

Adverse Childhood Experiences and Self-reported Liver Disease

New Insights Into the Causal Pathway

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Objective: To examine the relationship of adverse childhood experiences (ACEs), including abuse, neglect, and forms of household dysfunction, to the risk of liver disease by assessing the role of risk behaviors, such as substance abuse and high-risk sexual activity, as mediators of the ACEs–liver disease relationship.

Methods: Retrospective cohort study data were collected from 17 337 adult health plan members through a survey. Logistic regression adjusted for age, sex, race, and education was used to estimate the strength of the ACEs–liver disease relationship and the impact of the mediators in this relationship.

Results: Each of 10 ACEs increased the risk of liver disease 1.2 to 1.6 times ($P < .001$). The number of ACEs (ACE score) had a graded relationship to liver disease ($P < .001$).

Compared with persons with no ACEs, the adjusted odds ratio of ever having liver disease among persons with 6 or more ACEs was 2.6 ($P < .001$). The ACE score also had a strong graded relationship to risk behaviors for liver disease. The strength of the ACEs–liver disease association was reduced 38% to 50% by adjustment for these risk behaviors, suggesting they are mediators of this relationship.

Conclusions: The ACE score showed a graded relationship to the risk of liver disease that appears to be mediated substantially by behaviors that increase the risk of viral and alcohol-induced liver disease. Understanding the effect of ACEs on the risk of liver disease and development of these behaviors provides insight into causal pathways, which may prove useful in the prevention of liver disease.

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CHRONIC LIVER disease and cirrhosis is one of the 10 leading causes of death in the United States.^{1,2} It disproportionately affects both men and women in their prime working years (ie, ages 35-64 years) and is the fifth leading cause of death among men aged 45 to 64 years.¹⁻³

The two most important causes of chronic liver disease are alcohol abuse and viral hepatitis (hepatitis B virus [HBV] and hepatitis C virus [HCV]).⁴ It is estimated that 70% of those chronically infected with HCV will develop chronic liver disease, and 40% of all patients with chronic liver disease also have HCV infection.⁵⁻⁷ People using illegal drugs or engaging in high-risk sexual behaviors account for most persons with HBV and HCV infections.⁵⁻¹⁰ Moreover, HCV infection and alcohol abuse act synergistically¹¹⁻¹⁵ and cause accelerated progression of liver injury, high frequency of cirrhosis, and higher incidence of hepatocellular carcinoma.¹⁶⁻¹⁹

The most recent surveillance data from the Centers for Disease Control and Prevention (CDC) show that about 1.25 mil-

lion Americans are chronically infected with HBV and 2.7 million with HCV.^{5,6} Rates of HCV and HBV infection are high among persons infected with the human immunodeficiency virus (HIV), since these viruses share similar transmission modes, such as risky sexual behavior and parenteral drug use.²⁰⁻²⁵

To our knowledge, the relationship between exposure to childhood abuse, neglect, and household dysfunction and the risk of liver disease has not been studied, even though the risk of known causative factors for liver disease, such as alcoholism, parenteral drug abuse, sexual promiscuity, and sexually transmitted diseases (STDs), increases dramatically with the number of types of adverse childhood experiences (ACEs).¹⁷⁻²³ Previous reports from the ACE Study²⁶ have shown a strong, graded relationship between the number of ACEs (ACE score), multiple risk factors for leading causes of death in the United States, and priority health and social problems such as smoking, adult alcohol problems, unintended pregnancies, STDs, suicide attempts, and male involvement in teen pregnancy.²⁶⁻³² In the present article, we use data from the ACE Study²⁶ to describe the asso-

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ciation between ACEs and a history of liver disease and assess the mediating role of behaviors known to increase risk for liver disease on this ACEs–liver disease association.

METHODS

The data were collected as part of the ACE Study, a collaboration between Kaiser Permanente (San Diego, Calif) and the CDC (Atlanta, Ga). The study was approved by the institutional review boards of Kaiser Permanente and the Office of Protection from Research Risks at the National Institutes of Health, Rockville, Md. Potential participants received letters that accompanied the ACE Study questionnaire, informing them that their participation was voluntary and their answers would be held in strictest confidence and would never become part of their medical records.

STUDY POPULATION AND DATA COLLECTION

The study population consisted of adult members of the Kaiser Health Plan who received a standardized medical and biopsychosocial examination at Kaiser's Health Appraisal Center in San Diego. In any 4-year period, 81% of adult members received the examination, and more than 50000 members receive it annually. The primary purpose of the examination is to conduct a complete health assessment rather than provide symptom- or illness-based care.

The ACE Study consisted of 2 survey waves conducted among consecutive members visiting Health Appraisal Center. Wave I was performed among 13494 members between August 1995 and March 1996, and the response rate was 70% (n=9508). Wave II was performed between June and October 1997 among 13330 members, and the response rate was 65% (n=8667). The final study cohort includes 18175 persons with a response rate of 68%.

The ACE questionnaire was mailed to members 2 weeks after their examination and collected information on ACEs, including abuse (emotional, physical, or sexual), neglect (emotional or physical), or household dysfunction (parental separation or divorce, domestic violence, substance abuse, crime, or mental illness), as well as health-related behaviors from adolescence to adulthood. The wave II questionnaire added questions about emotional and physical neglect and more detailed questions about health topics shown to be important during the analysis of wave I data.^{27,29}

ASSESSMENT OF REPRESENTATIVENESS AND RESPONSE OR REPORTING BIAS

As part of the wave I study design, standardized health examination data were abstracted for both respondents and nonrespondents to the ACE Study questionnaire, enabling a detailed assessment of possible bias in terms of demographic characteristics and health-related issues.³³ Although nonrespondents tended to be younger, less educated, and more likely to be members of racial and ethnic minority groups, the prevalence of both psychosocial and health problems were remarkably similar between respondents and nonrespondents after controlling for demographic differences. In addition, assessment of the relationships between childhood sexual abuse and numerous health behaviors, diseases, and psychosocial problems showed that they were virtually identical for respondents and nonrespondents.³³ Thus, we found no evidence that respondents were biased toward attributing their health problems to childhood experiences, such as sexual abuse.³³

To assess the accuracy of the responses to the question about liver disease, we performed test-retest reliability analysis³⁴ among 644 persons who serendipitously visited the clinic during wave I and II operations and were inadvertently in-

cluded in the ACE Study twice. We found that 87% of persons who reported a history of liver disease in wave I also did so in wave II; and 97% who did not report liver disease in wave I did not report liver disease in wave II. Cohen kappa (κ) for the reliability of this question was 0.7. Thus, persons in the study are highly consistent in their responses to this question based on Cohen κ and the reliability of the question is good.³⁴

EXCLUSIONS FROM THE STUDY COHORT

Respondents who coincidentally underwent examinations during the time frames for both waves were excluded (n=754 [4%]). Another 17 respondents were excluded owing to missing information about race, and 67 were excluded owing to missing information about education. The final study sample included 17337 members (wave I=8708; wave II=8629 [95% of participants]).

DEFINITIONS OF ACEs

All questions about ACEs referred to the respondents' first 18 years of life. To assess emotional and physical neglect, we used questions from the Childhood Trauma Questionnaire³⁵ from survey wave II only, which was scored on a 5-point Likert scale (response categories of never true, rarely true, sometimes true, often true, and very often true). Some items from the Childhood Trauma Questionnaire were reverse scored to reflect the framing of the question.³⁵ Questions used to define emotional and physical abuse and growing up with a battered mother were adapted from the Conflict Tactics Scale (response categories of never, once or twice, sometimes, often, or very often).³⁶

- *Emotional abuse*: Emotional abuse was defined if participants responded often or very often to either of the following 2 questions: "How often did a parent, stepparent, or adult living in your home swear at you, insult you, or put you down?" and "How often did a parent, stepparent, or adult living in your home act in a way that made you afraid that you might be physically hurt?"
- *Physical abuse*: Physical abuse was assessed with the following 2 questions: "Sometimes parents or other adults hurt children. While you were growing up, that is, in your first 18 years of life, how often did a parent, stepparent, or adult living in your home (1) push, grab, slap, or throw something at you? or (2) hit you so hard that you had marks or were injured?" Physical abuse was defined if the response was either often or very often to the first question or sometimes, often, or very often to the second.
- *Sexual abuse*: Childhood sexual abuse was assessed using 4 questions adapted from Wyatt,³⁷ which asked whether an adult or someone who was at least 5 years older than themselves had ever (1) touched or fondled their body in a sexual way; (2) had them touch his or her body in a sexual way; (3) attempted to have any type of sexual intercourse with them (oral, anal, or vaginal); or (4) actually had any type of sexual intercourse with them (oral, anal, or vaginal). Childhood sexual abuse was defined when subjects responded affirmatively to any of these 4 questions.
- *Emotional neglect*: To measure emotional neglect, the following 5 statements were used: (1) "There was someone in my family who helped me feel important or special"; (2) "I felt loved"; (3) "People in my family looked out for each other"; (4) "People in my family felt close to each other"; and (5) "My family was a source of strength and support." For each respondent, all responses were reverse scored and summed to determine the Childhood Trauma Questionnaire clinical scales. A respondent with a score of 15 or higher (moderate to extreme) was defined as emotionally

neglected. This information was available only in wave II data.

- *Physical neglect*: Responses to 5 questions were scored and summed for each respondent (1) "I didn't have enough to eat"; (2) "I knew there was someone there to take care of me and protect me"; (3) "My parents were too drunk or too high to take care of me"; (4) "I had to wear dirty clothes"; and (5) "There was someone to take me to the doctor if I needed it." Questions 2 and 5 were reverse scored. A respondent with a score of 10 or higher (moderate to extreme) was defined as being physically neglected. This information was collected only in survey wave II.
- *Battered mother*: Four questions from the Conflict Tactics Scale were used to define childhood exposure to a battered mother: "Sometimes physical blows occur between parents. While you were growing up in your first 18 years of life, how often did your father (or stepfather) or mother's boyfriend do any of these things to your mother (or stepmother): (1) push, grab, slap, or throw something at her; (2) kick, bite, hit her with a fist, or hit her with something hard; (3) repeatedly hit her for at least a few minutes; or (4) threaten her with a knife or gun or use a knife or gun to hurt her?" Persons with response of sometimes, often, or very often to at least 1 of the first 2 questions or any response other than never to either one of the last 2 questions were defined as having had a battered mother.
- *Household substance abuse*: During their childhood if respondents lived with a problem drinker or alcoholic^{37,38} or anyone who used street drugs.
- *Mental illness in household*: If anyone in the household was depressed or mentally ill or had attempted suicide during respondent's childhood.
- *Parental separation or divorce*: This was defined as an affirmative response to the question "Were your parents ever separated or divorced?"
- *Criminal household member*: If anyone in the household had gone to prison during the respondent's childhood.

THE ACE SCORE

The total number of ACEs experienced by respondents became their ACE score, which was used to assess the cumulative effect of multiple ACEs. The ACE score has repeatedly been shown to have a strong, graded relationship to numerous health and social problems.²⁶⁻³²

BEHAVIORS KNOWN TO INCREASE RISK FOR LIVER DISEASE

An affirmative response to any of the following questions would define a respondent as having been exposed to that behavior:

- Ever used illicit drugs: "Have you ever used street drugs?"
- Ever an injection drug user: "Have you ever injected street drugs?"
- Sexually transmitted disease: "Have you ever been treated for or told you had any venereal disease?"
- At risk of AIDS: "Do think you are at risk of AIDS?"
- Alcoholic: "Have you ever considered yourself to be an alcoholic?"
- "Ever a heavy drinker" was defined by someone who consumed 14 or more drinks per week during any 10-year period from age 19 years to the present. Only wave II collected this information.

DEFINITION OF SELF-REPORTED LIVER DISEASE

Information on liver disease was collected as part of the standardized medical history in the Health Appraisal Center. Plan

members who answered yes to the following screening question were classified as having liver disease: "Have you ever had or been told you have yellow jaundice, hepatitis, or any liver trouble?"

STATISTICAL ANALYSIS

The SAS System (version 8.02) (SAS Institute Inc, Cary, NC) was used for all analysis. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were obtained from multivariate logistic regression models that estimated the strength of the associations between each of the 10 categories of ACEs and self-reported liver disease. The ACE score was entered into logistic models as a set of dummy variables (1, 2, 3, 4-5, and 6-8 ACEs). The ACE scores of 4 or 5 and 6, 7, or 8 were combined into 2 categories owing to a small number of respondents with these scores. The strength of the relationship between the ACE score to known risk factors for liver disease, including alcohol and drug abuse and risky sexual behaviors, was also assessed and tested using logistic regression. Covariates in all models included age at the interview, sex, race (black, Asian, Hispanic, Native American, and others vs white), and education (high school diploma, some college, or college graduate vs less than high school). Using SAS diagnostics, we found no evidence of collinearity (high degree of correlation) between the ACEs and demographic factors.

Persons who provided incomplete information about an ACE (n=516 [6%]) were considered not to have had that experience. Theoretically, this might attenuate the relationships between liver disease and ACEs slightly because persons who had potentially been exposed to an experience would always be classified as unexposed.³⁹ To assess the potential effect of this assumption, the analyses were repeated after excluding respondents with missing information on any of the ACEs and no differences were found in the results.

ASSESSMENT OF MEDIATION BY KNOWN RISK FACTORS

Finally, we assessed the potential mediating role of behaviors known to increase risk of liver disease in the relationship between the ACE score and liver disease using logistic models while controlling, or not, for these variables (ie, full and single models). Our proposed causal pathway between ACEs and liver disease includes known risk behaviors that have also been shown to be strongly associated with ACEs. Thus, the logistic models that included both the known risk behaviors and the ACE score (full model) treated these behaviors as potential mediating (sometimes termed "intermediate") variables, as recommended by Rothman.³⁹

The reduction in the ORs (risk decrement) observed comparing the full model with the single model was calculated as follows:

$$(\text{OR} [\text{single model}] - \text{OR} [\text{full model}]) / (\text{OR} [\text{single model}] - 1) \times 100\%$$

RESULTS

CHARACTERISTICS OF THE STUDY POPULATION

The study population included 9367 (54%) women and 7970 (46%) men. The mean age was 55 years for women and 57 years for men, and 73% of women and 76% of men were white. Most women (35%) and men (45%) were college graduates; only 8% of women and 6% of men had not graduated from high school.

RELATIONSHIP BETWEEN KNOWN RISK BEHAVIORS AND THE LIKELIHOOD OF LIVER DISEASE

Table 1. Prevalence and Adjusted OR of Liver Disease by Category of ACE

Category of ACE	No. of Subjects	Prevalence, %	Adjusted OR* (95% CI)	P Value
Abuse				
Emotional abuse				
No	15 508	6.5	1.0 (Referent)] <.001
Yes	1829	9.6	1.6 (1.4-2.0)	
Physical abuse				
No	12 425	6.3	1.0 (Referent)] <.001
Yes	4912	8.2	1.4 (1.2-1.6)	
Sexual abuse				
No	13 751	6.3	1.0 (Referent)] <.001
Yes	3586	8.8	1.5 (1.3-1.7)	
Household dysfunction				
Battered mother				
No	15 136	6.6	1.0 (Referent)] <.001
Yes	2201	8.6	1.5 (1.2-1.7)	
Parental separation or divorce				
No	13 306	6.5	1.0 (Referent)] <.001
Yes	4031	7.7	1.3 (1.1-1.5)	
Mental illness in household				
No	13 978	6.6	1.0 (Referent)] <.001
Yes	3359	7.8	1.3 (1.1-1.5)	
Household substance abuse				
No	12 682	6.5	1.0 (Referent)] <.001
Yes	4665	7.7	1.3 (1.1-1.5)	
Criminal household member				
No	16 356	6.7	1.0 (Referent)] >.05
Yes	809	7.5	1.2 (0.9-1.6)	
Neglect†				
Emotional neglect				
No	7273	6.6	1.0 (Referent)] <.001
Yes	1256	9.6	1.4 (1.1-1.7)	
Physical neglect				
No	7693	6.9	1.0 (Referent)] <.05
Yes	836	9.1	1.4 (1.1-1.8)	

Abbreviations: ACE, adverse childhood experience; CI, confidence interval; OR, odds ratio.

*Adjusted for age at survey, sex, race, and educational attainment.

†Wave II data only (women = 4674; men = 3955).

PREVALENCE AND CHARACTERISTICS OF LIVER DISEASE

Overall, 6.8% of respondents reported having a history of liver disease. Native Americans had the highest prevalence (9.5%), followed by whites (7.3%), Hispanics (7.0%), Asians (4.6%), and blacks (3.4%). The prevalence was nearly twice as high in older persons (≥ 65 years, 7.8%) than in younger persons (< 35 years, 4.4%).

RELATIONSHIP BETWEEN ACEs AND THE LIKELIHOOD OF LIVER DISEASE

An increased likelihood of reporting liver disease for each of 10 ACEs was observed. For each category, the OR ranged from 1.2 to 1.6 after adjustment for sex, race, educational attainment, and age at interview (**Table 1**).

A substantially higher prevalence of liver disease was reported among respondents exposed to known risk factors, especially among injection drug users (**Table 2**). Among persons who reported that they were alcoholic and injected drugs, the prevalence was more than 7 times higher than among persons who were neither alcoholic nor injection drug users.

The results showed strong associations between behaviors known to increase the risk of liver disease and reported history of liver disease after adjusting for demographic factors. The risk for liver disease was 1.6 times greater in persons with risky sexual activities and 7.7 times greater in persons who were injection drug users. Persons with a history of alcoholism as well as parenteral drug use had more than 10 times greater likelihood of liver disease than persons without such a history (Table 2).

RELATIONSHIP BETWEEN THE ACE SCORE, RISK BEHAVIORS, AND LIVER DISEASE

As the ACE score increased, the number of known risk factors increased in a strong, graded fashion (**Table 3**). Compared with persons with no ACEs, the likelihood of having engaged in known behaviors in respondents with 6 or more ACEs was up to 22.8 times greater. The highest risk was seen in persons who reported both parenteral drug use and alcoholism (Table 3).

We found a positive graded relationship between the ACE score and the likelihood of reporting liver disease (**Table 4**). Compared with persons with no ACEs, the likelihood of having liver disease among persons with 6 or more ACEs was more than twice as high. When adjusting simultaneously for 8 known risk factors, the strength of the association (adjusted ORs) between the ACE score and liver disease was reduced substantially, suggesting mediation by these behaviors (Table 4). After entering known risk factors into the model, the risk decrement in the ORs was 33% to 50% for each level of the ACE score (Table 4).

The addition of risk behaviors as mediating variables to the full model significantly increased the log likelihood ratio compared with the single model ($\chi^2_{16} = 159.11$; $P < .001$). This indicates that the 8 risky behaviors partially account for a statistically significant amount of the variance in liver disease.

To test for the significance of the graded relationship between the ACE score and the risk of liver disease, the ACE score was entered as an ordinal variable into logistic regression models, with adjustment for demographic covariates. The ordinal OR was 1.2, suggesting that for every increase in the ACE score the risk for liver disease increased by 20%.

COMMENT

To our knowledge, this study is the first to demonstrate the association between a broad range of ACEs and liver disease. The results showed compelling evidence that be-

aviors that are strongly associated with ACEs and known to increase the risk of liver disease³² are mediators of this relationship. The chain of events beginning with childhood experiences of abuse, neglect, and household dysfunction, which lead to the adoption of health behaviors^{28,29,32} that increase the risk of liver injury,³⁻¹⁵ provides a novel perspective on the origins of liver disease. Thus, the findings of this study support a plausible pathway by which ACEs lead to liver disease.

Multiple ACEs indicate a disordered social environment and stressful exposures that can negatively affect the developing brain and emotional and social well-being.⁴⁰ Thus, as supported by findings of this analysis, the effects of childhood trauma on occurrence of liver disease may operate through resultant behaviors such as alcohol consumption, drug abuse, and sexual promiscuity, which, in turn, may be attempts to cope with unpleasant affective states and alterations in brain function³⁹ that likely result from ACEs.^{26,27,31}

The relationship of the ACE score to liver disease is strong and graded, and it was reduced 33% to 50% by adjustment for these behaviors, suggesting they function as mediators in this relationship. While these behaviors appear to account for a substantial proportion of the increased risk of liver disease (as seen by comparing single model with the full model that includes the behaviors), the association between the ACE score and the likelihood of liver disease remained statistically significant after adjusting 8 risk behaviors.

Several potential limitations need to be considered when interpreting the results of this study. A history of liver disease was determined based on responses to the question of ever having jaundice, hepatitis, or liver trouble. This may have led to underreporting of liver disease, and this question did not provide information on the specific type of liver disease. However, this screening question likely captured the most common forms of symptomatic or clinically manifested liver disease. Furthermore, this type of screening question is routinely included in patients' medical history or review of systems. Thus, the data presented apply to the type of information gathered and decision making in everyday medical practice.

In addition, because information on the age at which liver disease occurred was unavailable, it is uncertain whether in some cases reported liver disease may have preceded the exposure to ACEs. However, with the exception of acute symptomatic viral hepatitis, most forms of liver disease (eg, chronic active hepatitis and alcoholic cirrhosis) require many years or decades to become clinically manifest; thus, it is likely that most symptomatic liver disease cases did in fact follow, rather than precede, the onset of exposure to various categories of ACEs.

Liver disease may also have been underreported owing to its tendency to be asymptomatic. For instance, alcohol-induced liver disease in its early stage (fatty liver) is usually asymptomatic; it takes approximately 10 years of heavy drinking to develop cirrhosis.^{15,41} Moreover, since most cases of cirrhosis occur later in life, young adults in this study who experienced childhood trauma may not have had enough time to develop the clinical signs and symptoms needed for diagnosis. Most viral hepatitis is also asymptomatic; about 30% of persons infected with

Table 2. Prevalence and Adjusted ORs for Liver Disease by Known Risk Factors

Known Risk Factor	No. of Subjects	Liver Disease	
		Prevalence, %	Adjusted OR* (95% CI)
Ever used street drugs			
No	14 494	6.4	1.0 (Referent)
Yes	2843	8.9	1.8 (1.5-2.1)
Injected street drugs			
No	17 150	6.5	1.0 (Referent)
Yes	187	32.1	7.7 (5.6-10.6)
Problems with alcohol			
No	15 579	6.4	1.0 (Referent)
Yes	1758	10.6	1.7 (1.5-2.0)
Alcoholic			
No	16 241	6.4	1.0 (Referent)
Yes	1096	12.6	2.0 (1.7-2.5)
Ever a heavy drinker†			
No	7404	6.4	1.0 (Referent)
Yes	1125	11.6	1.9 (1.5-2.3)
Injected street drugs and alcoholic			
No	17 246	6.6	1.0 (Referent)
Yes	91	42.8	11.4 (7.4-17.5)
Intercourse, y			
≥15	16 325	6.6	1.0 (Referent)
<15	1012	9.9	1.6 (1.3-2.0)
No. of lifetime intercourse partners			
<50	16 747	6.7	1.0 (Referent)
≥50	590	11.0	1.6 (1.3-2.2)
Ever had an STD			
No	15 782	6.5	1.0 (Referent)
Yes	1555	10.4	1.9 (1.6-2.2)
At risk of AIDS			
No	16 704	6.7	1.0 (Referent)
Yes	633	10.9	2.0 (1.5-2.5)

Abbreviations: CI, confidence interval; OR, odds ratio; STD, sexually transmitted disease.

*Adjusted for age at survey, sex, race, and educational attainment.

†Wave II data only (women = 4674; men = 3955).

P<.001 for all factors.

HBV and 80% of persons with HCV have no signs or symptoms.^{41,42} Finally, less common forms of liver disease such as hepatitis A, inflammatory diseases, genetic abnormalities, and liver damage due to toxic chemical exposures, which are unlikely to be associated with ACEs, could not be differentiated from the more common forms in this study. However, if we had been able to measure both the dates of occurrence and the types of liver disease, the relationship between ACEs and liver disease would likely have been stronger than those reported here.

The estimates of the strength of the relationship between ACEs and liver disease and the amount of mediation by known risk factors are both likely to be conservative. Longitudinal follow-up of adults whose childhood abuse was well documented has shown that their retrospective reports of childhood abuse are likely to underestimate actual occurrence.^{43,44} Since each of the questions about ACEs addressed sensitive topics, and the questions about ACEs and liver disease were retrospective, both the exposure (ACEs) and the outcome (liver disease) were possibly underreported. This may have

Table 3. Association Between the ACE Score and the Behaviors Known to Increase Risk of Liver Disease

Risk Behavior	ACE Score*	No. Exposed to Behaviors	Risk Behavior Prevalence, %	Adjusted OR†‡ (95% CI)	P Value
Ever used street drugs	0	495	5.0	1.0 (Referent)	...
	1	624	9.0	1.5 (1.3-1.7)	<.001
	2	553	8.9	2.1 (1.8-2.4)	<.001
	3	411	9.0	2.6 (2.2-3.1)	<.001
	4-5	554	9.9	3.7 (3.1-4.3)	<.001
	6-8	206	14.6	5.2 (4.1-6.6)	<.001
Injected street drugs	0	14	21.4	1.0 (Referent)	...
	1	28	25.0	2.2 (1.2-4.2)	<.05
	2	38	29.0	4.2 (2.3-7.8)	<.001
	3	27	37.0	4.9 (2.5-9.4)	<.001
	4-5	53	30.2	8.8 (4.8-16.1)	<.001
	6-8	27	48.1	14.5 (7.3-28.5)	<.001
Problems with alcohol	0	309	7.4	1.0 (Referent)	...
	1	386	7.5	1.7 (1.5-2.0)	<.001
	2	326	11.0	2.4 (2.0-2.8)	<.001
	3	250	8.0	3.3 (2.7-4.0)	<.001
	4-5	361	14.7	5.2 (4.4-6.2)	<.001
	6-8	126	20.6	7.4 (5.8-9.5)	<.001
Alcoholic	0	158	8.2	1.0 (Referent)	...
	1	229	9.2	2.0 (1.6-2.5)	<.001
	2	205	14.6	2.6 (2.0-3.2)	<.001
	3	174	8.6	3.5 (2.7-4.5)	<.001
	4-5	140	25.7	4.8 (3.8-6.1)	<.001
	6-8	90	25.6	10.6 (7.5-14.8)	<.001
Ever a heavy drinker§	0	181	13.8	1.0 (Referent)	...
	1	157	18.5	1.4 (1.2-1.7)	<.001
	2	96	21.9	1.7 (1.4-2.1)	<.001
	3	63	17.5	2.2 (1.8-2.8)	<.001
	4-5	74	43.2	2.7 (2.2-3.4)	<.001
	6-8	32	40.6	3.5 (2.5-5.0)	<.001
Injected street drugs and alcoholic	0	5	4.0	1.0 (Referent)	...
	1	12	16.7	2.8 (1.0-8.0)	<.001
	2	15	46.7	4.9 (1.8-13.5)	<.001
	3	13	30.8	7.0 (2.5-19.9)	<.001
	4-5	31	41.9	15.7 (6.0-40.9)	<.001
	6-8	15	66.7	22.8 (8.0-65.1)	<.001
Age at initiation of sexual intercourse <15 y	0	148	5.4	1.0 (Referent)	...
	1	232	9.9	2.0 (1.6-2.5)	<.001
	2	182	9.3	2.5 (2.0-3.1)	<.001
	3	143	9.1	3.4 (2.7-4.3)	<.001
	4-5	206	10.7	5.0 (3.9-6.2)	<.001
	6-8	101	16.8	10.4 (7.7-13.9)	<.001
No. of lifetime intercourse partners ≥50	0	139	7.9	1.0 (Referent)	...
	1	131	9.2	1.2 (1.0-1.6)	>.05
	2	114	7.9	1.8 (1.4-2.3)	<.001
	3	77	11.7	2.2 (1.6-2.9)	<.001
	4-5	99	18.2	3.1 (2.3-4.1)	<.001
	6-8	30	20.0	4.4 (2.8-6.8)	<.001
Ever had an STD	0	331	7.3	1.0 (Referent)	...
	1	369	9.8	1.4 (1.2-1.6)	<.001
	2	279	11.1	1.5 (1.3-1.8)	<.001
	3	221	13.6	2.0 (1.7-2.5)	<.001
	4-5	260	11.1	2.3 (1.9-2.7)	<.001
	6-8	95	12.6	3.1 (2.4-4.0)	<.001
At risk of AIDS	0	173	12.1	1.0 (Referent)	...
	1	147	8.8	1.1 (0.8-1.3)	>.05
	2	104	12.5	1.1 (0.9-1.4)	>.05
	3	75	12.0	1.3 (1.0-1.7)	<.001
	4-5	89	12.4	1.4 (1.0-1.8)	<.001
	6-8	45	4.4	2.3 (1.6-3.3)	<.001

Abbreviations: ACE, adverse childhood event; CI, confidence interval; OR, odds ratio; STD, sexually transmitted disease.

*The sample size for each ACE score group: 0 = 6255; 1 = 4514; 2 = 4514; 3 = 2758; 4-5 = 1690; 6-8 = 441.

†Adjusted for age at survey, sex, race, and educational attainment.

‡The trend test for increasing risk of exposure to all risk factors at all levels of ACE scores is significant ($P < .001$).

§Wave II data only.

Table 4. Association Between the ACE Score and Prevalence and Adjusted OR of Liver Disease, With and Without Adjustment for Risk Behaviors

ACE Score	No. of Subjects	Prevalence, %	Adjusted* OR† (95% CI) (Single Model)	P Value	Adjusted* OR† (95% CI) (Full Model)	P Value	Risk Decrement, %
0	6255	5.9	1.0 (Referent)	...	1.0 (Referent)
1	4514	6.5	1.1 (0.9-1.3)	>.05	1.1 (0.9-1.3)	>.05	0
2	2758	6.7	1.2 (1.0-1.5)	<.05	1.1 (0.9-1.4)	>.05	50
3	1650	8.1	1.6 (1.3-1.9)	<.001	1.4 (1.1-1.7)	<.01	33
4-5	1690	8.0	1.8 (1.5-2.3)	<.001	1.5 (1.2-1.9)	<.001	38
6-8	441	10.9	2.6 (1.9-3.5)	<.001	1.8 (1.3-2.5)	<.001	50

Abbreviations: ACE, adverse childhood event; CI, confidence interval; OR, odds ratio; STD, sexually transmitted disease.

*Single models are adjusted for age at survey, sex, race, and educational attainment; full models are adjusted for age at survey, sex, race, educational attainment, and behaviors known to increase risk of liver disease (drug use, injection of street drugs, alcoholism, problem with alcohol, age at first sexual intercourse younger than 15 years, 50 or more lifetime sex partners, history of STDs, and at risk of AIDS).

†The trend test for increasing risk of exposure to all risk factors at all levels of ACE scores is significant ($P < .001$).

biased the results toward the null.³⁹ The same situation is true of the assessment of mediating variables, which, because of their sensitive nature, were also likely to be underreported, thereby leading to underestimation of the amount of mediation by the ACE-related behaviors.

The estimates of the prevalence of ACEs in the present study are similar to estimates from nationally representative surveys,^{45,46} indicating that the experiences of participants of this study are comparable with those of the general adult population. These similarities suggest that the findings of this study are probably applicable to other settings.

Efforts to prevent liver disease (HBV, HCV, and alcohol-induced liver disease) have focused on biological and behavioral interventions, such as vaccination (which has proven to be highly effective)⁴⁷ and prevention of alcohol and drug abuse.^{48,49} The findings of this study suggest that current liver disease prevention and intervention efforts may be improved by understanding that behaviors that increase the risk of common liver diseases often have their origins in the types of childhood stressors examined. Thus, it may be that attempts to alter these risk behaviors apply short-term solutions for long-term social, environmental, and familial problems that often have their onset during childhood.³²

Improvement in the understanding of disease causation is basic to better medical practice. Therefore, primary care practitioners should recognize and routinely ask about ACEs.⁵⁰ In clinical practice, appropriate counseling may help prevent and control health risk behaviors that are a result of these traumatic childhood experiences, such as alcohol and substance abuse and certain sexual behaviors. This may eventually lead to further reductions in the occurrence of common liver diseases.

In summary, a graded relationship was observed between the ACE score and the risk of liver disease, which appeared to be mediated substantially by behaviors known to increase the risk of liver disease. Efforts to prevent liver disease will likely benefit from preventing ACEs and treating individuals exposed to them. Understanding that ACEs lead to risk behaviors that subsequently increase the likelihood of liver disease may provide novel insights that will improve prevention efforts.

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