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Adult outcomes of an underdiagnosed and often overlooked childhood migraine population

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Abstract

Background: Migraines are one of the most common causes of disability affecting both children and adults. Children and adolescents who suffer from migraines often continue to experience migraine attacks in adulthood. Previous studies of child migraine sufferers have not included those whose migraines were diagnosed after childhood. This study included these individuals in examining childhood migraine onset as a predictor of adult symptomology. **Methods:** Participants were 4,502 United States adult migraine sufferers (202 males, 4300 females; mean age 45y 9mo, SD 10y 2mo) who completed a retrospective survey on a migraine community website. We grouped participants into three cohorts based on the age of migraine symptom onset: Childhood-Onset (0-12 years), Adolescence Onset (13-18 years), and Adulthood Onset (19+). **Results:** As adults, the Childhood-Onset Cohort experienced the most migraine symptoms ($F(2,4499)=78.16$; $p<.001$), triggers ($F(2,4499)=114.99$; $p<.001$), attacks per month ($F(2,4499)=7.22$; $p=.001$), and days per month with symptoms ($F(2,4499)=12.05$; $p<.001$) as well as the longest time between symptom onset and formal migraine diagnosis ($F(2,4499)=354.64$; $p<.001$). Childhood-onset had a significant indirect effect on the number of adult triggers through diagnosis delay ($B=0.12$, $CI=0.02, 0.23$), but diagnosis delay did not mediate the relationship between onset age and number of symptoms, attacks per month, or days with symptoms. **Conclusions:** Migraine sufferers whose symptoms began in childhood reported worse adult migraine outcomes and a longer diagnosis delay. However, the evidence did not suggest that diagnosis delay explained the relationship between onset age and adult migraine frequency. These results underscore the need to address other factors that may lead to unfavorable long-term outcomes for children experiencing migraines.

Keywords: Child, adolescent, headache, migraine, adult.

Background

According to the Global Burden of Disease Study 2015, migraine is the seventh leading cause of disability worldwide in terms of Years Lived with Disability [1]. Migraines affect one of every seven Americans [2]. In a national survey of 3,788 adult migraine sufferers in the United States, 69.2% of respondents reported that migraines had negatively impacted their work or career [3]. The international prevalence of migraine among children and adolescents is 7.7-9.1%, with female juveniles having a higher risk of migraine than males [4, 5].

Several longitudinal studies have demonstrated that juvenile migraine disorders often persist into adulthood. Bille began one of the first major longitudinal childhood migraine studies in 1955. The study followed 73 children who experienced at least one migraine per month for 40 years. At the 40-year follow-up, 51% of participants still experienced migraines, and subjects reported that although migraines were less frequent, migraine attack intensity had not changed significantly since childhood [6]. In a more recent study, 53% of children with migraine had no significant change in frequency, intensity, or duration of migraines after seven years [7]. Kienbacher et al. (2006) found that 48.6% of children and adolescents still experienced migraines five to eight years after their first presentation to a headache center [8]. Migraine onset during early childhood (0-6 years) is associated with unfavorable clinical progression compared to later-onset (6-11 years) [9].

Specific migraine symptoms associated with childhood migraine can persist into adulthood. For instance, Alice in Wonderland Syndrome (AWS) is an episodic symptom presenting as a distorted perception of one's own body or surroundings that can occur before, during, or after a migraine attack [10]. A recent longitudinal study found that 18% of pediatric headache patients with AWS continued to have AWS 30 years later [11].

An important limitation of the longitudinal studies described above is that they did not account for the time between symptom onset and formal migraine diagnosis. Several juvenile-specific diagnostic challenges may contribute to this diagnostic delay.

Pediatric migraine sufferers may have a more difficult time articulating their migraine symptoms to care providers. One study found that 30% of children with headaches were unable to describe the quality of their pain, and 16% were unable to report photophobia and phonophobia [12]. Communication difficulties may contribute to previous studies' findings that 11-52% of juveniles with headache disorders do not seek medical consultation [13, 14].

Migraine diagnostic assessments often rely on input from parents and/or caregivers, but studies have shown that parents and caregivers consistently underestimate and underreport their children's migraine symptoms [15]. In addition, pediatric migraine sufferers' clinical symptoms differ considerably from those of adults. For instance, juvenile migraines are often bilateral, unlike unilateral ones typically associated with adult migraines. Juvenile migraine sufferers are more likely than adults to experience abdominal migraine and reoccurring limb pain associated with migraines [16, 17]. Pediatric migraine attacks are also relatively short compared to adult attacks, usually lasting less than 4 hours. Medical practitioners who are unfamiliar with children's atypical migraine patterns may miss or misdiagnose juvenile migraines [18].

Because of diagnostic delay, marking the beginning of migraine disorders by the time of formal diagnosis, as previous studies have done, may obscure important information about the relationship between age of symptom onset and migraine progression. To the best of the authors' knowledge, the relationship between early migraine symptom onset and adult migraine outcomes has not been studied in a way that accounts for the diagnostic delay.

This study aimed to clarify the relationship between the age of migraine symptom onset and adult migraine symptomology. By asking participants to indicate the age of symptom onset, the retrospective self-report methodology allowed for the inclusion of previously overlooked participants whose symptoms began in childhood but did not receive a formal diagnosis until adolescence or adulthood. The authors hypothesized that childhood age of migraine symptom onset is associated with the following adult migraine outcomes: (i) a higher number of migraine symptoms, (ii) a higher number of triggers, (iii) a higher incidence of migraine attacks per month, and (iv) a higher number of days per month with migraine symptoms.

Methods

Recruitment

The study recruited individuals from a popular online migraine-specific website (Migraine in America, "MIA", website: https://migraine.com). Adults 18 years or older that currently reside in the United States and reported a diagnosis of migraine headaches by a physician using ICD-9 or ICD-10 criteria were invited to participate. Migraine community discussion forums, online banner advertisements, referrals from healthcare providers, and internet searches referred migraine sufferers to the MIA study website.

Procedures

The [removed for blind review] IRB approved this study. The survey was accessible on the MIA website from May 2015 to July 2015. There was no a priori power analysis, and the study recruited as many participants as possible in the allotted study timeframe. Participants were informed: 1) study participation was voluntary, 2) with no financial compensation, 3) information would be anonymous, and 4) it would take 30-40 minutes. Participants indicated informed consent prior to entering the survey.

The survey included demographics, socioeconomic status, migraine symptomology, migraine frequency, and migraine treatments. Participant IP addresses were logged to prevent participants from responding to the survey multiple times. Participants selected symptoms they typically experience with migraine attacks from a list of migraine symptoms. A similar item assessed migraine triggers. Participants also indicated the timespan between symptom onset and formal diagnosis, the typical number of migraine attacks experienced per month, the average number of days per month with migraine symptoms, and the age of first migraine-related symptoms. The survey was adaptive, omitting certain questions as indicated by previous answers. Thus, the number and content of survey questions differed slightly for each participant.

We created three groups based on the participants' age of migraine symptom onset: the Childhood Cohort (0-12 years), the Adolescence Cohort (13-18 years), and the Adulthood Cohort (19+). This grouping allowed for a clearer examination of the relationships between childhood symptom onset and adult outcomes.

Data Analysis

We performed all statistical analyses using SPSS v.24.0 (IBM Corp., Armonk, NY, USA). We analyzed participant demographics using descriptive statistics. We used one-way Analyses of Variance (ANOVAs) with Tukey's posthoc tests and Chi-square tests to investigate differences between cohorts. To explore diagnosis delay as a possible explanation for these group differences, we used post-hoc exploratory analyses, including ANOVA and mediation tests. We tested mediation using the SPSS macro PROCESS with 5,000 bootstrapped replications [19]. We used the HC0 parameter estimator in PROCESS to account for heteroskedasticity, which was identified using the Breusch-Pagan & Koenker Test macro by Garcia-Granero (2002) [20, 21]. The model was considered consistent with mediation if the 95% indirect effect confidence interval did not include zero.

Results

Participants and Demographics

A total of 4,502 individuals met the inclusion criteria and completed the entire MIA survey. The median time for survey completion was 37 minutes. Of the participants, 95.5% were female, and over half (74%) were older than 40 years. The mean age

of participants was 45y 9mo, SD 10y 2mo. A majority of adult participants (59.2%) had experienced migraine symptom onset before 18. See Table 1 for further demographic information.

Table 1. Participant demographics and timespan until formal migraine diagnosis.

Gender	**n**	**%**
Male	202	4.5
Female	4,300	95.5
Age in Years		
18- 24	84	1.9
25-34	554	12.3
35-44	1,267	28.1
45-54	1,455	32.3
55-65	941	20.9
65 <	201	4.5
Age of Migraine Onset		
0-11 years old	1,107	24.6
12-18	1,558	34.6
19 or more	1,837	40.8
Ethnicity		
Caucasian	4,106	91.2
non-Caucasian	329	7.3
Prefer not to answer	67	1.5
Household Income		
Less than $30,000	689	15.3
$30,000 – $49,000	661	14.7
$50,000 – $74,900	797	17.7
$75,000 – $99,999	544	12.1
$100,000 – $199,999	710	15.8
Over $200,000	148	3.3
Prefer not to answer	953	21.2
Timespan until formal migraine diagnosis		
Less than 6 months	669	14.9
6 months to a year	522	11.6
1 year	367	8.2
2 years	341	7.6
3 years	210	4.7
4 years	189	4.2
5 years	356	7.9
6 to 10 years	688	15.3
10 to 15 years	498	11.1
More than 15 years	662	14.7

Adult Outcomes

There were significant differences between the three cohorts in adult number of migraine symptoms ($F(2,4499)=78.16$; $p<.001$; $\eta^2= .034$) and triggers ($F(2,4499)=114.99$; $p<.001$; $\eta^2= .049$). In addition, the cohorts differed significantly in adult number of migraine attacks per month ($F(2,4499)=7.22$; $p=.001$; $\eta^2= .003$) and days per month with migraine symptoms ($F(2,4499)=12.05$; $p<.001$; $\eta^2= .005$). The Childhood Cohort reported the worst adult outcome for each of these measures. The Adolescence Cohort reported the second-highest number of adult symptoms and migraine triggers. The Adolescence and Adulthood Cohorts did not differ significantly in the number of migraine attacks per month or days per month with migraine symptoms.

Chi-square tests were used to determine differences between the cohorts in adult symptom incidence. Of the 52 listed symptoms, there were 46 for which adult incidence was higher among the Childhood Cohort than the Adulthood Cohort ($p<.05$) (See Table 2). Adult symptoms with the largest incidence difference for those with childhood symptom onset were Sensitivity to smell, Sensitivity to touch, Food cravings, AWS, and Difficulty communicating (See Figure 1).

Table 2. Frequency of adult migraine symptoms by onset cohort

Symptom [a]	**Childhood %**	**Adolescence %**	**Adulthood %**	χ^2	ϕ
Alice in Wonderland Syndrome	13.4† §	8.7‡	4.8	67.8***	0.12
Anger/Rage/Irritability	38.1† §	31.2	27.7	35.2***	0.09
Aura	44.7§	41.4‡	33	46.9***	0.1
Brain fog	66.7† §	60.5‡	55.5	36.0***	0.09
Clumsiness	47.6† §	41.5‡	34.7	49.1***	0.1
Confusion	48.1† §	43.3	40.4	16.3***	0.06
Constipation	16.8† §	13.2	11.9	14.6***	0.06
Diarrhea	21.7§	19.3	16.4	13.0**	0.05
Difficulty concentrating	77.3† §	70.5	68.2	29.0***	0.08
Difficulty communicating/Aphasia	49.1† §	39.5‡	35.2	55.8***	0.11
Dizziness/Lightheadedness	55.1§	52.8‡	48.1	15.2***	0.06
Euphoria	4.5§	2.8	2.4	10.9**	0.05
Excessive urination	17.1† §	11.2	10.2	32.6***	0.09
Eye pain	54.7§	51.7‡	46.2	21.9***	0.07
Fatigue	71.1† §	64.6	63.3	19.8***	0.07
Food cravings	29.6† §	20.8‡	16.7	69.7***	0.12
Hallucinations (including sound or smell)	15.4§	12.6‡	9.4	24.6***	0.07
Head pain	93.8† §	90.5	90.3	11.9**	0.05
Hiccups	3.3†	1.6	2	9.6**	0.05
Itchy nose	8.3† §	5.3	4	24.4***	0.07
Memory loss	27.2† §	21.4	23	12.4**	0.05
Metallic taste	9.2§	8	6.1	10.5**	0.05
Mood changes	42.3† §	35	31.9	32.8***	0.09
Nausea- moderate/severe	59.4† §	53.2‡	45.9	52.3***	0.11
Neck Pain	67.1§	65.7‡	61.6	10.9**	0.05
Numbness/tingling/" pins and needles"	31.0§	26.9	24.1	16.9***	0.06
Puffy eyelid	20.0§	18.7	16.4	6.7*	0.04
Restless leg	11.8§	11.2‡	8.2	13.4***	0.06
Sense of foreboding	17.2† §	12.5	10.4	28.6***	0.08
Sensitivity to light	88.4§	86.5‡	82.3	23.6***	0.07
Sensitivity to smell	76.3† §	69.0‡	58.1	110.5***	0.16
Sensitivity to sound	84.2† §	79.7‡	74.7	38.5***	0.09
Sensitivity to touch	44.8† §	35.0‡	27.5	92.3***	0.14
Sinus symptoms	42.6† §	37.7‡	31.3	40.4***	0.1
Sneezing	6.1§	4.9	3.4	11.4**	0.05
Sore skin	21.5† §	15.7‡	12.6	41.3***	0.1
Stiff neck	55.9§	53.5	51.2	6.2*	0.04
Strange sounds	8.3§	6.8	5.6	8.5*	0.04
Swollen lymph nodes	4.6§	3.8	2.8	6.5*	0.04
Tingling	19.8§	16.7	14.9	11.8**	0.05
Unable to move one side of body or face	8.8§	6.4	5.1	15.8***	0.06
Vertigo or feeling off-balance	40.6§	36.5	35.4	8.1*	0.04
Visual changes	51.9† §	46.1‡	40.8	35.0***	0.09
Vomiting	43.3† §	37.6‡	28.8	68.3***	0.12
Watery eyes	26.5§	23.2‡	18.1	30.8***	0.08
Weakness	36.8† §	30.6	28.3	23.7***	0.07
Yawning	32.0† §	27.1‡	20.9	46.5***	0.1

[a] Only symptoms with significant χ^2 ($p \leq .05$) are included; * $p \leq .05$; ** $p \leq .01$;*** $p \leq .001$; † Difference between Childhood and Adolescence ($p \leq .05$); § Difference between Childhood and Adulthood ($p \leq .05$); ‡ Difference between Adolescence and Adulthood ($p \leq .05$)

Table 3. Frequency of adult migraine triggers by onset cohort.

Trigger [a]	**Childhood %** §	**Adolescence %**	**Adulthood %**	χ^{2}***	ϕ
Alcohol/Drugs	43.1†	36.5‡	32.2	35.2	0.09
Allergies	37.4	34.3‡	26.8	41.7	0.1
Blinking or flashing lights	58.9†	53.3‡	43	77.9	0.13
Bright light/Fluorescent light	64.1†	56.0‡	48.2	71.9	0.13
Caffeine	21	18.7‡	13.7	29.2	0.08
Certain food or drinks	53.9†	48.1‡	38.5	71.9	0.13
Certain smells	62.8†	53.7‡	44.1	99.3	0.15
Cigarette smoke	40.7	37.0‡	28.1	57	0.11
Crying	40.3†	32.7‡	25.8	67.9	0.12
Dehydration	56.5†	51.6‡	40.6	79.8	0.13
Driving or travel	32	28.8‡	23.2	29.2	0.08
Environmental	73.5†	68.7‡	62.2	42.5	0.1
Fatigue	55	51.7‡	46.7	20.5	0.07
Heat	52.8†	44.0‡	34.5	97.9	0.15
Hormones/Menstrual Cycle	55.7	55.5‡	41.3	89.1	0.14
Missing meals	59.5†	50.3‡	40.1	107.5	0.16
Noise/loud sounds	43.3†	37.2	35.7	17.7	0.06
Physical activity	36.9†	27.0‡	23	67.2	0.12
Sleep (irregular/lack/ too much)	69.0†	63.9‡	58.6	33.2	0.09
Stress "let down"	55.0†	47.8‡	36.3	106.6	0.15
Tension-type headache	42	43.3‡	37.1	15.2	0.06
Watching TV or movies	11.6†	8	6.5	23.9	0.07

[a] Only triggers with significant χ^{2} ($p \leq .05$) are included; ***$p \leq .001$ for all included triggers; §Difference between Childhood and Adulthood ($p \leq .05$) for all shown triggers; † Difference between Childhood and Adolescence ($p \leq .05$); ‡Difference between Adolescence and Adulthood ($p \leq .05$)

Of the 24 listed migraine triggers, there was a higher incidence among the Childhood Cohort than the Adulthood Cohort for 22 triggers (See Table 3). The triggers with the largest incidence difference for those with childhood symptom onset were Missing meals (ϕ=.13), Certain smells (ϕ=.12), Heat (ϕ=.12), and Stress "let down" (ϕ=.12) (See Figure 2).

Post-Hoc Testing

Diagnosis Delay

We used ANOVAs to investigate the relationship between onset age and diagnosis delay. The cohorts differed significantly in time from symptom onset until a formal diagnosis was made ($F(2,4499)=354.64$; $p<.001$; $\eta^2= .136$). Participants whose symptoms began during childhood experienced the longest diagnosis delay, followed by those whose symptoms began during adolescence.

Diagnosis delay did not mediate the relationship between onset cohort and the following adult outcome variables: migraines per month (CI=-0.04, 0.17), days per month with symptoms (CI=-0.16, 0.17), or the number of symptoms (CI=-0.04, 0.29). However, the onset cohort had a significant indirect effect on the adult number of triggers through diagnosis delay (B=0.12, CI=0.02, 0.23).

Analyzing only data from members of the Childhood Cohort, diagnosis delay did not mediate the relationship between onset age and adult number of migraines per month (CI=-0.02, 0.001), days per month with symptoms (CI=-0.04, 0.001), symptoms (CI=-0.03, 0.005), or triggers (CI=-0.01, 0.01).

Discussion

The present study examined the association between the age of migraine symptom onset and adulthood symptomology. The findings support our hypotheses. In adulthood, childhood symptom onset was associated with a higher number of typical migraine symptoms, triggers, attacks per month, and days per month with symptoms than onset during adolescence or adulthood. The Childhood Cohort also had a higher adult incidence of symptoms and triggers. Finally, consistent with the findings of Viticchi et al. (2011) that younger-onset is associated with a longer delay in migraine diagnosis, the current study found childhood symptom onset to be associated with a longer diagnostic delay than adolescent and adult symptom onset [22].

Taken together, the worse adult outcomes and longer diagnostic delay found in the Childhood Cohort are suggestive, raising the question of whether diagnosis delay causes or contributes to worse adult outcomes. Delayed diagnosis is harmful to juvenile migraine sufferers who may have prolonged exposure to otherwise treatable migraine symptoms. These delays result in pointless medical consultations, unnecessary medical bills, and untreated migraine burdens, and the impact on undiagnosed patients' quality of life as they continue to experience migraine attacks. Lack of a diagnosis and, in turn, inadequate treatment increase susceptibility to psychosocial complications such as depression, anxiety, and interpersonal relationship challenges, which may further increase vulnerability to ongoing migraine symptoms and attacks. In addition, there is evidence in various patient populations that undertreated acute pain is associated with the development of chronic pain [23]. Thus, it is reasonable to suspect that diagnosis delay among childhood migraine sufferers leads to worse adult outcomes.

However, this study found little evidence that delayed diagnosis explains the relationship between earlier onset and worse adult outcomes, especially once the analyses accounted for the variance from the onset cohort. The onset cohort had a significant but small indirect effect on several triggers through diagnosis delay, but diagnosis delay did not mediate the relationship between the onset cohort and any other adult outcome variables. Since longer diagnostic delay among adults may indicate milder symptoms, it is reasonable to expect diagnosis delay to explain worse adult outcomes only for the Childhood Cohort. However, within the Childhood Cohort, diagnosis delay did not mediate the relationships between onset age and any of the analyzed adult outcomes, including the number of triggers. Still, given the potential limitations of this self-report survey, more research is needed to understand whether delays in diagnosis and treatment may influence these and other measures of adult outcomes among migraine sufferers whose symptoms began in childhood.

An alternative explanation for the diagnostic delays and worse adult outcomes of childhood-onset migraine may be that early-onset migraine differs from adult-onset migraine in type, severity, and/or etiology. Medical providers may misdiagnose childhood migraine due to the unusual symptoms experienced within this cohort. These unusual symptoms may indicate underlying differences in type, severity, and/or etiology. For instance, Familial hemiplegic migraine (FHM) is a genetic type of migraine with symptoms usually beginning in childhood or adolescence. Symptoms of FHM less typically associated with migraine include numbness, facial paresthesias, limb paresthesias, Difficulty with speech, psychosis, or confusion. Other migraine presentations such as abdominal migraine and limb pain associated with childhood migraine could also present diagnostic challenges and may indicate underlying differences between child onset migraine and adult-onset migraine. Further research is needed to investigate whether particular symptoms associated with childhood migraine indicate underlying differences that contribute to diagnostic delay and unfavorable adult outcomes.

Clinical Implications

This study's results indicate that the burden of migraine disorders falls disproportionately upon migraine sufferers with childhood-onset. Regardless of the role diagnostic delay plays in the adult outcome, it is important to promptly and accurately diagnose and treat migraines in childhood. Besides typical diagnostic methods, unique strategies for promoting an appropriate diagnosis of childhood migraine include using headache drawings [24], asking caregivers which activities the child prefers during attacks, and asking clarifying questions about pain location since children may only indicate the area of most severe pain [25]. Parents, caregivers, and school nurses familiar with the

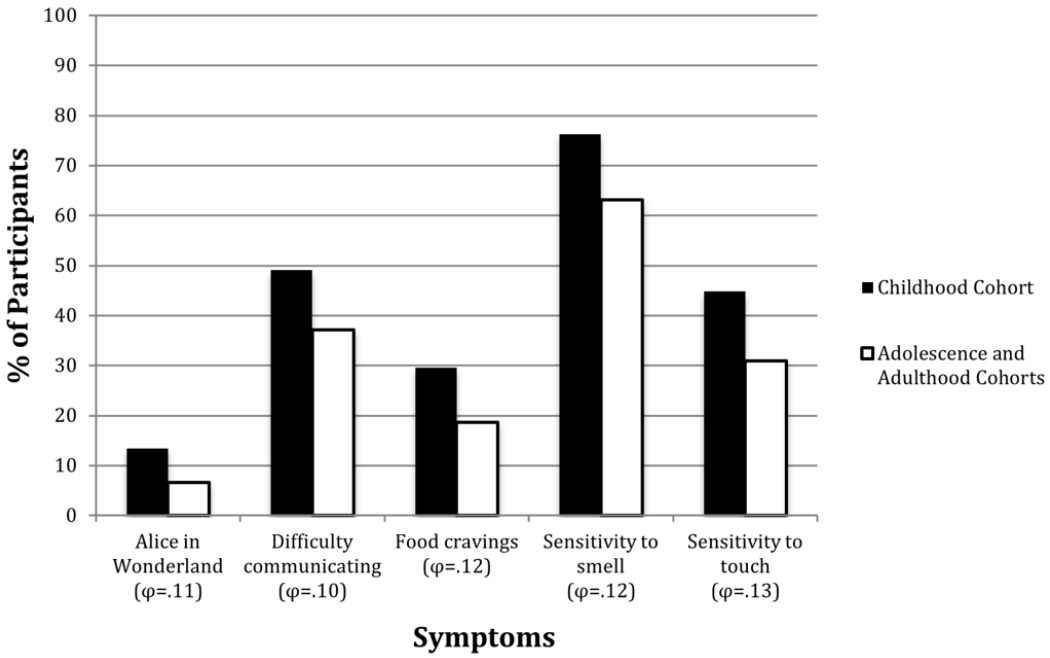

Figure 1. Symptoms with largest adult frequency differences for childhood age of onset, using Chi-square test ($\phi \geq .10,\ p < .001$).

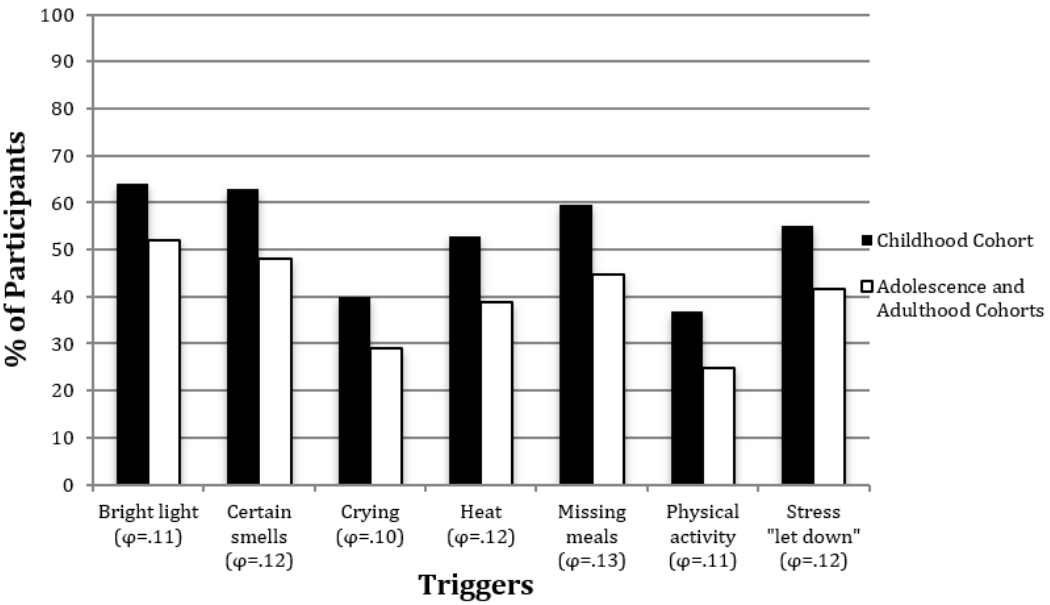

Figure 2. Symptoms with largest adult frequency differences for childhood age of onset, using Chi-square test ($\phi \geq .10,\ p < .001$).

unique expressions of migraine in children can help recognize migraine and promote appropriate medical diagnosis and care [26].

Strengths, Limitations, and Future Directions

Pediatric migraine studies have predominantly been conducted in clinics. The current study was the first to assess a large, national migraine population's age of symptom onset in relation to adult symptomology. This study's use of online recruitment and the retrospective design allowed for the inclusion of childhood migraine sufferers who may not have been included in the study by traditional clinical recruitment since their migraines were not appropriately diagnosed during childhood. This phenomenon was supported by this study's results, which found that many childhood migraine sufferers were not diagnosed until 10 to 15 years after symptom onset.

This study has several limitations. First, the study used a self-reporting survey, so self-selection bias cannot be discounted. Second, the study had narrow demographics that limited the generalisability of its findings. As with previous migraine research [27], most migraine sufferers in this study were female (95.5%). Third, this study, like other retrospective self-reporting studies, is susceptible to recall bias. Several retrospective migraine stud-

ies have attributed migraine sufferers' tendency to incorrectly remember their age of migraine onset to recall bias [28, 29]. Evidence shows that recall bias causes many participants to underestimate symptomology at younger ages and overestimate symptomology at older ages [30]. Thus, participants in this study may have tended to report migraine symptom onset at a later age than symptom onset occurred. Collecting symptom onset information from patients at the time of diagnosis rather than years later could help minimize recall bias in future research.

Future research should also explore underlying reasons for the relationship between early migraine onset and adult outcome. Specifically, it is important to seek further clarification of the long-term consequences of diagnostic delay and possible differences in type, severity, and etiology indicated by migraine onset age and/or particular symptoms and triggers.

Conclusion

Compared to migraine suffers whose symptoms began in adolescence or adulthood, those whose symptoms began in childhood reported worse symptomology in a number of domains as adults, including a higher number of migraine attacks per month, days per month with migraine symptoms, typical migraine symptoms, and migraine triggers. Childhood migraine suffers also reported a longer time between symptom onset and formal diagnosis. Evidence was not found to suggest that diagnosis delay could explain either the relationship between onset age and migraine frequency or between onset age and number of symptoms.

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Competing interests

The authors have no competing interests to declare.

Author contributions

All authors reviewed, revised, and approved the final manuscript. In addition, all authors contributed to the data analysis and writing of the manuscript.AW was involved in study design and conception, data analysis, and manuscript writing.

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