

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



Insights Into Causal Pathways for Ischemic Heart Disease: Adverse Childhood Experiences Study

Maxia Dong, Wayne H. Giles, Vincent J. Felitti, Shanta R. Dube, Janice E. Williams, Daniel P. Chapman and Robert F. Anda

Circulation 2004;110;1761-1766; originally published online Sep 20, 2004;

DOI: 10.1161/01.CIR.0000143074.54995.7F

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

Copyright © 2004 American Heart Association. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circ.ahajournals.org/cgi/content/full/110/13/1761>

Subscriptions: Information about subscribing to *Circulation* is online at
<http://circ.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
<http://www.lww.com/reprints>

Insights Into Causal Pathways for Ischemic Heart Disease Adverse Childhood Experiences Study

Maxia Dong, MD, PhD; Wayne H. Giles, MD, MS; Vincent J. Felitti, MD; Shanta R. Dube, MPH;
Janice E. Williams, PhD; Daniel P. Chapman, PhD; Robert F. Anda, MD, MS

Background—The purpose of this study was to assess the relation of adverse childhood experiences (ACEs), including abuse, neglect, and household dysfunction, to the risk of ischemic heart disease (IHD) and to examine the mediating impact on this relation of both traditional IHD risk factors and psychological factors that are associated with ACEs.

Methods and Results—Retrospective cohort survey data were collected from 17 337 adult health plan members from 1995 to 1997. Logistic regression adjusted for age, sex, race, and education was used to estimate the strength of the ACE–IHD relation and the mediating impact of IHD risk factors in this relation. Nine of 10 categories of ACEs significantly increased the risk of IHD by 1.3- to 1.7-fold versus persons with no ACEs. The adjusted odds ratios for IHD among persons with ≥ 7 ACEs was 3.6 (95% CI, 2.4 to 5.3). The ACE–IHD relation was mediated more strongly by individual psychological risk factors commonly associated with ACEs than by traditional IHD risk factors. We observed significant association between increased likelihood of reported IHD (adjusted ORs) and depressed affect (2.1, 1.9 to 2.4) and anger (2.5, 2.1 to 3.0) as well as traditional risk factors (smoking, physical inactivity, obesity, diabetes and hypertension), with ORs ranging from 1.2 to 2.7.

Conclusions—We found a dose-response relation of ACEs to IHD and a relation between almost all individual ACEs and IHD. Psychological factors appear to be more important than traditional risk factors in mediating the relation of ACEs to the risk of IHD. These findings provide further insights into the potential pathways by which stressful childhood experiences may increase the risk of IHD in adulthood. (*Circulation*. 2004;110:1761-1766.)

Key Words: risk factors ■ stress ■ heart diseases ■ ischemia

Causal pathways to ischemic heart disease (IHD) have been studied extensively. However, only about half of the variance in IHD prevalence can be explained by so-called traditional risk factors, such as smoking, diabetes, and physical inactivity.¹ Several prospective studies, however, have shown that certain psychological attributes and psychiatric states, such as depression, anger, and hostility, appear to affect both the development of IHD over time and the triggering of fatal and nonfatal IHD events^{2,3} and were well recognized as independently associated with a substantial increase in the risk of IHD.⁴

Reports from the Adverse Childhood Experiences (ACEs) Study have shown that childhood abuse, neglect, and household dysfunction are strongly associated with many risk factors for IHD, including smoking, obesity, physical inactivity, and depression.^{5,6} However, no previous research has provided evidence to link IHD in adulthood as a possible long-term consequence of childhood trauma. To address this issue, we used data from a large sample of health maintenance organization members to examine the ACE–IHD association and to assess whether both established traditional and

psychological risk factors that are related to ACEs mediate this relation.

Methods

Study Population and Data Collection

Data were collected from the ACE study, a collaboration between Kaiser Permanente's Health Appraisal Center (HAC) in San Diego, Calif, and the Centers for Disease Control and Prevention. The study was approved by the institutional review boards of Kaiser Permanente and the Office for Protection from Research Risks at the National Institutes of Health.

Annually at HAC, more than 50 000 members undergo a standardized medical examination. In any 4-year period, some 80% of adult members complete the examination that is primarily for health assessment rather than symptom- or illness-based care. Between 1995 and 1997, the ACE Study conducted 2 survey waves among 26 824 consecutive adult members examined at the HAC. The response rates were 70% and 65% for waves I and II, respectively, and the overall response rate was 68% (n=18 175). After excluding respondents who coincidentally underwent examinations for both waves (n=754) and those missing information about race and education (n=84), the final sample included 9367 (54%) women and 7970 (46%) men. The mean age in years was 56 (SD, 15.2).

Received January 15, 2004; revision received April 15, 2004; accepted April 15, 2004.

From the National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Ga (M.D., W.H.G., S.R.D., D.P.C., R.F.A.); the Department of Preventive Medicine, Southern California Permanente Medical Group (Kaiser Permanente), San Diego, Calif (V.J.F.); and the Department of Neurology, Emory University, Atlanta, Ga (J.E.W.).

Correspondence to Maxia Dong, MD, PhD, CDC, DACH, K-67, 4770 Buford Hwy, NE, Atlanta, GA 30341. E-mail mfd7@cdc.gov

© 2004 American Heart Association, Inc.

Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/01.CIR.0000143074.54995.7F

Seventy-five percent of participants were white and 39% were college graduates. Only 7% had not graduated from high school.

ACE Questionnaire

The ACE questionnaire, which was mailed to members 2 weeks after their medical history was recorded, contained detailed questions about childhood abuse, neglect, and household dysfunction as well as health-related behaviors from adolescence to adulthood.

All ACE questions in Table 1 pertained to the first 18 years of life. Questions from the Conflict Tactics Scale⁷ were used to define emotional and physical abuse and domestic violence. Questions on emotional and physical neglect were contained only in wave II. They were adapted from the Childhood Trauma Questionnaire⁷ and were scored on a Likert scale. Childhood sexual abuse was assessed by using 4 questions adapted from Wyatt,⁸ and it was determined by a "yes" response to one or more of the questions. The ACE score (the number of categories of ACEs reported) was used to assess the cumulative effect of multiple ACEs. The prevalence of individual ACE and the ACE scores are shown in Table 1.

Traditional and Psychological Risk Factors for IHD

Traditional risk factors included smoking (smoked ≥ 100 cigarettes lifetime), physical inactivity (no participation in recreational physical activity in the past month), obesity (body mass index ≥ 30 kg/m²), and medical history of or drug treatment for hypertension or diabetes.

To measure the psychological risk factors anger and depressed affect, the following questions were used: (1) "Have you ever had reason to fear your anger getting out of control?" (2) "Have you had or do you now have depression or feel down in the dumps?"

Self-Reported IHD

History of IHD was collected as part of the standardized medical examination and was defined as a positive response to any of 3 questions: "Have you had or ever been told you have a heart attack (coronary)?" "Do you get pain or heavy pressure in your chest with exertion?" "Do you use nitroglycerine?"

Assessment of Representativeness and Reliability of Data

In wave I, standardized health examination data were abstracted for both respondents and nonrespondents to the ACE questionnaire, enabling a detailed assessment of possible response bias in terms of demographic characteristics and health-related issues. We found no evidence that respondents were biased toward attributing their health problems to childhood experiences.⁹

To assess the accuracy of the responses to the question about IHD, we performed test-retest reliability analysis¹⁰ among 658 persons who, serendipitously, visited the clinic during wave I and II operations and were inadvertently included in the ACE Study twice. Cohen's kappa (κ) was 0.6, showing high test-retest reliability of this question.¹⁰

We used data from wave I to compare the measure of depressed affect with a validated screening tool developed by the RAND¹¹ for lifetime prevalence of major depression or dysthymia. In this comparison (2 \times 2 table), depressed affect was significantly associated with the RAND measure ($\chi^2=1458$, $df=1$; $P<0.0001$). The sensitivity, specificity, and positive predictive value of the question about depressed affect for a lifetime prevalence of major depression or dysthymia based on the RAND screener were 54%, 86%, and 59%, respectively.

Data Analysis

The SAS System was used for all analyses. Adjusted odds ratios and 95% confidence intervals and adjusted prevalence were obtained from multivariate logistic regression and general linear models that estimated the strength of the associations of self-reported IHD with ACE score and each of the 10 categories of ACEs. The ACE score (1, 2, 3, 4, 5 to 6, 7 to 8) was entered into logistic models as a set of dummy variables. Scores of 5 or 6 and 7 or 8 were combined because

the sample sizes for these scores were relatively small. The strength of the relation of the ACE score to traditional and psychological risk factors for IHD was also assessed and tested by using logistic regression.

Covariates in all models included age at survey, sex, race (nonwhite versus white), and education (high school diploma, some college, or college graduate versus less than high school). Using SAS diagnostics, we found no evidence of collinearity between the ACEs and demographic factors.

To measure the potential mediating impact of traditional and psychological risk factors for IHD on the ACE-IHD relation, we used 4 logistic models with and without controlling for these variables. Model I included the ACE score adjusted for demographic covariates. Models II and III included all variables in model I and additionally controlled for traditional (II) or psychological (III) risk factors, respectively. Model IV contained all variables in model I and both traditional and psychological risk factors. In models II, III and IV, traditional and psychological risk factors were treated as potential mediating variables, as recommended by Rothman.¹²

We used the risk decrement to estimate the amount of mediation effect of traditional and psychological risk factors on the ACE-IHD relation by comparing models I and IV. It was calculated as follows: [OR (model I)–OR (model IV)]/[OR (model I)–1] \cdot 100%.

Persons who provided incomplete information about an ACE were considered not to have had it. Theoretically, this would slightly attenuate the ACE-IHD relation, because no doubt some persons who had potentially been exposed to an experience would always be classified as unexposed.¹² To assess the potential effect of this assumption, we repeated the analyses after excluding respondents with missing information on any of the ACEs and found no differences in the results.

Results

Overall, 10.6% of respondents reported a history of IHD. The prevalence was slightly higher in men (11.3%) than in women (9.9%). Blacks had the highest prevalence (13%), with Asians and American Indians at 11% and whites and Hispanics at 10%. The prevalence of IHD was nearly twice as high (15%) in older (≥ 65 years) or less educated (less than high school) persons as in younger (less than 35 years) or college graduates (8%).

ACEs, Mediators, and Likelihood of IHD

The prevalence and likelihood of having IHD significantly increased among persons exposed to any individual ACE (Table 2) except parental marital discord. A substantially higher prevalence of IHD was reported among respondents exposed to either traditional or psychological risk factors (Table 3). However, the adjusted ORs for depression and anger [2.5 (2.1 to 3.0); 2.1 (1.9 to 2.4)] were substantially greater than for traditional risk factors in general.

The Figure depicts a graded association of the ACE scores with psychological and some traditional risk factors for IHD. Notably, the adjusted prevalence of depressed affect and anger was increased 2- to 3-fold among persons with ≥ 4 ACEs than among those with 0 ACEs. This was similar for diabetes and hypertension, though the trend of association was less obvious (data not shown).

Measure of Mediation

A positive graded relation was seen between the ACE score and the likelihood of IHD that was substantially mediated by either traditional or psychological risk factors (Table 4). Persons with ≥ 7 ACEs were >3 times as likely as persons

TABLE 1. Definition and Prevalence of Each Category of ACE and ACE Score

Category	Total (n=17 337)
Abuse	
Emotional	10.6
Did a parent or other adult in the household, ever, sometimes, often or very often. . .	
(1) Swear at you, insult you, or put you down?	
(2) Act in a way that made you afraid that you might be physically hurt?	
Physical	28.3
Did a parent or other adult in the household, often or very often. . .	
(1) Push, grab, slap, or throw something at you?	
(2) 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, or (2) Have you touch their body in a sexual way?	
(3) Attempt, or (4) Actually have oral, anal, or vaginal intercourse with you?	
Neglect*	
Emotional	14.8
Following statement is never, rarely, often, very often true.	
(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.	
(5) My family was a source of strength and support.	
Physical	9.9
Following statement is never, rarely, often, very often true.	
(1) I didn't have enough to eat.	
(2) I knew there was someone there to take care of and protect me.	
(3) My parents were too drunk/high to take care of me.	
(4) I had to wear dirty clothes.	
(5) There was someone to take me to the doctor if I needed it.	
Household dysfunction	
Substance abuse	26.9
Lived with anyone who	
(1) Was a problem drinker or alcoholic?	
(2) Used street drugs?	
Mental illness	19.4
(1) Was depressed or mentally ill?	
(2) Attempted suicide?	
Domestic violence	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?	
Criminal household member	4.7
Did a household member go to prison?	
Parental marital discord	23.3
Parents ever separated or divorced?	
ACE Score	
0	36.1
1	26.0
2	15.9
3	9.5
≥4	12.5

*Wave II data only.

TABLE 2. Prevalence and Adjusted Odds Ratio of Ischemic Heart Disease by ACE

ACE	N	Prevalence of IHD, %	Adjusted OR*	95% CI
Abuse				
Emotional				
No	15 508	10.2	1.0	Referent
Yes	1829	13.5	1.7	1.5–1.9
Physical				
No	12 425	9.7	1.0	Referent
Yes	4912	12.7	1.5	1.4–1.9
Sexual				
No	13 751	10.0	1.0	Referent
Yes	3586	12.7	1.4	1.3–1.6
Household dysfunction				
Domestic violence				
No	15 136	10.2	1.0	Referent
Yes	2201	12.8	1.4	1.2–1.6
Parental marital discord				
No	13 306	10.7	1.0	Referent
Yes	4031	10.2	1.0	0.9–1.2
Mental illness				
No	13 978	10.3	1.0	Referent
Yes	3359	11.7	1.4	1.2–1.6
Substance abuse				
No	12 682	10.4	1.0	Referent
Yes	4655	11.0	1.3	1.2–1.4
Crime				
No	16 356	10.4	1.0	Referent
Yes	809	14.6	1.7	1.3–2.0
Neglect†				
Emotional				
No	7273	10.3	1.0	Referent
Yes	1256	12.3	1.3	1.1–1.6
Physical				
No	7693	10.2	1.0	Referent
Yes	836	14.7	1.4	1.2–1.8

*Adjusted for age, sex, race, and education.

†Wave II data only.

with no ACEs to report a IHD. The addition of traditional or psychological risk factors as mediating variables in model I substantially reduced the strength of the association between the ACE score and IHD risk (model II, $\chi^2=222$, $df=6$, $P<0.001$; model III, $\chi^2=198$, $df=2$, $P<0.001$). The mediating effect of psychological risk factors was even greater than that of traditional risk factors. When both traditional and psychological risk factors were entered simultaneously in model IV, additional reduction in the strength of the ACE–IHD relation was observed ($\chi^2=388$, $df=13$, $P<0.001$). The risk decrement in the ORs for each level of the ACE score ranged from 50% to 100%, suggesting strong mediation by both traditional and psychological risk factors (Table 4). Although women had a higher prevalence of depression,

TABLE 3. Prevalence and Adjusted Odds Ratios for Traditional and Psychological Risk Factors of Ischemic Heart Disease

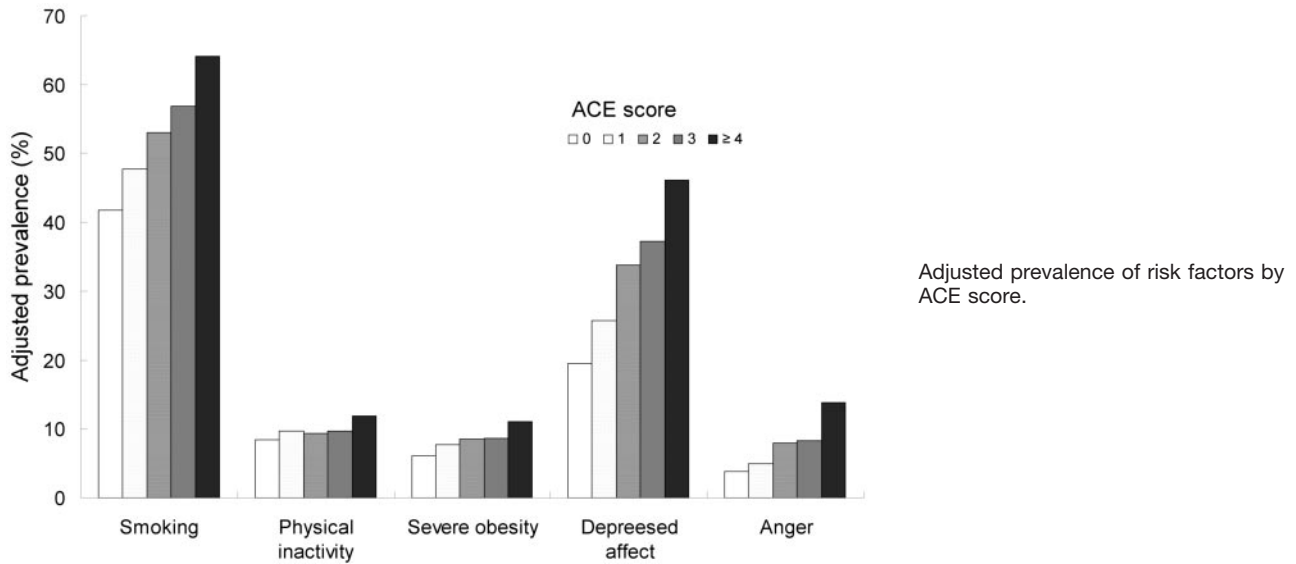
Risk Factor	N	%	Adjusted OR*	95% CI
Traditional				
Diabetes				
No	1663	10.1	1.0	Referent
Yes	167	20.8	1.9	1.6–1.3
Hypertension				
No	1026	8.2	1.0	Referent
Yes	804	16.8	1.9	1.7–2.1
Smoker				
Never	811	9.2	1.0	Referent
Former	849	12.0	1.2	1.1–1.3
Current	170	11.4	1.3	1.1–1.6
Physical inactivity				
No	1398	9.0	1.0	Referent
Yes	242	13.2	1.6	1.4–1.9
BMI (kg/m²)				
<30	1226	9.4	1.0	Referent
30–34	371	12.9	1.4	1.2–1.6
35–39	138	15.4	1.8	1.5–2.2
40–44	50	18.5	2.4	1.8–3.3
≥45	31	18.3	2.7	1.8–4.0
Psychological				
Depressed affect				
No	1101	8.9	1.0	Referent
Yes	729	14.8	2.1	1.9–2.4
Anger				
No	1614	10.0	1.0	Referent
Yes	216	19.4	2.5	2.1–3.0

*Adjusted for age, sex, race, and education.

separate analyses done by gender yielded similar results (data not shown).

To test for the significance of the graded relation between the ACE score and the risk of IHD, the ACE score was entered as an ordinal variable into logistic regression models, with adjustment for covariates. The ordinal OR (model I) was 1.2 (Table 4), suggesting that for every increase in the ACE score the likelihood of reporting IHD increased by 20% ($P<0.001$). After controlling for traditional and psychological risk factors (model IV), it was reduced to 10%.

To test effects of predictive value of reported heart attack or angina in our study, we repeated our analyses after excluding persons under age 50 as true prevalence of IHD rises dramatically after age 50. The positive predictive value of any screening test for an outcome goes up as the prevalence of the clinical outcome (IHD) goes up.¹² We hypothesized that the strength of the relation between the ACE score (as well as the sets of risk factors) and IHD would increase in strength among older persons and this increase would be a result of the inherent increase in the positive predictive value of the IHD questions we used. We found the strength of the graded relation between the ACE score and IHD increased in the reanalysis; likewise, the evidence of mediation impact of



traditional and psychological risk factors was stronger. These findings among older respondents strengthen the validity of the findings we reported.

Discussion

The present analysis adds to the already abundant evidence^{5,13} that adverse childhood experiences, or ACEs, are major determinants of health problems in adulthood. The fact that all but one ACE increased the risk of IHD, when combined with our finding of a graded relation between the number of ACEs and risk of the disease, offers particularly compelling evidence that a tie can indeed be drawn between childhood experiences and the subsequent risk of IHD. As we expected, the ACE-IHD relation appears to be mediated substantially by both traditional and psychological factors, both of which are strongly associated with ACEs. We found that the

strength of the relation of the ACE score to IHD was reduced 50% to 100% by adjusting for these variables. Even so, as the graded relation between the ACE score and the likelihood of IHD remained significant after the adjustment, it appears that there may be unmeasured or as yet unidentified pathways by which ACEs affect the risk of IHD.

Multiple ACEs indicate a disordered social environment and stressful exposures that can negatively affect the developing brain as well as emotional and social well-being.¹⁴ The chain of events begins with childhood exposure to abuse, neglect, and household dysfunction, which lead to the development of unpleasant affective states, depression and anger/hostility, as a result of long-term effect of physiological response to stress.¹⁴ Attempts to cope with these stresses may also lead to the adoption of risk behaviors, such as smoking, overeating, and physical inactivity.

TABLE 4. Association Between ACE Score and Prevalence and Adjusted OR of IHD, With and Without Adjustment for Traditional and Psychological Risk Factors

ACE Score	N (%)	OR (95% CI)				Risk Decrement Model I Vs IV, %
		Model I*	Model II†	Model III‡	Model IV§	
0	621 (9.9)	1.0	1.0	1.0	1.0	...
1	445 (9.9)	1.1 (0.9–1.2)	1.1 (0.9–1.2)	1.0 (0.9–1.2)	1.0 (0.9–1.2)	100
2	272 (9.9)	1.2 (0.9–1.4)	1.1 (0.9–1.3)	1.0 (0.9–1.2)	1.0 (0.9–1.2)	100
3	200 (12.1)	1.6 (1.3–1.9)	1.5 (1.3–1.8)	1.4 (1.2–1.6)	1.3 (1.1–1.6)	50
4	130 (12.1)	1.7 (1.4–2.1)	1.6 (1.3–2.0)	1.4 (1.1–1.7)	1.3 (1.0–1.6)	57
5–6	127 (13.9)	2.0 (1.7–2.5)	1.9 (1.5–2.3)	1.6 (1.3–2.0)	1.5 (1.2–1.9)	50
7–8	35 (20.1)	3.6 (2.4–5.3)	3.1 (2.0–4.6)	2.6 (1.7–3.9)	2.3 (1.5–1.9)	50
Ordinal OR		1.2 (1.1–1.2)	1.1 (1.1–1.2)	1.1 (1.1–1.1)	1.1 (1.1–1.1)	
Likelihood ratio (χ^2)		360.5	583.3	558.2	748.3	
df		5	11	7	18	
P (vs model I)			<0.001	<0.001	<0.001	

*Adjusted for covariates (age, sex, race, and education).
 †Adjusted for covariates and traditional risk factors (smoking, physical inactivity, body mass index, diabetes, and hypertension).
 ‡Adjusted for covariates and psychological risk factors (anger and depressed affect).
 §Adjusted for covariates, traditional, and psychological risk factors.

Although our findings have limitation to provide the evidence of the mechanisms by which ACE-related psychological factors increase the risk of IHD, depression and anger have been reported to cause hemodynamic, hemostatic, endocrine and immunologic changes. These changes subsequently might trigger acute or chronic pathophysiological alterations of the coronary artery through the release of catecholamines and corticosteroids that influence platelet function and other parts of the clotting process (hemostasis and thrombosis).^{3,15} Moreover, some ACE-related risk factors appear to be interrelated in increasing the IHD risk, for example, depressed people were reported more likely to smoke and less likely to quit.¹⁶

Other psychological factors, such as insomnia, panic, and stress, were collected and assessed. Although they had a positive graded relation to ACE score, there were no additional mediating effects of these variables for ACE-IHD relation.

Our study has several strengths. First, participants were unaware that their IHD history, which was recorded during a routine clinical examination, would be followed by a subsequent survey about ACEs, eliminating any bias toward attributing health problems such as IHD to ACEs. Second, estimates of the prevalence of ACEs in the present study are similar to estimates from nationally representative surveys,¹⁷ indicating that the experiences of participants in this study are comparable to these of the general adult population. Finally, a wide range of interrelated ACEs¹⁸ was studied, enabling us to assess the relation of each ACE to the risk of IHD and their cumulative deleterious effect on this disease. To our knowledge, this study is the first of its kind to demonstrate the association between a wide range of stressful or traumatic childhood experiences and IHD in adulthood.

Several potential limitations need to be considered when interpreting our results. First, our findings were based on retrospective survey and could not explore biological mechanisms linking ACEs to IHD; however, they offered substantial evidence of a strong graded association between ACEs and adult IHD. Second, underreporting of IHD probably occurred, because IHD is frequently subclinical or asymptomatic; and because most IHD is clinically manifested later in life, younger adults who suffered childhood trauma may not have had enough time to develop the clinical signs and symptoms. Finally, because of the sensitive nature of questions about ACEs and affective problems, the responses probably represent an underreporting of their actual occurrence. When both exposure (ACE) and outcome (IHD) are likely to be underreported, this may have biased the results for the ACE-IHD relation toward the null.¹²

To date, efforts to prevent IHD have focused on behavioral interventions, such as smoking cessation, promotion of physical activity, and adoption of healthy eating habits. These changes are often either not realized or achieved with difficulty. The findings of this study may improve public health efforts by identifying the life experiences that underlie

the more obvious behavioral risk factors. It is important to understand that engagement in these risk factors may commonly be used to compensate for the chronic stress caused by ACEs that are overwhelmingly unrecognized. Thus, recognition, treatment, and prevention of ACEs may provide an important avenue for the prevention of IHD.

Acknowledgments

The ACE study was supported under cooperative agreement No. TS-44-10/11 from the Centers for Disease Control and Prevention through the Association of Teachers of Preventive Medicine, and a grant from the Garfield Memorial Fund. Dr Dong was supported by this cooperative agreement.

References

1. Wielgosz AT, Nolan RP. Biobehavioral factors in the context of ischemic cardiovascular diseases. *J Psychosom Res*. 2000;48:339–345.
2. Williams JE, Paton CC, Siegler IC, et al. Anger proneness predicts coronary artery heart disease risk: prospective analysis from the atherosclerosis risk in communities (ARIC) study. *Circulation*. 2000;101:2034–2039.
3. Carney RM, Blumenthal JA, Stein PK, et al. Depression, heart rate variability, and acute myocardial infarction. *Circulation*. 2001;104:2024–2028.
4. Anda R, Williamson D, Jones D, et al. Depressed affect, hopelessness, and the risk of ischemic heart disease in a cohort of US adults. *Epidemiology*. 1993;4:285–294.
5. Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: the Adverse Childhood Experiences (ACE) Study. *Am J Prev Med*. 1998;14:245–258.
6. Anda RF, Croft JB, Felitti VJ, et al. Adverse childhood experiences and smoking during adolescence and adulthood. *JAMA*. 1999;282:1652–1658.
7. Straus M, Gelles RJ. *Physical Violence in American Families: Risk Factors and Adaptations to Violence in 8,145 Families*. New Brunswick, NJ: Transaction Press; 1990.
8. Wyatt GE. The sexual abuse of Afro-American and white-American women in childhood. *Child Abuse Negl*. 1985;9:507–519.
9. Edwards VJ, Anda RF, Nordenberg DF, et al. Bias assessment for child abuse survey: factors affecting probability of response to a survey about childhood abuse. *Child Abuse Negl*. 2001;25:307–312.
10. Fleiss JL. *Statistical Methods for Rates and Proportions*. 2nd ed. New York: John Wiley & Sons; 1981.
11. Burnam MA, Wells KB, Leake B, et al. Development of a brief screening instrument for detecting depressive disorders. *Med Care*. 1988;26:775–789.
12. Rothman KJ. *Modern Epidemiology*. 2nd ed. Philadelphia: Lippincott-Raven; 1998.
13. Dong M, Dube SR, Felitti VJ, et al. Adverse childhood experiences and self-reported liver disease: New insights into the causal pathway. *Arch Intern Med*. 2003;163:1949–1956.
14. Perry BD, Pollard R. Homeostasis, stress, trauma, and adaptation: a neurodevelopmental view of childhood trauma. *Child Adolesc Psychiatr Clin N Am*. 1998;7:33–51.
15. Laghrissi-Thode F, Wagner WR, Pollock BG, et al. Elevated platelet factor 4 and β -thromboglobulin plasma levels in depressed patients with ischemic heart disease. *Biol Psychiatry*. 1997;42:290–295.
16. Anda RF, Williamson DF, Escobedo LG, et al. Depression and the dynamics of smoking: a national perspective. *JAMA*. 1990;264:1541–1545.
17. Finkelhor D, Hotelling G, Lewis IA, et al. Sexual abuse in a national survey of adult men and women: prevalence, characteristics, and risk factors. *Child Abuse Negl*. 1990;14:19–28.
18. Dong M, Anda RF, Felitti VJ, et al. The interrelatedness of multiple forms of childhood abuse, neglect, and household dysfunction. *Child Abuse Negl*. 2004;28:771–784.