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## Research Submission

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### Adverse Childhood Experiences and Frequent Headaches in Adults

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**Background.**—A variety of studies have linked childhood maltreatment to headaches, including migraines, and to headache severity. This study assesses the relationship of adverse childhood experiences (ACEs) to frequent headaches during adulthood.

**Methods.**—We used data from the Adverse Childhood Experiences (ACE) study, which included 17,337 adult members of the Kaiser Health Plan in San Diego, CA who were undergoing a comprehensive preventive medical evaluation. The study assessed 8 ACEs including abuse (emotional, physical, sexual), witnessing domestic violence, growing up with mentally ill, substance abusing, or criminal household members, and parental separation or divorce. Our measure of headaches came from the medical review of systems using the question: “Are you troubled by frequent headaches?” We used the number of ACEs (ACE score) as a measure of cumulative childhood stress and hypothesized a “dose–response” relationship of the ACE score to the prevalence and risk of frequent headaches.

**Results.**—Each of the ACEs was associated with an increased prevalence and risk of frequent headaches. As the ACE score increased the prevalence and risk of frequent headaches increased in a “dose–response” fashion. The risk of frequent headaches increased more than 2-fold (odds ratio 2.1, 95% confidence interval 1.8–2.4) in persons with an ACE score  $\geq 5$ , compared to persons with an ACE score of 0. The dose–response relationship of the ACE score to frequent headaches was seen for both men and women.

**Conclusions.**—The number of ACEs showed a graded relationship to frequent headaches in adults. Future studies should examine general populations with headache, and carefully classify them. A better understanding of the link between ACEs and migraine may lead to new knowledge regarding pathophysiology and enhanced additional therapies for headache patients.

**Key words:** headache, adverse childhood experience, stress, traumatic stress

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Childhood maltreatment is a major public health concern worldwide.<sup>1</sup> Recent surveys from multicenter headache clinic populations demonstrated that in adults with migraine, the prevalence of childhood sexual abuse, physical abuse, and physical neglect ranged between 20% and 25%,<sup>2,3</sup> similar to estimates in the general population.<sup>4</sup> Emotional abuse and neglect were recalled by nearly 40% of those migraineurs surveyed in headache clinic, nearly 4-fold greater than population estimates. Moreover, the headaches in these clinic patients reporting childhood maltreatment were more likely to be chronic in

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*Conflict of Interest:* None

frequency, disabling, and associated with depression, anxiety, and other pain conditions.<sup>3,5,6</sup>

Despite the high prevalence of childhood maltreatment in persons with headache and the association of headache disability and psychiatric comorbidity, there is a paucity of research examining the relationship of childhood maltreatment to the frequency of headache in the general population. One of the earliest studies in a health maintenance organization (HMO) population reported an association between childhood abuse and headache; chronic headache occurred in almost half of persons reporting sexual abuse histories, and this was nearly twice that of a non-abused control group.<sup>7</sup> In a larger primary care survey study restricted to women ( $n = 1931$ ), the prevalence of childhood sexual abuse or physical abuse was 22%, with nearly half of the abused individuals reporting frequent severe headache.<sup>8</sup> A meta-analysis of sexual assault history and headache in 7500 adolescents and adults demonstrated that headache was significantly more common among persons with a history of sexual assault than among those without (odds ratio [OR] 1.7, 1.40-2.07).<sup>9</sup> Other abuse types were not included in the survey. A study in a community-based sample of 3032 adult men and women examined the relationship of childhood physical abuse to self-reported migraine.<sup>10</sup> After adjusting for demographic factors and psychiatric disorders, physical abuse increased the risk of migraine nearly 3-fold (OR 2.7, 1.2-5.8). A community-based study of childhood adverse events in adolescents, using the Global Family Environment Scale,<sup>11</sup> found that physical abuse was associated with chronic daily headache, as defined by the Silberstein-Lipton criteria, and was the only study to use defined headache classification criteria.<sup>12,13</sup> In a random sample of 1225 women receiving care through an HMO,<sup>14</sup> emotional, physical, and sexual abuse were assessed using the Childhood Trauma Questionnaire<sup>15</sup> to examine the relationship of maltreatment and common physical symptoms, including headache.<sup>16</sup> Childhood abuse and neglect was reported by 43% of the women, and an increased risk of headache was associated with both sexual (OR 1.3, 1.1-1.6) and non-sexual (OR 1.2, 1.0-1.4) maltreatment.

The Adverse Childhood Experiences (ACE) study is an ongoing collaboration between the Centers for Disease Control and Prevention and Kaiser Permanente (San Diego, CA). This study combines retrospective reports of childhood experiences in adults at baseline and prospective follow-up of the study cohort to examine the incidence of diseases, health care utilization, premature mortality, and causes of death.<sup>17-20</sup> The primary objective of the ACE study is to assess the impact of numerous, interrelated ACEs (including childhood sexual, physical, and emotional abuse). Prior publications from this study have demonstrated a cumulative or "dose-response" relationship between the number of ACEs (the ACE score) and a wide variety of health and social problems.<sup>21,22</sup> The purpose of this investigation is to explore the relationship of ACEs to frequent headaches in adults.

## METHODS

The ACE study was approved by the institutional review boards of Kaiser Permanente, Emory University, and the US Department of Health and Human Services.

**Study Population.**—The study population was drawn from the Department of Preventive Medicine's Health Appraisal Clinic (HAC), which provides standardized medical, psychosocial, and preventive health evaluations to adult members of the Kaiser Health Plan in San Diego County. Visits to the HAC are primarily for the purposes of complete health assessments, rather than symptom or illness-based care; all persons evaluated at the HAC completed a standardized questionnaire, which includes health histories and health-related behaviors, a medical review of systems, and psychosocial evaluations. This information was included in the ACE study database.

Two weeks after their HAC evaluation, each person who was evaluated at the HAC between August 1995 and March 1996 (wave I) and June and October 1997 (wave II) received the ACE study questionnaire by mail. The study was done in 2 waves to assess response rates, assemble a preliminary database, and identify potential problems with the questionnaire. Late spring and summer months were not included in the survey period because of more fre-

quent cancellation and “no shows” for clinic appointments during those months. The questionnaire collected detailed information about ACEs (eg, abuse), household dysfunction (eg, domestic violence), and health-related behaviors from adolescence to adulthood. The response rate for both survey waves combined was 68%, for a total of 18,175 responses.

We excluded 754 respondents who coincidentally underwent examinations during the time frames for both survey waves. The unduplicated total number of respondents was 17,421. After exclusion of 17 respondents with missing information about race and 67 with missing information about educational attainment, the final study sample included 95% of the respondents (17,337/18,175; wave I = 8708, wave II = 8629).

**Definitions of Adverse Childhood Experiences (ACEs).**—Questions used to define ACEs are listed in Table 1. All questions about ACEs pertained to the respondents’ first 18 years of life ( $\leq 18$  years of age). For questions adapted from the Conflict Tactics Scale (CTS)<sup>15</sup> there were 5 response categories: “never,” “once or twice,” “sometimes,” “often,” or “very often.” We defined 3 types of childhood abuse: emotional abuse (2 questions), physical abuse (2 questions) came from the CTS. We defined contact sexual abuse using Wyatt’s criteria (4 questions).<sup>23</sup> In addition, we defined 5 exposures to household dysfunction during childhood: exposure to substance abuse (defined by 2 questions),<sup>24</sup> mental illness (2 questions), violent treatment of mother or stepmother (4 questions),<sup>25</sup> criminal behavior in the household (1 question), and parental separation or divorce (1 question). Respondents were defined as exposed to a category if they responded “yes” to 1 or more of the questions in that category. The total number of these exposures (range: 0-8) was summed to create the ACE score. Due to small sample sizes, ACE scores of 5 or more were combined into 1 category ( $\geq 4$ ). Thus, analyses were conducted with the summed score as 4 dichotomous variables (yes/no) with 0 experiences as the referent.

**Questions About Frequent Headaches.**—The following question about frequent headaches was included in the HAC: “Are you troubled by frequent headaches?”

**Statistical Analysis.**—All analyses were conducted using SAS version 8.2 (SAS Institute Inc., Cary, NC, USA). Adjusted ORs and 95% confidence intervals (CIs) were obtained from multiple logistic regression models that estimated the likelihood of the selected health behavior or outcome with the ACE score stratified by birth cohort. Covariates in all models were included on a priori reasoning, rather than using step-wise selection and included age (continuous variable), sex, race, and education (high school diploma, some college, or college graduate vs less than high school). In the data that we present herein, persons with incomplete information about an ACE were considered not to have had that experience. Thus, persons with incomplete information who did have ACEs were classified as not having them. Thus, our results are conservative (biased toward the null).

To test for a trend (graded relationship) between the ACE score and the risk of frequent headaches we entered the ACE score as an ordinal variable into logistic models, with adjustment for the demographic covariates (sex, age, race, and education). Prevalences of frequent headaches by ACE score and sex were adjusted for demographic covariates (sex, age, race, and education) using multiple linear regression (general linear model [GLM]).

## RESULTS

**Characteristics of Study Population.**—The study population included 9367 women (54%) and 7970 men (46%). The mean age was 56 years (standard deviation = 15.2 years). Seventy-three percent of participants were white; 39% were college graduates; 36% had some college education; and 18% were high school graduates. Only 7% had not graduated from high school.

**Adverse Childhood Experiences.**—The prevalence of each individual ACE and of the ACE scores is shown in Table 1. Women were more likely than men to report ACEs, with exception of physical abuse.

**Frequent Headaches.**—The prevalence of frequent headaches was 16.6%. After adjusting for demographic factors using logistic regression, frequent headaches were more common in women, younger adults, and persons with lower educational attainment (Table 2).

**Table 1.—Definition and Prevalence of Each Category of Adverse Childhood Experience and the Adverse Childhood Experiences (ACE) Score**

	Total n = 17,337
Childhood abuse	
Emotional	10.6
(Did a parent or other adult in the household . . .)	
(1) Often or very often swear at you, insult you, or put you down?	
(2) Sometimes, often, or very often act in a way that made you think that you might be physically hurt?	
Physical	28.3
(Did a parent or other adult in the household . . .)	
(1) Often or very often push, grab, slap, or throw something at you?	
(2) Often or very often hit you so hard that you had marks or were injured?	
Sexual	20.7
(Did an adult or person at least 5 years older ever . . .)	
(1) Touch or fondle you in a sexual way?	
(2) Have you touch their body in a sexual way?	
(3) Attempt oral, anal, or vaginal intercourse with you?	
(4) Actually have oral, anal, or vaginal intercourse with you?	
Household dysfunction	
Substance abuse	26.9
(1) Live with anyone who was a problem drinker or alcoholic?	
(2) Live with anyone who used street drugs?	
Mental illness	19.4
(1) Was a household member depressed or mentally ill?	
(2) Did a household member attempt suicide?	20.7
Mother treated violently	12.7
(Was your mother [or stepmother]):	
(1) Sometimes, often, or very often pushed, grabbed, slapped, or had something thrown at her?	
(2) Sometimes, often, or very often kicked, bitten, hit with a fist, or hit with something hard?	
(3) Ever repeatedly hit over at least a few minutes?	
(4) Ever threatened with or hurt by a knife or gun?	
Incarcerated household member	4.7
(1) Did a household member go to prison?	
Parental separation or divorce	23.3
(1) Were your parents ever separated or divorced?	
Number of adverse childhood experiences (ACE score)	
0	36.1
1	26.0
2	15.9
3	9.5
4	6.2
≥5	6.3

**Adverse Childhood Experiences and Frequent Headaches.**—Each of the 8 categories of ACEs were associated with a higher prevalence of each frequent headache (Table 3); after adjusting simultaneously for demographic variables, the adjusted odds of frequent headaches ranged from 1.1 for parental separation or divorce to 1.7 for emotional or physical abuse (Table 3).

**The Adverse Childhood Experiences Score and Frequent Headaches.**—Because the categories of ACEs are highly interrelated,<sup>18,19</sup> we used the ACE score to assess the relationship of the cumulative impact of these childhood experiences to frequent headaches in adulthood.

Compared to persons with an ACE score of 0, those with an ACE score of 5 or more were 2.1 (95%

**Table 2.—Prevalence and Risk of Frequent Headaches and Frequent Headaches by Sex, Age, Race, and Educational Attainment**

	Sample Size n	Prevalence of Headache (%)	OR† (95% CI)
Sex			
Men	7970	9.2	1.0 (Reference)
Women	9367	22.8	2.7 (2.5-3.0)
Age (years)			
18-34	1721	26.6	1.0 (Reference)
35-49	4494	22.9	0.9 (0.5-0.7)
50-64	5534	15.7	0.6 (0.5-0.7)
≥65	5588	9.2	0.3 (0.3-0.4)
Race			
White	12,964	15.1	1.0 (Reference)
Black	789	19.5	1.1 (0.9-1.3)
Hispanic	1942	22.8	1.2 (1.0-1.3)
Asian	1244	18.4	0.9 (0.8-1.1)
Other	398	21.4	1.3 (1.0-1.7)
Educational attainment			
No high school diploma	1251	19.9	1.0 (Reference)
High school graduate	3044	17.1	0.8 (0.7-0.9)
Some college	6220	18.1	0.8 (0.6-0.9)
College graduate	6822	14.4	0.6 (0.5-0.7)

†Odds ratios adjusted for all demographic variables simultaneously using logistic regression.

CI: 1.8-2.4) times more likely to report frequent headaches (Table 4); the trend for increasing odds for frequent headaches with increasing ACE score was statistically significant ( $P < .0001$ ).

After adjusting for age, race, and educational attainment, the prevalence of frequent headaches increased in a graded fashion as the ACE score increased for both women and men (Fig.); this trend was statistically significant ( $P < .0001$ ).

## DISCUSSION

This is the largest study to date examining the relationship of recurrent headache to childhood abuse and other adverse experiences, in adult men and women. We made 2 important observations: (1) frequent headache is associated with each type of adverse experience of childhood, particularly emotional abuse; and (2) the prevalence of frequent headaches increased with increasing ACE score for both men and women. The correlation of headache with childhood abuse and other adversities mirrors the

results from earlier more restricted studies.<sup>7-11,14</sup> The important role of emotional abuse in migraine clinic studies is in accord with these data.<sup>2,5,6</sup> The nature of the association of headache and adversity is uncertain, although the consistency of this finding in a variety of study populations and the “dose–response” relationship between the number of ACEs and frequent headaches in the current study suggest a possible causal relationship.<sup>17</sup>

There are mounting biological data that childhood stress can affect numerous brain structures and functions, which contribute to the credibility of this theory.<sup>17</sup> Most recently it has been found that early stress induces lifelong epigenetic changes. In 1 study, for example, childhood abuse altered DNA, thereby reducing levels of hippocampal glucocorticoid receptors, which are important for responding to stress.<sup>26</sup> In an animal model, early life stress led to changes in a specific regulatory region of the genome, affecting the expression of a mood-controlling hormone, arginine vasopressin, in the hypothalamic paraventricular

**Table 3.—Relationship of Adverse Childhood Experiences (ACEs) to Frequent Headaches**

Type of Adverse Childhood Experience	Sample Size n	Prevalence of Headache (%)	OR† (95% CI)
Emotional abuse			
No	15,508	15.3	1.0 (Reference)
Yes	1829	26.9	1.6 (1.4-1.7)
Physical abuse			
No	12,425	14.9	1.0 (Reference)
Yes	4912	20.8	1.4 (1.3-1.5)
Sexual abuse			
No	13,751	15.6	1.0 (Reference)
Yes	3586	21.5	1.3 (1.1-1.4)
Witnessed domestic violence			
No	15,136	15.6	1.0 (Reference)
Yes	2201	22.9	1.3 (1.2-1.5)
Household substance abuse			
No	12,682	14.9	1.0 (Reference)
Yes	4655	21.1	1.2 (1.1-1.3)
Household mental illness			
No	13,978	15.1	1.0 (Reference)
Yes	3359	22.8	1.3 (1.2-1.5)
Parental separation/divorce			
No	13,306	15.6	1.0 (Reference)
Yes	4031	19.6	1.1 (1.0-1.2)
Household member imprisoned			
No	16,528	16.2	1.0 (Reference)
Yes	809	23.7	1.2 (1.1-1.5)

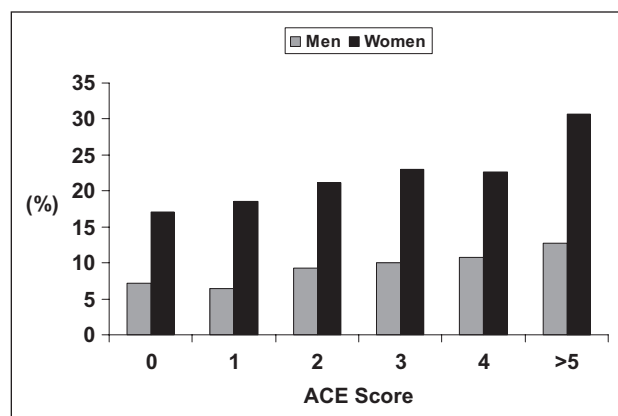
†Odds ratios adjusted for all demographic variables simultaneously using logistic regression.

**Table 4.—Relationship of the Adverse Childhood Experiences (ACE) Score to the Prevalence and Risk of Frequent Headaches**

ACE Score	Sample Size n	Prevalence of Headache (%)	OR† (95% CI)
0	6255	13.0	1.0 (Reference)
1	4514	14.2	1.2 (1.1-1.3)
2	2758	18.0	1.4 (1.3-1.6)
3	1650	20.9	1.7 (1.5-1.9)
4	1071	22.5	2.0 (1.7-2.3)
≥5	1089	30.5	2.1 (1.8-2.4)

The trend for increasing odds for frequent headaches with increasing ACE score is significant ( $P < .0001$ ).

†Odds ratios adjusted for all demographic variables simultaneously using logistic regression.



**Figure.**—Prevalence of frequent headaches by Adverse Childhood Experiences (ACE) score and gender. Estimates adjusted for age, race, and educational attainment; trend in increasing prevalence by ACE score is significant for both men and women ( $P < .001$ ).

nucleus, an area involved in regulating hormones linked to stress.<sup>27</sup> Stress, particularly when chronic, seemingly affects both peripheral and central nociception, thereby leading to hyperalgesia and chronic head pain.<sup>28</sup>

The obvious limitation of this study is the imprecision of the term “frequent headache,” included on a screening questionnaire in a preventive health assessment clinic. The frequency and characteristics of the headaches of persons that endorsed this question are unknown, since participants were not individually interviewed to see if their headaches met the criteria for migraine, as defined by the International Classification of Headache Disorders (ICHD)-II.<sup>29</sup> The Landmark study, however, found that of 1203 patients who complained of a headache to their physician, the vast majority met ICHD-II criteria for migraine (76%), or probable migraine (18%).<sup>30</sup> Among these, some also likely met recently established criteria for chronic migraine, with 15 or more days of headache per month, and at least 8 of these headaches being migraines, with this pattern for at least 3 months.<sup>31</sup> Although we do not have enough data to extrapolate the findings from the Landmark study to our population, speculation that many of those with “frequent headache” in our population also had migraine, probable migraine, or chronic migraine is supported by the similarities in prevalence rates and in demographic profiles between our population and populations with

migraine. We found “frequent headaches” were reported by 23% of women and 9% of men. This was consistent with the female to male ratio found in 3 very large migraine studies,<sup>32-34</sup> with migraine prevalence of about 18% in women and 6% in men. In chronic migraine, female to male ratios ranged between 2.5 and 6.5.<sup>35</sup> Both in general population studies of migraine,<sup>32</sup> and our population with frequent headache, headache prevalence was most common in younger adults and declined with age.<sup>36</sup> We found that prevalence was higher in those with low educational attainment, a condition that has been found to be associated with increased risk of headache chronification.<sup>37</sup>

## CONCLUSION

The ACE score showed a graded relationship to frequent headaches in adults. Future studies should examine general populations with headache, and carefully classify them. A better understanding of the link between ACEs and migraine may lead to new knowledge regarding pathophysiology and enhanced additional therapies for all headache patients.

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