8)	3	3.3	1.80 (0.51-6.4)
Non-respondents	2	20.0	1.98 (0.261-8.6)	5	50.0	2.84 (0.74-10.9)	3	30.0	0.210 (0.054-1.09)*	0	0.0	-
<i>Income class<sup>a</sup></i>												
A, B	16	17.2	Reference	67	72.0	Reference	7	7.5	Reference	3	3.2	Reference
C	19	9.4	0.49 (0.242-1.03)	157	77.3	0.75 (0.43-1.33)	17	8.4	0.90 (0.333-2.19)	10	4.9	0.67 (0.140-2.28)
D, E	5	11.6	0.65 (0.200-1.81)	30	69.8	1.12 (0.49-2.46)	4	9.3	0.78 (0.217-3.26)	4	9.3	0.333 (0.059-1.66)
Total	40	11.8		254	74.9		28	8.3		17	5.0	

Note: No headache: no headache lifetime; LFEH: Headaches in the past year and less than 5 days of headache per month in the last 3 months; IFEH: From 5 to 9 days of headache per month in the last 3 months; HFH: 10 or more days of headache per month in the last 3 months.

Abbreviations: HFH, high-frequency headaches; IFEH, intermediate-frequency episodic headache; LFEH, low-frequency episodic headaches.

<sup>a</sup>Income classes defined according to the Brazilian Economic Classification Criteria. Classes A and B represent the upper economic classes, D and E describe different levels of poverty, and C is the middle class.

\* $p < 0.05$ .



TABLE 3 The average score of RSCA indexes, scales, and subscales in the total sample and according to the headache frequency groups

	No headache		LFEH		IFEH		HFH		Total sample	
	M	SD	M	SD	M	SD	M	SD	M	SD
<i>Sense of mastery</i>	52.0	11.9	50.6	11.9	45.9	11.8	43.9	11.4	50.1	12.0
<i>Optimism</i>	18.6	4.9	18.1	4.9	16.4	4.6	15.1	5.0	17.9	4.9
<i>Self-efficacy</i>	25.1	6.8	24.1	6.8	22.0	6.7	21.1	5.6	23.9	6.8
<i>Adaptability</i>	8.0	2.4	8.4	2.3	7.3	2.1	7.9	2.1	8.3	2.3
<i>Sense of relatedness</i>	67.4	15.7	63.7	15.0	63.1	14.5	58.9	11.4	63.8	14.9
<i>Trust</i>	19.1	5.2	18.6	4.9	17.9	5.3	16.6	4.8	18.5	4.9
<i>Support</i>	18.5	4.6	17.4	4.8	16.8	4.7	17.5	3.5	17.5	4.7
<i>Comfort</i>	10.9	3.1	10.4	3.4	10.8	2.9	9.2	4.0	10.4	3.4
<i>Tolerance</i>	19.1	4.9	17.0	4.5	17.7	4.9	15.2	5.1	17.3	4.7
<i>Emotional reactivity</i>	28.5	16.8	30.4	14.8	36.1	16.9	38.4	13.6	31.0	15.3
<i>Sensitivity</i>	10.3	5.3	11.1	4.8	13.1	5.1	13.9	5.3	11.3	4.9
<i>Recovery</i>	5.5	4.6	6.2	4.0	7.8	3.8	7.0	4.1	6.3	4.1
<i>Impairment</i>	12.7	8.8	13.1	8.6	15.2	10.3	17.5	7.0	13.5	8.7
<i>Resources index (RI)</i>	59.7	13.1	57.2	12.1	54.5	12.2	51.4	8.0	57.0	12.1
<i>Vulnerability index (VI)</i>	-31.2	22.4	-26.8	20.0	-18.4	20.9	-13.1	17.7	-25.9	20.6

Note: No headache: no headache lifetime; LFEH: Headaches in the past year and less than 5 days of headache per month in the last 3 months; IFEH: From 5 to 9 days of headache per month in the last 3 months; HFH: 10 or more days of headache per month in the last 3 months.

Abbreviations: HFH, high-frequency headaches; IFEH, intermediate-frequency episodic headache; LFEH, low-frequency episodic headaches; M, average; SD, standard deviation.

The Adaptability subscale score and the Relatedness Tolerance subscale score are not interpreted separately for children ages 9–11.<sup>13</sup>

## DISCUSSION

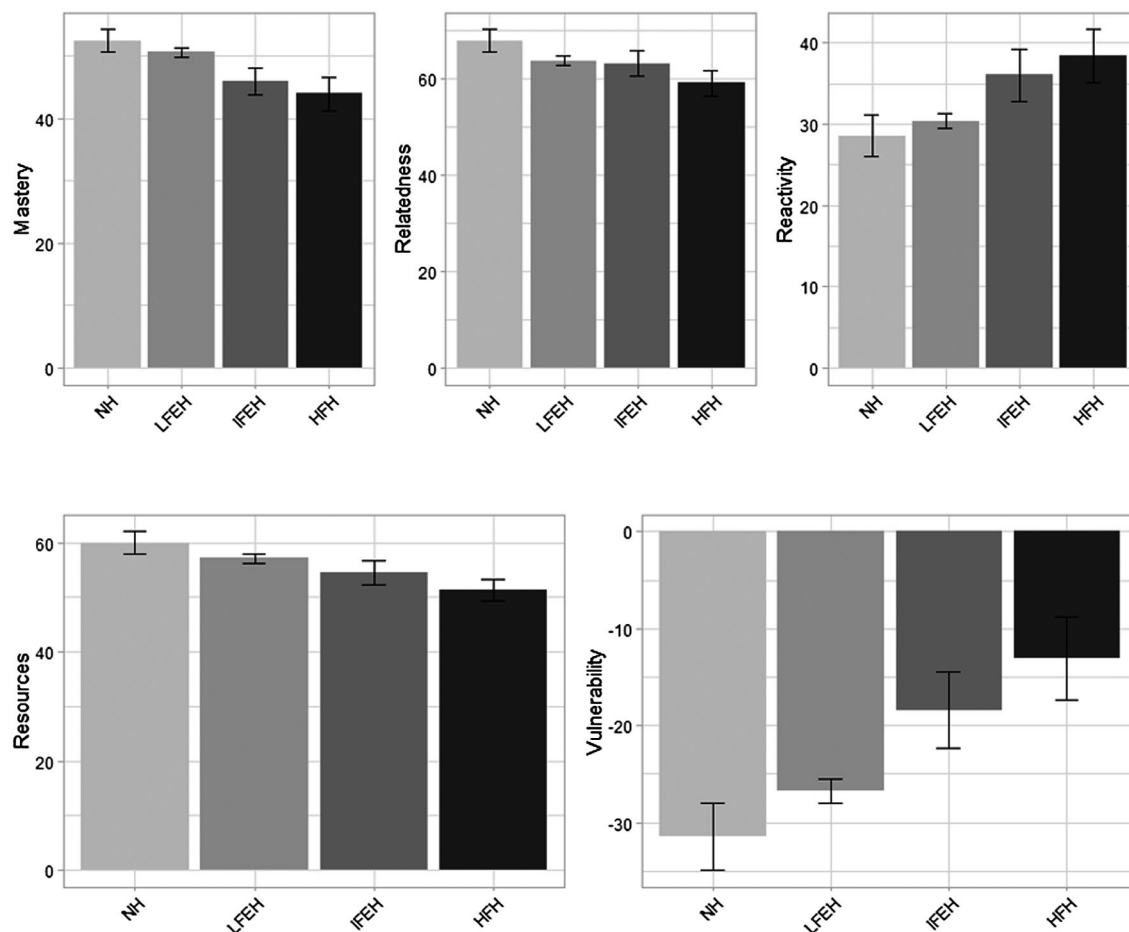
High RRs have been reported to be associated with less functional disability, better school functioning, and less depressive symptoms among children with chronic illnesses.<sup>24,28,44</sup> Therefore, descriptions of RRs and VR in children and adolescents with primary headaches are particularly important for clinicians to identify groups of individuals with a high risk of poor outcomes and implement early interventions. The present study examined the extent to which headache frequency and diagnosis are associated with RRs and VR in a population adolescents using structured and validated self-reported questionnaires completed by the adolescents, their parents, and their teachers. Our findings can be summarized as follows: (1) relative to non-headache controls, adolescents with HFH were more likely to have a lower SM, higher ER, lower RRs, and higher VR, (2) adolescents with IFEH were more likely to have a lower SM and higher VR than non-headache controls, (3) predictors of low RRs among adolescents with primary headache, revealed by the logistic regression analyses, include female gender and psychosocial adjustment problems, (4) prenatal exposure to tobacco was the only predictor of high VR in this group of adolescents.

The SM scale assesses core characteristics of resilience in children and adolescents. According to the RSCA framework, the SM scale comprises optimism, self-efficacy, and adaptability (or flexibility), which are important psychological attributes of problem-solving skills.<sup>13</sup> Optimism has been reported to be a predictor of quality of life in children and adolescents who suffer from chronic pain by

minimizing pain-related fear and catastrophizing.<sup>45</sup> A previous pediatric study suggested that higher levels of pain self-efficacy and pain acceptance were associated with more positive outcomes in children and adolescents with chronic headaches.<sup>24</sup> In the present study, adolescents with  $\geq 10$  headache attacks per month had lower levels of SM compared with non-headache controls.

Compared with healthy adolescents, those who experience chronic pain often report social functioning difficulties, are more likely to suffer from social isolation, and have lower motivation to participate in social, leisure, and school activities.<sup>46</sup> However, systematic research on SR in children and adolescents with headaches is currently lacking. In the present study, we did not find a significant effect of headache frequency on SR scores. One of the possible reasons is that HFF, although they can decrease motivation for social activities, do not compromise the adolescent's sense of trust, support, comfort, and tolerance perceived from his peers.

Emotion regulation is a core component in mental health by modulating individual management of emotional responses.<sup>47</sup> ER implies the speed and intensity of a child's negative emotional response.<sup>3,13</sup> According to the literature, strong ER is associated with behavioral difficulties and vulnerability to psychopathology and is an important factor in the development of resilience.<sup>2,11</sup> A recent study also shows a high correlation between the ER score by the means of the RSCA and the resting vagally mediated heart rate variability, a biomarker of emotion regulation capacity mediated by neural pathways between prefrontal cortex, limbic structures, autonomic,



**FIGURE 1** The average score of RSCA indexes and scales according to the headache frequency groups. No headache: No headache lifetime; LFEH: Headaches in the past year and less than 5 days of headache per month; IFEH: From 5 to 9 days of headache per month; HFH: 10 or more days of headache per month. HFH, high-frequency headaches; IFEH, intermediate-frequency episodic headache; LFEH, low-frequency episodic headaches

and endocrine systems.<sup>47</sup> In our sample, adolescents with HFH had higher ER compared with non-headache controls.

The plausibility of our findings is supported by emerging evidence linking common brain circuitries that are associated with resilience processes and pain control. Anatomical changes have been reported in the anterior cingulate gyrus, prefrontal cortex, and insula in patients with chronic pain.<sup>48</sup> Structural and functional studies have showed abnormalities in cortical and subcortical regions associated with pain modulation, emotion, cognitive reserve, and resilience in migraine patients.<sup>49–51</sup> Changes in these cortical regions may affect the interactions between cortical and subcortical networks including the trigeminovascular system and sensory processing networks contributing to headache chronification.<sup>51</sup> The same brain areas play a central role in neurobiological mechanisms of stress resilience<sup>52</sup> and may explain the lower RRs and higher VR that were observed in adolescents with HFH in the present study.

As mentioned above, headache diagnosis did not significantly influence the RSCA indexes or scales. In previous population-based studies, we found that headache frequency rather than other headache characteristics or headache diagnosis was a risk factor for behavior and emotional symptoms,<sup>31</sup> psychosocial adjustment

problems,<sup>32</sup> lower school achievement,<sup>53</sup> and ADHD diagnosis in children.<sup>54</sup> These findings prompted us to examine whether resilience could be mediating the association of HFF and the above-mentioned poor outcomes in children and adolescents.

Female gender was identified as a predictor of low RRs among adolescents with primary headache. One of the possible reasons is the significantly higher prevalence of males within the no headache group. According to the RSCA's standardization, gender differences were not found concerning RRs and VR in the adolescent sample. The LR also identified psychosocial adjustment problems as a predictor of low RRs. This finding may be explained by other studies showing that psychosocial adjustment problems are associated with an increased risk for migraine,<sup>32</sup> high-frequency headache,<sup>32</sup> and low RRs.<sup>55</sup> Prenatal exposure to tobacco has been considered a risk factor for mental health problems<sup>56–58</sup> and our previous work showed its association with chronic daily headache in children<sup>59</sup>; however, little is known about its effect on the development of RRs. In the present study, we found a positive report of prenatal exposure to tobacco as a predictor of high VR among adolescents with primary headache. However, given the discrepant results obtained in the linear regression model, we must be cautious to generalize to the greater population at this time.



TABLE 4 Robust ANOVA results of RSCA indexes and scales as a function of headache frequency

		Bootstrapping					Confidence interval		
	Original	Bias	SE	Median	Skew	Kurtosis	Lower	Upper	p value*
Sense of mastery									
Intercept	52.7	0.0	1.7	52.7	−0.1	−0.2	49.5	56.0	<0.0001
LFEH	−1.9	0.0	1.9	−1.9	0.0	−0.2	−5.6	1.8	0.314
IFEH	−6.5	0.0	2.8	−6.5	−0.1	0.0	−12.0	−1.0	0.018
HFH	−8.4	−0.2	3.6	−8.5	−0.1	−0.2	−15.2	−1.2	0.016
Emotional reactivity									
Intercept	27.7	−0.1	2.8	27.6	0.0	−0.3	22.3	33.4	<0.0001
LFEH	1.7	0.1	3.0	1.8	0.0	−0.3	−4.2	7.5	0.564
IFEH	6.5	0.0	4.0	6.5	−0.1	−0.3	−1.5	14.4	0.110
HFH	11.1	−0.1	4.5	10.9	0.0	0.7	2.4	20.00	0.013
Resource index									
Intercept	60.8	0.0	1.9	60.8	−0.1	−0.2	57.0	64.6	<0.0001
LFEH	−3.2	0.0	2.1	−3.2	0.1	0.0	−7.3	0.9	0.126
IFEH	−5.7	0.0	3.0	−5.8	−0.1	0.1	−11.6	0.2	0.059
HFH	−9.4	0.1	2.8	−9.3	0.0	0.0	−15.0	−4.1	<0.0001
Vulnerability index									
Intercept	−30.9	−0.1	3.8	−30.9	0.0	0.2	−38.2	−23.3	<0.0001
LFEH	4.0	0.1	4.0	4.1	0.0	0.0	−4.0	11.8	0.318
IFEH	11.0	0.2	5.5	11.2	0.2	0.1	0.1	21.5	0.043
HFH	18.3	−0.2	5.7	18.3	−0.1	−0.2	7.4	29.7	0.001

Note: No headache: no headache lifetime; LFEH: Headaches in the past year and less than 5 days of headache per month in the last 3 months; IFEH: From 5 to 9 days of headache per month in the last 3 months; HFH: 10 or more days of headache per month in the last 3 months.

Abbreviations: HFH, high-frequency headaches; IFEH, intermediate-frequency episodic headache; LFEH, low-frequency episodic headaches.

\*p values approximated from bootstrapped samples.

TABLE 5 Predictors of having low resilience resources or high vulnerability risk for adolescents with primary headache

Predictors	Risk of low resilience resources				Risk of high vulnerability			
	OR	CI	Statistic	p	OR	CI	Statistic	p
(Intercept)	0.56	0.020-15.6	-0.34	0.731	0.066	0.001-2.39	-1.46	0.145
Age	0.82	0.64-1.03	-1.63	0.104	0.96	0.73-1.25	-0.32	0.749
Race [Other]	1.13	0.363-3.16	0.23	0.817	0.49	0.09-1.77	-0.99	0.323
Sex [Female]	3.07	1.16-9.3	2.15	<b>0.032</b>	2.73	0.89-10.3	1.65	0.099
SES [C]	0.51	0.177-1.44	-1.29	0.197	0.342	0.088-1.23	-1.62	0.105
SES [DE]	0.67	0.121-2.91	-0.5	0.617	0.351	0.042-1.93	-1.11	0.266
Sleeping [yes]	1.18	0.128-7.1	0.17	0.868	3.34	0.378-20.2	1.23	0.220
Premature [yes]	1.59	0.41-5.0	0.75	0.456	1.04	0.151-4.3	0.04	0.964
Smoking [yes]	0.88	0.222-2.93	-0.2	0.840	5.6	1.57-20.9	2.66	<b>0.008</b>
Alcohol [yes]	0.96	0.181-3.75	-0.06	0.951	0.63	0.088-2.76	-0.55	0.583
Psychosocial adjustment problems [yes]	7.5	2.51-22.4	3.67	<b>&lt;0.001</b>	1.02	0.137-4.5	0.02	0.985
Observations	314				314			
R <sup>2</sup> Tjur	0.101				0.051			

Note: The bold values express a significant p.

The identification of predictors of low RR and high VR in children and adolescents with primary headache favors the development of risk-resilience models for pediatric headaches and may help the clinician in the early identification of adolescents with primary headaches at risk of worse outcomes.

Compared with non-headache controls, higher VR among adolescents with more than four headache attacks per month allied with the lower RRs among those with more than 10 headache attacks per month may have potential clinical implications. First, accumulating evidences suggest that RRs can be successfully taught,<sup>21,60</sup> thereby opening the door for the so-called "Resilience Psychology"<sup>61</sup> that may improve the course of headaches in these groups of adolescents. Second, future observational and/or experimental longitudinal studies may answer an important cause-and-effect question not answered by the present cross-sectional design study, in which having higher VR and lower RRs may be a consequence of having more frequent headaches, a risk factor for the headache chronification, or both of them. Nonetheless, the scarcity of prospective studies on headache in children and adolescents, a recent large cohort study<sup>62</sup> has shown that successful coping with stress, a recognized RR,<sup>63</sup> significantly contributed to remission of pediatric headache after 2 years in children aged between 9 and 15 years. The authors concluded that other psychological characteristics had only small predictive value.<sup>62</sup> Randomized controlled studies showing the persistence, improvement, or remission of headaches in response to effective interventions on RR and VR would help us to better understand and manage this group of children and adolescents. Third, a recent nationwide cross-sectional study showed that adverse childhood experiences (ACEs) were associated with a progressively higher risk of having frequent and severe headache.<sup>64</sup> One unresolved issue is whether or not RRs and VR may modify the effects of ACEs on headache characteristics and evolution from childhood to adulthood. Another issue is whether ACEs impair RRs and/or increase VR, thereby increasing the risk of having severe and frequent headaches or whether the converse is true. Do children with lower RRs and/or higher VR who are exposed to ACEs have a higher risk to develop more severe and frequent headaches?

Strengths and limitations of the present study deserve comment. Among the strengths, we highlight the population-based design, large sample size, use of validated questionnaires completed by the adolescents, their parents, and their teachers, and multivariate adjustments. Studying adolescents with primary headaches who were identified from a population-based sample avoided potential bias that could be caused by convenience samples or the selection of target patients from tertiary clinics who likely have a higher risk of significant functional impairment. Finally, by incorporating a strengths-based approach in the assessment of resilience, the present study contributes to the development of an ecological and original resilience-risk model of pediatric headache. The present study also has limitations. First, headache frequency was not prospectively reported in diaries but rather by the parents and the adolescents retrospectively when filling out the questionnaire. However, this is

no different from what is often seen in large cross-sectional studies of headache prevalence in pediatric populations.<sup>65</sup> Moreover, three general pediatric population-based studies have shown an overestimation of headache duration and intensity and a good agreement of headache frequency between the children's retrospective report and prospective diary information.<sup>66-68</sup> Second, the RSCA are based on the self-reporting of individuals, so the results are solely contingent on an individual's accurate reporting and responding. Third, although teachers have been trained on how to supervise the adolescents in completing the self-report questionnaire avoiding any interference in their responses, we admit that it may have occurred to some extent.

Notwithstanding the unresolved issues and the above-mentioned limitations, our findings add to the literature one more piece of information on the multifaceted burden of headaches in children and adolescents. The development of a risk-resilience model of pediatric headaches may contribute to the emergence of novel and successful interventions that effectively control pain and promote mental health in children and adolescents with high-frequency primary headaches.

## CONFLICT OF INTEREST

The authors declare that there is no relevant conflict of interest. Unrelated to this study, Dr. Bigal is a CEO of Ventus Therapeutics, Inc.

## AUTHOR CONTRIBUTIONS

*Study concept and design:* Marco A. Arruda, M. E. Bigal. *Acquisition of data:* Marco A. Arruda, Renato Arruda. *Analysis and interpretation of data:* Marco A. Arruda, L. Anunciação, M. E. Bigal. *Analysis or interpretation of data:* Renato Arruda, J. Landeira-Fernandez. *Drafting/Revising of the manuscript:* Marco A. Arruda, Renato Arruda, J. Landeira-Fernandez, L. Anunciação, M. E. Bigal. *Critical revision of the manuscript for important intellectual content:* Marco A. Arruda, J. Landeira-Fernandez, L. Anunciação, M. E. Bigal. *Study supervision:* Marco A. Arruda, L. Anunciação, M. E. Bigal. *Statistical analysis:* L. Anunciação.

## ETHICS APPROVAL

The present study and surveys received approval from the Human Research Committee, São José do Rio Preto School of Medicine (São Paulo, Brazil). Written informed consent was discussed and obtained from the parents (or the adolescents' guardians) and participating teachers.

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