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RESEARCH SUBMISSIONS

Adverse childhood experiences and onset of migraine in Canadian adolescents: A cohort study

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Abstract

Background: Adverse childhood experiences (ACEs) are cross-sectionally associated with headache, including migraine, in pediatric populations.

Objective: The objective of this study was to determine whether ACEs are prospectively associated with incident health-professional diagnosed migraine and prevalence of non-migraine frequent headache in adolescence, either directly or indirectly through symptoms of depression and anxiety.

Methods: We used data from the National Longitudinal Survey of Children and Youth, a Canadian cohort study that followed children aged 0/1 at baseline, and the person most knowledgeable about them (PMK) until the child reached adolescence. The PMK reported on 14 ACEs (e.g., parental death) when the child was 4/5 and 6/7 years, and symptoms of depression and anxiety in late childhood (age 8/9 years), using a validated tool. Migraine (primary outcome) was ascertained via PMK report of a health-professional diagnosis, and non-migraine frequent headache (>1 time per week) was adolescent self-report, both measured at age 14/15. We estimated direct and indirect effects (IEs) on the log-odds scale through symptoms of depression and anxiety (mediator). We adjusted for sex, parental migraine, and economic deprivation. The analytic sample sizes were: $n = 2058$ (migraine) and $n = 1730$ (frequent headache).

Results: There were $n_{unweighted} = 71$ respondents with migraine (3.4%, 71/2058) and $n_{unweighted} = 204$ with non-migraine frequent headache (11.8%, 204/1730). Most respondents experienced no ACEs (weighted percentage = 55.7), followed by 1 ACE (weighted percentage = 34.7) and greater than or equal to two ACEs (weighted percentage = 9.6), respectively. There were direct associations between experiencing one (odds ratio [OR] = 1.71, 95% confidence interval [CI]: 1.01–2.87) and equal to or greater than two (OR = 2.33, 95% CI: 1.13–4.80) ACEs and migraine, but not for non-migraine frequent headache. There were no indirect relationships through symptoms of depression and anxiety for migraine (1 ACE: OR = 1.06, 95% CI: 0.99–1.13 and ≥2 ACEs: OR = 1.11, 95% CI: 0.98–1.28) or non-migraine frequent headache (1 ACE: OR = 0.99, 95% CI: 0.95–1.03 and ≥2 ACEs: OR = 0.98, 95% CI: 0.90–1.07).

Conclusions: ACEs may confer an increased risk of migraine onset in adolescence. The association was not explained by symptoms of depression and anxiety in late childhood.

Abbreviations: ACEs, adverse childhood experiences; CI, confidence interval; HPA, hypothalamic-pituitary-adrenal; IE, indirect effects; NLSCY, National Longitudinal Survey of Children and Youth; OR, odds ratio; PMK, person most knowledgeable.

KEYWORDS
adverse childhood experiences, cohort study, epidemiology, headache, migraine

INTRODUCTION

Adverse childhood experiences (ACEs) are associated with pain, including headache, in adulthood.[1] There is also longitudinal evidence to support a prospective relationship with migraine in adulthood.[2] The relationship between ACEs and incident headache in childhood and adolescence is less studied. Cross-sectional evidence has demonstrated associations between ACEs and chronic pain,[3] including migraine and other headache disorders, in children and adolescents.[4–6] To our knowledge, to date, no study has provided longitudinal evidence for a relationship between reported ACEs and the onset of headache disorders before adulthood.

Conceptually, the relationships between early life adversity and headache may be explained by risk factors drawn from the biopsychosocial model of pain.[7] Risk factors may include mental health symptoms and the youth's lived experiences, such as their family environment, or other biopsychosocial factors.[7] Pediatric chronic pain[7] and headache[8] models posit that exposure to stressful or traumatic life events may lead to internalizing symptoms of depression, anxiety, and subsequently pain in childhood and adolescence. In essence, one of many postulated mechanisms includes an indirect effect from stress to headache disorders. As a result of the lack of causal evidence linking ACEs with the onset of childhood pain, prospective, longitudinal work is needed,[7] and may advance our understanding of the etiological origins of headache disorders. A population-based study spanning many years of follow-up found indirect associations between chronic family-level stressors (such as family dysfunction) and migraine through symptoms of depression and anxiety.[9] Although, it is unknown whether such relationships will transfer to the study of stressors at the level of ACEs.[10]

To our knowledge, this is the first cohort study to examine the relationship between ACEs experienced as a young child and incident health-professional diagnosed migraine and prevalence of non-migraine frequent headache in adolescence. Building on the work of others who examined longitudinal relationships between ACEs and migraine onset in adulthood,[2] we sought to determine whether ACEs are associated with an earlier developmental onset of migraine and to explore the association with non-migraine frequent headache. We hypothesized that ACEs would be directly and indirectly, through symptoms of depression and anxiety, associated with an increased likelihood of headache disorders in adolescence.

METHODS

Data source

The National Longitudinal Survey of Children and Youth (NLSCY) is a cohort study of child development.[11] The target population for cycle 1 of the NLSCY was the non-institutionalized population aged 0–11 years residing in Canada's provinces.[12] Excluded from the survey were institutionalized or incarcerated persons, persons living in some remote regions, on First Nations reserves or Crown lands, and full-time members of the Canadian Armed Forces.[12] For purposes of this study, we were interested in the youngest of the cohort followed prospectively and age 0–1 at baseline (1994/1995, cycle 1). This cohort represents those most likely to have the least exposure to stress after birth. The NLSCY identified the person most knowledgeable (PMK) about the child and asked them to report on behalf of the child.[11] The child respondent and their PMK were followed until the child reached adolescence (age 14–15 years) in 2008/2009 (cycle 8). The PMK was most often the biological mother (>90%). Participants were surveyed every 2 years by trained interviewers,[13] with data collected via in-person or telephone-based interviews.[11] The NLSCY has a complex survey design, and Statistics Canada produced survey weights.[11] More information on the NLSCY and its sampling procedure is included in the Supporting Appendix.

Standard protocol approvals, registrations, and patient consents

Data were accessed in a secure setting through the national Research Data Centres Program,[13] regulated by Statistics Canada. Research Ethics Board approval was not required as per Article 2.2 of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans.[14] The PMK provided written informed consent to Statistics Canada before survey participation.

Measures

Primary outcome

The primary study outcome was PMK report of incident health-professional diagnosed migraine when the child was 14/15 years. Specifically, the PMK was asked for the first time whether the child had "… conditions that have lasted or are expected to last 6 months or more and have been diagnosed by a health professional," with "migraines" included as one of the queried clinical diagnoses (yes/no).

Secondary outcome

The secondary study outcome was past 6-month prevalence of non-migraine frequent self-reported headache, measured when the child was 14/15 years. The youths were asked, "During the past 6 months, how often have you had or felt the following? [headache]." Response options were "seldom or never," "about once a month," "about once

a week," "more than once a week," and "most days." Consistent with past work,[9] we created a dichotomous variable representing unclassified frequent headache (>1 headache per week) versus less than frequent headache (all other response options). In the case where a youth self-reported frequent headache and their PMK also reported a migraine diagnosis, they were only classified as having migraine to ensure mutually exclusive study outcomes.

Exposures

ACEs were measured when the child was 4/5 and 6/7 years (cycles 3/4). For the cohort of children age 0/1 at baseline, cycles 3 and 4 were the first times their PMK was asked about ACEs. Specifically, the PMK was asked: "… has [child] experienced any event or situation that has caused him/her a great amount of worry or unhappiness?" (yes/no). If yes, the PMK was asked to report on all applicable ACEs, up to a maximum of 14: "death of parents," "death in family (other than parents)," "divorce/separation of parents," "move," "stay in hospital," "stay in foster home," "other separation from parents," "illness/injury of child," "illness/injury of a family member," "abuse/fear of abuse," "change in household members," "alcoholism or mental health disorder in family," "conflict between parents," and "other." If the PMK reported an ACE when the child was 4/5 or 6/7 years, the child was considered exposed (experienced a stressful life event). Children whose PMK did not report ACEs at either of the time points were classified as unexposed.

Mediator

Symptoms of depression and anxiety were reported by the PMK when the child was age 8/9 (cycle 5). For our cohort of interest, cycle 5 was the first time the mediator was measured after the exposures were ascertained. The seven-items were drawn from the revised Ontario Child Health Study scales, based on the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III)-R criteria.[15] The PMK was asked: "Using the answers never or not true, sometimes or somewhat true, or often or very true, how often would you say that [child] …" "seems to be unhappy or sad?," "is not as happy as other children," "is too fearful or nervous," "is worried," "cries a lot," "is nervous, high strung, or tense," and "has trouble enjoying himself." Together, the items produce a total scale score (range: 0–14), with higher scores reflecting more depressive and anxious symptoms. The total scale score was validated in the NLSCY (Cronbach's alpha = 0.76).[11]

Covariates

We adjusted for three covariates: sex of the child, parental migraine, and a measure of economic deprivation. Parental migraine status was assessed at child age 0/1 (baseline) and was asked in the same manner as the primary study outcome, detailed above. A dichotomous variable was created to represent whether neither or one or both parents, the PMK, or their spouse/partner (if applicable), experienced health-professional diagnosed migraine. In the event of missing information on the measures of parental migraine, we coded the missing data to represent absence of migraine. As a measure of economic deprivation, we used the child age 4/5 years derived ratio of each child's household income relative to the low-income cutoff for the size of the family and their residential area.[11] The low-income cutoff is the point at which a family is considered to spend more on the basic necessities of life (food, shelter, and clothing) than an average Canadian family and is defined for each area by Statistics Canada.[16] Spending is only considered in the calculation of the low-income cutoff.[16] Whether a family is classified as falling above or below the cutoff is entirely determined by their household income.[16] The ratio was categorized into quartiles. Within our cohort, all participants entered the survey at 0/1 years, negating the need to adjust for age in our longitudinal analyses.[2]

Statistical analyses

Statistics Canada approved the analytic plan before the authors were granted data access. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC), with the threshold for statistical significance set at $p < 0.05$, two-tailed. Descriptive statistics (percentage [%], means [M], and standard errors [SEs]) were computed to describe the overall sample and compare respondents with migraine and their peers with non-migraine frequent headache. In line with Statistics Canada data release guidelines, descriptive data and associated comparisons were weighted to account for the NLSCY's sampling design. For descriptive comparisons, we used proc survey-means and proc surveyfreq (Rao-Scott Chi-Square). To examine the direct relationships between ACEs and study outcomes, we conducted two traditional logistic regression models, one for each study outcome. We used PROCESS[17] (version 3.5), a path analysis macro, for our mediational analyses (https://www.processmacro.org/download.html). The software is described in our Supporting Appendix.

Using PROCESS, direct relationships between ACEs and headache outcomes, and potential indirect effects (IEs), through symptoms of depression and anxiety, were estimated along with their corresponding 95% confidence intervals (CIs). For the estimate of the IE, a bootstrap CI was computed using the percentile method (bootstrap samples = 10,000). Bootstrap sampling is a non-parametric method conducted with sampling with replacement. A common seed (23543) was used for all models to allow for replication of study results. All regression-based methods were unweighted as the path analysis macro is not yet equipped to handle survey weights. The relationships between the exposure and mediator (path *a*, Figure 1) were estimated using linear regression due to the continuous nature of the mediator. For path *a*, the reported regression coefficient can be interpreted as an X-unit change in the mediator (i.e., symptoms of depression and anxiety) for each increase in the exposure category (i.e., ACEs). In estimating coefficients for all other paths, PROCESS used logistic regression, allowing for the exponentiation

of coefficients to derive odds ratios (ORs) as a result of the underlying log-odds metric of the modeling, a result of the dichotomous nature of the headache outcomes. These three remaining paths were: (1) the relationship between the mediator and headache outcomes (path *b*), (2) the direct relationship of the exposure on headache outcomes, holding the mediator constant (path *c*'), and (3) the estimate of the IE, through the mediator, on headache outcomes (product of coefficients: *ab*). All paths were adjusted for the study covariates. Multiple data checking and screening methods were used: visual inspection, collinearity investigation (e.g., variance inflation factor), and Hosmer-Lemeshow goodness-of-fit tests. A sensitivity analysis was conducted to assess the impact of exclusion of respondents with missing data on the measures of parental migraine.

Analytic sample

We included only those baseline respondents 0/1 years surveyed when the exposures were ascertained ($n = 3565$; Figure 2). We then selected those respondents also surveyed when the mediator and outcomes were measured. Prior to the removal of respondents with missing data on all measures except for parental migraine status, the sample size was $n = 2349$. After removing those with missing data, the final sample size for the primary and secondary headache outcomes was $n = 2058$ and $n = 1730$, respectively. For the sensitivity analyses, missing on parental migraine status was also removed, and the sample sizes for the primary and secondary headache outcomes were $n = 1875$ and $n = 1586$, respectively. No statistical power calculation was conducted prior to the study. The sample sizes were based on the available data.

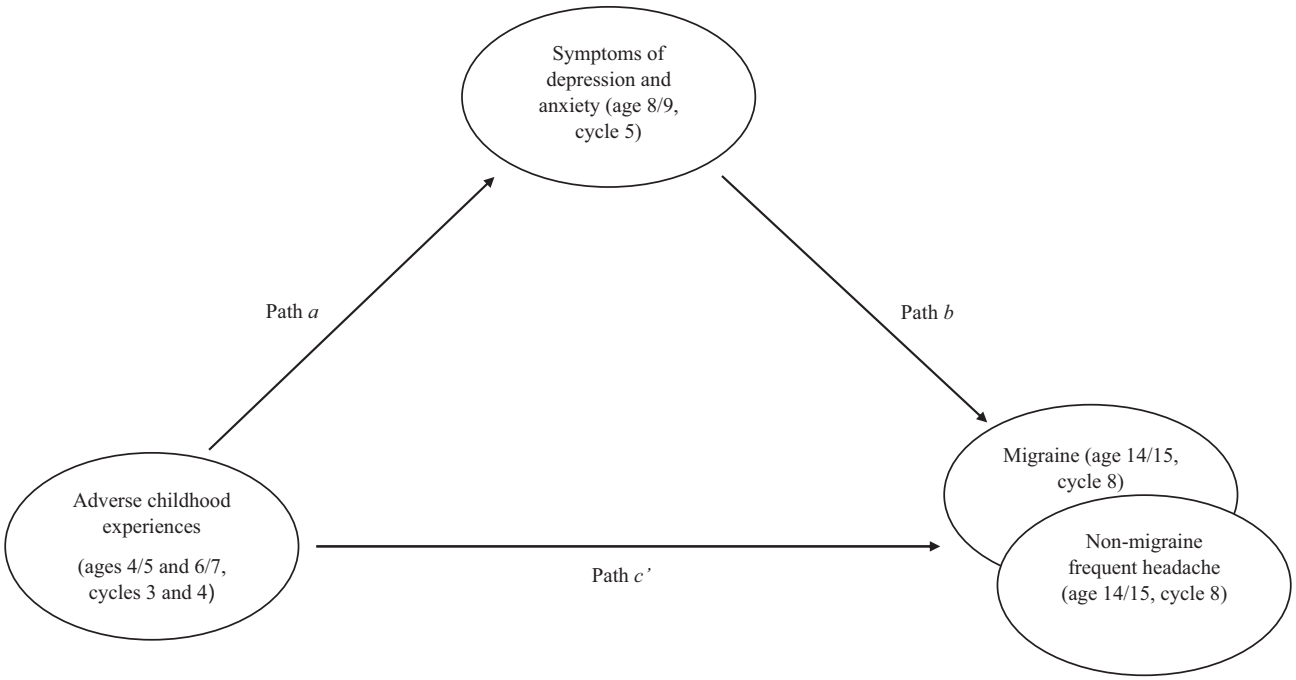
RESULTS

Loss to follow-up and missing data

Respondents lost to follow-up and with missing data are described in the Supporting Appendix.

Respondent characteristics

There were $n_{unweighted} = 71$ respondents with migraine (3.4%, 71/2058) and $n_{unweighted} = 204$ with non-migraine frequent headache (11.8%, 204/1730). Respondents with frequent headache were more likely to be women (69.0%, $p = 0.020$) when compared with respondents with migraine (47.8%; Table 1). Respondents with migraine were more likely to have one or more parents with migraine



Path *a*: Relationship between adverse childhood experiences (exposure) and symptoms of depression and anxiety (proposed mediator). Path *b*: Relationship between mediator and headache outcomes, holding the exposure constant. Path *c'*: Direct relationship between adverse childhood experiences and headache outcomes, holding the mediator constant. Not pictured: estimate of the indirect effect, product of coefficients of paths *a* and *b* (*ab*).

FIGURE 1 Conceptual diagram of proposed longitudinal relationships between adverse childhood experiences and headache outcomes

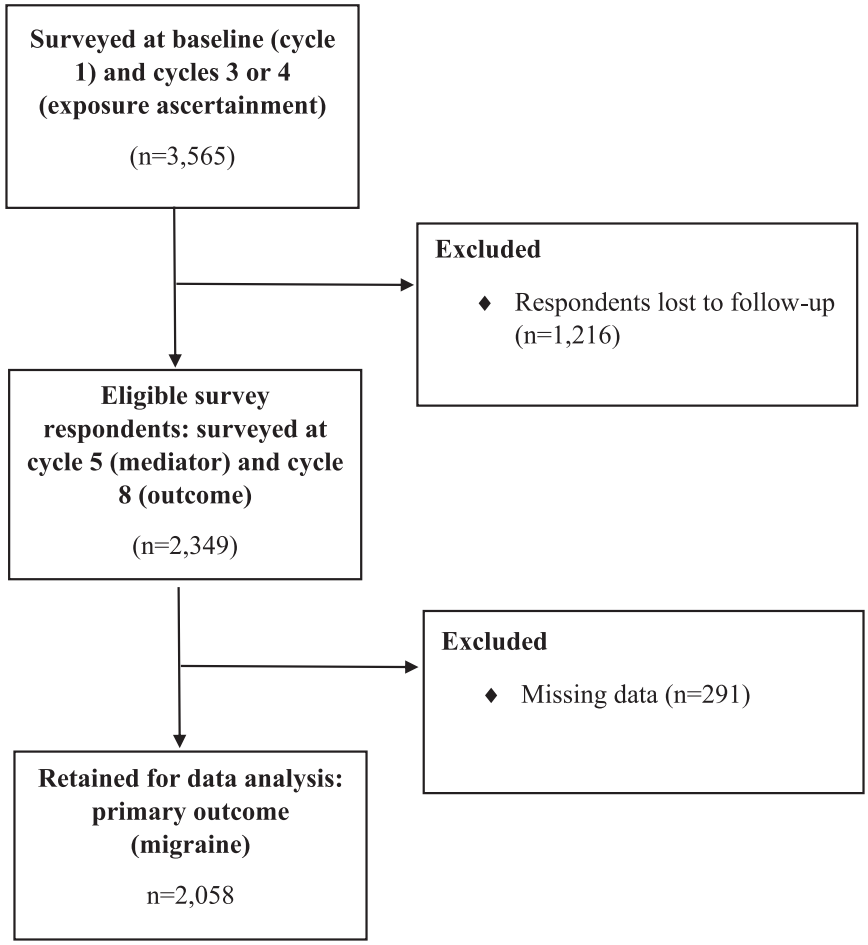


FIGURE 2 Longitudinal survey population and analysis cohort

(33.7%, $p = 0.036$), and to have more symptoms of depression and anxiety ($M = 3.80$ [SE = 0.53], $p = 0.041$). Respondents with incident health-professional diagnosed migraine and frequent headache did not statistically differ on measures of economic deprivation and the ordinal measure of ACEs. Although not statistically different, more respondents with migraine experienced early life stress (1 ACE: 50.3%, ≥2 ACEs: 19.2%) compared with respondents with frequent headache (1 ACE: 33.1%, ≥2 ACEs: 14.4%, $p = 0.062$). In a dichotomized version of exposure to ACEs (no ACE exposure vs. ≥1 ACEs), respondents with migraine were significantly more likely to be exposed to ACEs (69.5%, $p = 0.011$) than their non-migraine frequent headache counterparts (47.4%).

Longitudinal associations

In traditional logistic regression models (Table 2), there were direct associations between experiencing ACEs and migraine. A dose-response relationship was observed, with the odds of migraine increasing as the number of ACEs increased. Compared with respondents not exposed to ACEs, children exposed to one ACE were 1.71 times (95% CI: 1.01–2.87) more likely to have migraine in adolescence, while those exposed to greater than or equal to two ACEs were 2.33 times (95% CI: 1.13–4.8) more likely. In contrast, there were no direct associations between ACEs and frequent headache (1 ACE: OR = 1.03, 95% CI: 0.74–1.42, ≥2 ACEs: OR = 1.25, 95% CI: 0.77–2.02), with the ORs close to 1.00, suggesting a null association.

In mediational models (Table 3), an increasing number of ACEs were associated with more symptoms of depression and anxiety in late childhood. In the migraine and frequent headache models, exposure to one ACE and greater than or equal to two ACEs were on average associated with a 0.6 unit ($p < 0.001$) and a 1.2 unit ($p < 0.001$) increase in symptoms of depression and anxiety, respectively, when compared with respondents with no ACE exposure. Symptoms of depression and anxiety in late childhood were not associated with migraine (OR = 1.09, 95% CI: 0.99–1.20) or frequent headache (OR = 0.99, 95% CI: 0.92–1.06) in adolescence. We found no statistical evidence of an indirect effect of childhood ACEs on either migraine (1 ACE: OR = 1.06, 95% CI: 0.99–1.13, ≥2 ACEs: OR = 1.11, 95% CI: 0.98–1.28) or frequent headache (1 ACE: OR = 0.99, 95% CI: 0.95–1.03, ≥2 ACEs: OR = 0.98, 95% CI: 0.90–1.07) through symptoms of depression and anxiety. There was some slight strengthening of the direct and indirect relationships between ACEs and migraine as ACEs increased. Further, the positive coefficients for the indirect migraine relationship indicate that exposure to more ACEs is associated with more symptoms of depression and

TABLE 1 Respondent characteristics weighted to the Canadian population ($n_{unweighted}$ = 2058)

Characteristic	$n_{unweighted}$ = 2058[a]	%	% With migraine ($n_{unweighted}$ = 71)	% Without migraine ($n_{unweighted}$ = 1987)	% With frequent headache ($n_{unweighted}$ = 204)	% Without frequent headache ($n_{unweighted}$ = 1526)	*p* value
Sex							0.020
Male	1005	49.1	52.2	49.0	31.0	49.2	
Female	1050	50.9	47.8	51.0	69.0	50.8	
Economic deprivation							0.266
Quartile 1	515	24.9	16.8	25.2	27.8	24.2	
Quartile 2	515	23.9	27.2	23.7	21.7	23.4	
Quartile 3	515	25.6	20.3	25.8	28.4	25.8	
Quartile 4	510	25.6	35.7	25.3	22.1	26.6	
Parental migraine							0.036
Neither parent	1835	89.1	66.3	89.9	83.6	90.0	
≥1 parent	225	10.9	33.7	10.1	16.4	10.0	
Adverse childhood experiences							0.062
None	1140	55.7	30.5	56.6	52.6	56.3	
1	715	34.7	50.3	34.2	33.1	34.7	
≥2	205	9.6	19.2	9.2	14.4	9.0	
Symptoms of depression and anxiety [*M* (SE)]	2058	2.73 (0.07)	3.80 (0.53)	2.70 (0.07)	2.63 (0.20)	2.73 (0.08)	0.041

Note: Percentages (%) may not total 100% due to rounding error.

[a]In accord with Statistics Canada data release policy to prevent respondent identification, frequency counts (*n*) for categorical variables are rounded to the nearest base 5.

TABLE 2 Logistic regression models of the relationship between adverse childhood experiences and headache outcomes

	Migraine ($n = 2058$)			Frequent headache ($n = 1730$)		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Adverse childhood experiences						
None	Referent			Referent		
1	1.71	1.01, 2.87	0.044	1.03	0.74, 1.42	0.868
≥2	2.33	1.13, 4.8	0.022	1.25	0.77, 2.02	0.375

Note: All models adjusted for sex, economic deprivation, and parental migraine status.

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.

TABLE 3 Mediational models of the relationship between adverse childhood experiences and headache outcomes

	Migraine ($n = 2058$)				Frequent headache ($n = 1730$)			
		95% CI				95% CI		
	Coefficient	LL	UL	*p* value	Coefficient	LL	UL	*p* value
Outcome: depression and anxiety (path *a*)								
Adverse childhood experiences								
None	Referent				Referent			
1	0.6	0.4	0.8	<0.001	0.6	0.3	0.8	<0.001
≥2	1.2	0.9	1.6	<0.001	1.2	0.9	1.6	<0.001
Outcome: headache								
Depression and anxiety (path *b*)	0.1	−0.01	0.2	0.076	−0.01	−0.1	0.1	0.712
Adverse childhood experiences (path *c*')								
None	Referent				Referent			
1	0.5	−0.1	1.0	0.083	0.04	−0.3	0.4	0.832
≥2	0.7	0.01	1.5	0.047	0.2	−0.3	0.7	0.362
Indirect effect (*ab*)								
Adverse childhood experiences								
None	Referent				Referent			
1	0.1	−0.01	0.1	–	−0.01	−0.05	0.03	–
≥2	0.1	−0.02	0.2	–	−0.02	−0.1	0.1	–

Note: All models adjusted for sex, economic deprivation, and parental migraine status. No *p* value is produced for estimates of the indirect effect; instead, an indirect effect is considered statistically significant when the 95% CI does not cross zero. Path *a*: X→M; path *b*: M→Y, holding the exposure constant; path *c*': X→Y, holding the mediator constant; indirect effect: X→M→Y using the product (path *a* * path *b*) method.

Abbreviations: 95% CI, 95% confidence interval; LL, lower limit; UL, upper limit.

anxiety and, in turn, a greater likelihood of migraine in adolescence. However, the 95% CI of the IE crossed 0, indicating that the associations were statistically nonsignificant.

Sensitivity analysis

In the sensitivity analysis, we excluded those with missing information on parental migraine. Findings were mostly consistent with the primary findings for traditional logistic regression models (Table S1) and mediational models (Table S2). The results are reported in the Tables S1-S4.

DISCUSSION

Using a cohort of Canadian children, we examined longitudinal associations between exposure to ACEs and headache outcomes in adolescence. There were direct associations between ACEs and incident health-professional diagnosed migraine in adolescence, but not for

non-migraine frequent headache. There was no evidence of an indirect effect of ACEs on headache outcomes, through symptoms of depression and anxiety. This finding is contrary to one hypothesis in the field,[18] and other work, which found an indirect relationship between migraine and exposures of chronic, family-level stress.[9] There are multiple hypotheses for how childhood maltreatment may affect the likelihood of migraine. Specifically, childhood factors may be directly or indirectly (through other health mechanisms) linked to migraine prevalence.[18] Our findings provide early support for the former hypothesis.

Our findings are consistent with the large body of work relating negative life events experienced early in life with later health outcomes.[1] ACEs have been linked to multiple painful health conditions in adulthood,[2] but there are notably fewer studies examining ACEs with pain in younger, pediatric populations. Recently, Groenewald et al.[3] established a cross-sectional association between ACEs and an overall measure of chronic pain, including headache, in young persons aged 6–17. Mansuri et al.[4] also found cross-sectional evidence for a graded relationship between ACEs and childhood pain, with exposure to a greater number of adverse events associated with a greater likelihood of frequent or severe headache, including migraine. Unfortunately, the authors were not able to differentiate between headache types.

Similarly, others have observed cross-sectional relationships between the number of ACEs and headache but did not investigate migraine independently.[5,6] Within the present study, the magnitude of the observed direct associations between the number of ACEs and incident health-professional diagnosed migraine are consistent with the associations reported in the other pediatric studies.[3–6] Because the number of adverse events tapered off quickly following two, we could not examine associations beyond two or more stressors. Statistics Canada data release policy precludes the release of small cell sizes ($n < 5$) to protect participant identification.

It is unclear why we did not observe associations between ACEs and our measure of non-migraine frequent headache. It is possible that the variability within the unclassified frequent headache group diluted the relationships. However, we attempted to mitigate this by combining the upper two most frequent headache frequencies (>1 headache per week).[9] Other than self-report of headache frequency, there was insufficient information to differentiate headache subtypes within this non-migraine frequent headache group. The NLSCY is not specifically a headache survey. Despite the lack of statistical significance for the associations with frequent headache, the results correspond with past work. Tietjen et al.[19] found that childhood maltreatment was more prevalent among individuals with migraine, and was associated with a greater likelihood of migraine diagnosis than episodic tension-type headache.

Contrary to our hypotheses, we did not find that symptoms of depression and anxiety mediated the relationship between ACEs and headache outcomes. In a clinical sample of adults with migraine, increasing amounts of reported childhood maltreatment were associated with a greater likelihood of self-reported symptoms of depression and anxiety.[18] Similarly, we found that as the number of ACEs increased, so too did the strength of the association with symptoms of depression and anxiety in late childhood. Because the mediator was most proximal to the ascertainment of ACEs, it is not surprising that ACEs were associated with more symptoms of depression and anxiety a short while later in childhood. We may not have observed an indirect effect because of the length of time between the measurement of the mediator and outcome (two complete survey cycles, corresponding to a ~6-year lag). Methodologically, having the mediator measured closer to the exposure than outcome reduced the chance of mediator/outcome overlap, minimizing the likelihood that headache were already present but not reported when symptoms of depression and anxiety were measured. A potential pitfall is that any effect of symptoms of depression and anxiety on the outcomes may be weakened by the passage of time.

In light of the lack of mediation by adverse mental health symptoms, we must hypothesize alternate mechanisms. Others have suggested that early life adversity could be related to adult migraine through different pathways, including an independent association, where the effects of ACEs are not transmitted through other factors.[18] There is longitudinal evidence of a direct relationship between ACEs, such as those captured here, and another pediatric chronic health condition: adolescent incident overweight or obesity.[20] Thus, relationships between ACEs and health outcomes appear not to be transmitted through psychopathology. Other non-psychological mechanisms that may explain the association between ACEs and migraine include biological factors, such as the disruption of the hypothalamic-pituitary-adrenal (HPA) axis and inflammation.[21] It is also possible that biopsychosocial risk factors may not operate in silos,[7] as hypothesized here. Empirical evidence of an indirect effect of ACEs on headache may be more likely when studying composite measures of biological (e.g., HPA axis dysregulation), psychological (cognitive, mental health), and social (e.g., pro and anti) risk, like those suggested by Nelson et al.[7]

Strengths and limitations

Study limitations include a lack of diagnostic tools to classify headache types. Our primary outcome (incident health-professional diagnosed migraine) required the PMK to report a health-professional diagnosis, whereas the secondary outcome (prevalence of non-migraine frequent headache) was adolescent self-reported. Parent-adolescent agreement in headache reporting is known to be low[22] and could not be estimated here due to fundamental differences in outcome questions. The use of the PMK report for our primary outcome may have led us to underestimate the prevalence of migraine. However, parent/caregiver-adolescent agreement may be most congruent when the parent/caregiver is female, and for adolescents aged 15/16,[22] findings that partially align with our methodology. Further, parents/caregivers are more likely to identify migraine over other headache subtypes and recognize headache when certain features are present: chronicity, duration, and photophobia or phonophobia.[22] The current study's stringent criteria of requiring a health-professional

diagnosis of migraine may mean respondents with the previously noted features were more likely to be captured here if the characteristics are correlated with help-seeking and ultimately a diagnosis. Unfortunately, we do not have information on headache-specific facilitators to health care utilization and diagnosis.

Respondent sex may have acted as a barrier to a health-professional diagnosis. It was somewhat surprising to find that more adolescents with frequent headache than migraine were female. There is literature[23] to suggest that, in young persons, female patients may be more likely to experience pain dismissal, including from physicians. Such sex-specific differences in interactions with the health care system may have contributed to the lower percentage of female patients diagnosed with migraine. Regardless, requiring a health-professional diagnosis may mean that our migraine measure is conservative, underestimating the number of youths with migraine. The same may be true for our parental measure of migraine. There may be residual confounding because some parents with headache may not have received a diagnosis, leading to their inclusion in our referent (absence of migraine) category.

Another limitation is that the mediational approach could not account for missing data through multiple imputation or other estimation methods. Respondents lost to follow-up and with missing data were more likely to come from the most economically deprived families (Supporting Appendix). Among children, there is a clear income gradient to the number of ACE exposures.[24] Approximately two-thirds (66.4%) of children residing in the lowest income households are exposed to ACEs.[24] In comparison, less than a third (27.4%) of children in the highest income households experience ACEs.[24] From age 12 years onward, the incidence of migraine is highest among persons residing in the lowest-earning households.[25] Altogether, the literature suggests that lower-earning families are more likely to have ACE exposure and a greater likelihood of new-onset migraine. The disproportionate exclusion of economically deprived respondents in these analyses may have weakened our associations.

Migraine diagnosis was first ascertained in the NLSCY at age 14/15, so some participants with migraine were likely diagnosed earlier in life (<14 years). However, most incident migraine is documented to occur after age 14 for both sexes (≥75%).[26] Despite noted limitations, the use of self-report of health-professional diagnosed migraine is routinely used in health research, including in other population-based work.[27] Unlike the original ACE study,[10] the ACEs captured here did not include specific physical, sexual, or psychological abuse measures, or household member imprisonment. We cannot rule out that between-study differences in the severity of ACEs may affect the magnitude of observations and the potential mechanism(s) of action. In their recent longitudinal study of youth with chronic pain, Nelson et al.[28] observed that the type of ACE (maltreatment vs. household dysfunction) and whether they co-occur might be differentially associated with internalizing symptoms. In the present study, the PMK had to indicate that the child had experienced an event or situation that caused them mental distress (worry or happiness) before being prompted to report the specific types of ACE(s). The prompt likely led to the exclusion of participants who did not experience ACE-related distress or for whom the PMK did not recognize the worry/unhappiness. The present study did not account for potential differences in associations by visible and nonvisible minority status. Work that can theoretically and quantitatively delineate the experience of minority stress experiences (e.g., discrimination) from ACEs in the development of headache disorders is needed.

Study strengths include the longitudinal study design spanning many (14) years of follow-up, starting near birth (age 0/1). However, we recognize that depending on individual pubertal timing and differences in ages of onset, many participants likely developed headache after the NLSCY concluded. Thus, our statistical power may have been limited. It would be advisable to follow participants from near birth through the entirety of adolescence to understand better how ACEs may be tied to adolescent-onset headache disorders. Unlike retrospective studies of ACEs that are subject to recall bias concerns, particularly for those experiencing pain,[29] the prospective cohort design of the NLSCY protects against this. Additionally, we treated ACEs as an ordinal variable in this analysis. It allowed us to observe a dose-response relationship between ACE exposure and migraine, strengthening the validity of this relationship.

CONCLUSION

This study addresses a gap in the literature by helping to clarify how stress experienced during a developmentally sensitive period may increase the risk of migraine pre-adulthood, information which may assist in preventive efforts.[30] We provide preliminary support for a direct longitudinal relationship between ACEs and migraine in adolescence, consistent with the adult literature. ACEs were not prospectively associated with non-migraine frequent headache. Most importantly, the lack of a mediational effect through symptoms of depression and anxiety suggests that, on their own, internalizing symptoms do not entirely explain the ACE-migraine link, at least in adolescence.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

DISCLAIMER

The Canada Research Chairs program, the Research Council of Norway, and the CGS-D program had no role in study design, data collection or analysis, nor did they influence the authors' decision to prepare and publish this manuscript.

AUTHOR CONTRIBUTIONS

Study concept and design: Nicole G. Hammond, Ian Colman, Serena L. Orr. *Acquisition of data*: Nicole G. Hammond, Ian Colman. *Analysis and interpretation of data*: Nicole G. Hammond, Ian Colman, Serena L. Orr. *Drafting of the manuscript*: Nicole G. Hammond. *Revising it for intellectual content*: Ian Colman, Serena L. Orr. *Final approval of the completed manuscript*: Nicole G. Hammond, Ian Colman, Serena L. Orr.

DATA AVAILABILITY STATEMENT

Due to the confidential and legally protected nature of the NLSCY, resulting from its coverage by the Statistics Act,[31] data cannot be deposited into a public use repository. Data are publicly available for access through the Research Data Centres Program[13] (see www.statcan.gc.ca/eng/microdata/data-centres).

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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