Long-Term Consequences of Early Trauma on Coronary Heart Disease: Role of Familial Factors


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Abstract

Early childhood trauma has been associated with increased risk for subsequent coronary heart disease (CHD), but little is known regarding what role genetic and shared familial factors play in this relationship. Early trauma was measured retrospectively in 562 male middle-aged twins with the Early Trauma Inventory. CHD was assessed by history and by myocardial perfusion imaging with positron emission tomography $^{13}$N ammonia. Coronary flow reserve, a measure of coronary microcirculatory function, was defined as the ratio of myocardial blood flow at rest to flow during stress. Early trauma was associated with a higher prevalence of CHD by clinical history, OR= 1.48 per early trauma inventory quartile increase, 95% CI [1.18, 1.86]. When within- and between-pair effects were estimated, only the between-pair association was significant, OR = 1.76, 95% CI [1.30, 2.40], showing that the odds of CHD in the twin pair increased as the average early trauma exposure in the pair increased. A marginal between-pair (but not within-pair) relationship was also found between early trauma and coronary flow reserve ($n = 416$, unstandardized $B = −0.04$, $SE B = 0.02$, $p = .036$). In conclusion, early trauma was associated with CHD and familial factors played a key role.

Growing evidence points to a possible link between psychological trauma occurring early in life and coronary heart disease (CHD; Dong et al., 2004; Rich-Edwards et al., 2012). It is possible that familial factors confound the association between early trauma and CHD. Specifically, early trauma could be a marker of unmeasured at-risk familial environment, including, for example, adverse parental/prenatal factors, lower socioeconomic status, and poor health behaviors in the original family.
To date, we know of only one study that has investigated the link between early trauma and CHD using objective measures of CHD (Rich-Edwards et al., 2012). Positron emission tomography allows myocardial blood flow quantification and computation of coronary flow reserve, which, in the absence of epicardial stenosis, is a noninvasive assessment of coronary microvascular function, an early indicator of CHD. In a sample of adult twins, we examined the relationship between retrospectively assessed early trauma and CHD in adulthood, and whether familial or genetic factors confound the association (MacGregor, Snieder, Schork, & Spector, 2000).

Method

Participants and Procedure

The current study examined the relationship between early trauma and CHD using previously collected data from the Emory Twin Study (ETS). The ETS included middle-aged male monozygotic and dizygotic twins from the Vietnam Era Twin Registry (Goldberg, Curran, Vitek, Henderson, & Boyko, 2002). Study details, procedures, measurements, and protocols have been provided in previous publications (Vaccarino et al., 2009, 2013). The sample included twin pairs discordant for major depression, twin pairs discordant for posttraumatic stress disorder (PTSD), and twin pairs free of major depression or PTSD. Twins were examined together at the Atlanta Clinical and Translational Science Institute (ACTSI) Clinical Research Network site at Emory Hospital. The original study protocol was approved by the Emory University Institutional Review Board, and informed consent was obtained from all subjects.

The study sample consisted of 562 (281 pairs) middle-aged male twins with a mean age of 55.46 years and a SD of 3.13 years. There were 67% of participants who had greater than a high school education, 75.9% who were married, and 73.1% who were employed.

Measures

Childhood traumatic experiences, before age 18, were measured retrospectively with the 27-item Early Trauma Inventory (ETI) self-report short form, a validated measurement of childhood trauma in the physical abuse domain (five items, e.g., “Were you ever slapped in the face with an open hand?”), emotional abuse domain (five items, e.g., “Were you often put down or ridiculed?”), sexual abuse domain (six items related to unwanted sexual exposure or contact, e.g., “Were you ever touched in an intimate or private part of your body?”), and general trauma (11 items, e.g., “Were you ever exposed to a life-threatening natural disaster?”; Bremner, Bolus, & Mayer, 2007). Participants responded yes or no to each question. A total ETI score with a range of 0 to 27 was computed and scored as a continuous variable, as well as categorized as ETI quartiles. The Cronbach’s α in the sample was .77. Medical history and behavioral factor information were obtained using standardized forms and questions from population studies. Symptomatic CHD included a prior myocardial infarction based on a physician-reported diagnosis or prior coronary revascularization procedures (coronary bypass surgery or percutaneous coronary angioplasty). Psychiatric diagnoses (history of depression, PTSD, alcohol and drug abuse) were assessed using the Structured Clinical Interview for DSM-IV (First, Spitzer, Williams,
Habitual physical activity was determined using the Baecke Questionnaire, a 16-question instrument documenting level of physical activity at work, during sports and nonsports activities. The global physical activity score was used in the analysis with a possible score of 0 to 15 (Richardson, Ainsworth, Wu, Jacobs, & Leon, 1995). Body mass index (BMI) was calculated as measured weight in pounds divided by the square of measured height in inches. Smoking status was determined using standardized questionnaires from population studies (Howard et al., 1998). We classified participants as never smokers—those who reported that they never smoked regularly—current smokers—those currently smoking cigarettes regularly—and past smokers—those who reported smoking more than 100 cigarettes in the past.

Twins underwent imaging of myocardial blood flow with positron emission tomography measurement of $^{13}$N ammonia during a single imaging session, as previously described (Vaccarino et al., 2009). Coronary flow reserve, the primary objective outcome, was defined as the ratio of myocardial blood flow during adenosine-induced stress to myocardial blood flow at rest across all 20 segments. We also examined the stress total severity score, a quantitative measure of abnormal perfusion in the epicardial coronary vessels (Garcia et al., 2007).

**Data Analysis**

We used generalized estimating equation models for categorical variables and mixed effects models for continuous variables with a random intercept for each pair (Carlin, Gurrin, Sterne, Morley, & Dwyer, 2005). All data met the statistical requirements of the analysis used. The distribution of the continuous outcome measures coronary flow reserve and stress total severity score was skewed; therefore, values were log transformed. The association between early trauma and CHD, with shared genetic and environmental factors in the model, was examined using generalized estimating equation models adapted for twin studies. The between-twin-pair estimate was the twin-pair average for the independent variable and the within-twin-pair estimate represented the individual twin difference from the twin-pair average. The within-pair analysis was a matched-pair analysis comparing twins discordant for ETI, using ETI as a categorical variable (twins differing for at least one ETI quartile). This approach included shared demographic, familial, and early environmental factors in the model. If the within-pair effects were smaller than effects seen when twins were analyzed as separate individuals, this was evidence that there was confounding by factors shared by co-twins or familial effects (McGue, 2010). Significance level was set at .05, two-sided. Because of missing data on BMI and physical activity, six (< 2%) twins were excluded from multivariable analyses. In addition, twins missing myocardial blood flow quantitation (146, 26%, twins) and perfusion data (92, 16%, twins) were excluded from the analyses involving these measures. SAS software version 9.3 was used.

**Results**

Individuals with symptomatic CHD had higher levels of early trauma (all $p$s < .01, Table 1). After adjusting for age, increasing exposure to early trauma was associated with 56.7% higher odds of symptomatic CHD per each increasing ETI quartile level (Table 2).
Adjustment for education, behavioral risk factors (alcohol and drug abuse, BMI, smoking status, and physical activity), and psychological risk factors (depression and PTSD) did not affect this association. Results were similar when examining myocardial infarction and coronary revascularization separately. Within-pair analyses did not result in any significant associations. No within-pair association was also noted when comparing twins discordant for 1 ETI quartile level (n= 110) or ≥2 ETI quartile levels (n= 50). No significant interaction between ETI and zygosity was found.

Comparing across twin pairs (between-pair effects), early trauma was associated with 76.4% higher odds of symptomatic CHD per each increasing ETI quartile level (Table 2). The odds of CHD in the twin pair increased as the average early trauma exposure in the pair increased, expressed as incremental ETI quartiles before and after adjusting for age, education, and behavioral and psychological risk factors (Table 2).

In twins analyzed as individuals, early trauma was not significantly related to coronary flow reserve (n= 416, unstandardized B = −0.01, SE= 0.01, p= .471), nor was it related to stress total severity score (n = 470, B = −0.02, SE= 0.06, p= .749. There was also no significant association within twin pairs discordant for early trauma. The between-pair association for coronary flow reserve, however, was significant after age adjustment (n = 416, B = −0.04, SE= 0.02, p= .036), although it was no longer significant after adjusting for education, and behavioral and psychological risk factors (n = 416, B = −0.02, SE = 0.02, p = .172).

**Discussion**

We found that early trauma was associated with symptomatic CHD, independent of demographic, cardiovascular, and behavioral and psychological risk factors. Familial factors, however, were implicated in this relationship because no significant differences in CHD were observed within twin pairs discordant for early trauma exposure. Between twin pairs, as the exposure to early trauma increased, the odds of CHD in the twin pair also increased. Because increased abuse severity is associated with higher levels of other risk factors in the family environment (Nelson et al., 2002), it may not be possible to fully separate the adverse effects of abuse from other unhealthy environmental factors in high-risk families. The null findings within pairs and the robust finding between pairs could also be due to the fact that the most pronounced trauma exposure occurred in families where both twins were abused, and these concordant twins were excluded from the within-pair analysis. The between-pair effect for early trauma and CHD was supported by a similar, albeit marginal, association found for coronary flow reserve, an objective indicator of CHD. These data support a link between early trauma and CHD, which is in part due to unfavorable familial factors. This is the first study of which we are aware to implicate familial factors, using a twin design, in the association between early trauma and CHD.

Our sample was mostly White and restricted to middle-aged male veterans, so it remains unclear the extent to which these results are generalizable to other groups. In addition, the cross-sectional design precludes our ability to infer causality. Recall bias could be a problem; however, underreporting tends to occur more often than false reporting (Fergusson, Horwood, & Woodward, 2000). Another limitation was that we were unable to confirm...
CHD through review of medical records. Our assessment, however, was based on reports of
diagnoses by physicians and previous hospitalizations and procedures for CHD, which was
shown to be relatively accurate (Barr, Tonkin, Welborn, & Shaw, 2009). Lastly, the short-
form ETI survey did not allow us to determine when the early trauma occurred in life, which
may be important (Gershon, Sudheimer, Tirouvanziam, Williams, & O’Hara, 2013). Future
studies should address how trauma during different early life stages may play a role in
subsequent CHD risk. In addition, future research including more diverse populations and
prospective assessments of CHD events continues to be needed in this field. Future research
should also elucidate the specific familial mechanisms involved in the relationship between
exposure to childhood trauma and CHD risk. This information should help design preventive
strategies to decrease the long-term adverse cardiovascular effects of early life trauma.

Acknowledgments

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Table 1
Prevalence of Coronary Heart Disease by Quartile of Early Trauma Inventory Score

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>CHD events</th>
<th>% CHD events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total symptomatic CHD by ETI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>162</td>
<td>7</td>
<td>4.3</td>
</tr>
<tr>
<td>Q2</td>
<td>136</td>
<td>19</td>
<td>14.0</td>
</tr>
<tr>
<td>Q3</td>
<td>144</td>
<td>19</td>
<td>13.2</td>
</tr>
<tr>
<td>Q4</td>
<td>120</td>
<td>24</td>
<td>20.0</td>
</tr>
<tr>
<td>Myocardial infarction by ETI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>162</td>
<td>3</td>
<td>1.9</td>
</tr>
<tr>
<td>Q2</td>
<td>136</td>
<td>5</td>
<td>3.7</td>
</tr>
<tr>
<td>Q3</td>
<td>144</td>
<td>10</td>
<td>6.9</td>
</tr>
<tr>
<td>Q4</td>
<td>120</td>
<td>13</td>
<td>10.8</td>
</tr>
<tr>
<td>Coronary revascularization by ETI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1</td>
<td>162</td>
<td>4</td>
<td>2.5</td>
</tr>
<tr>
<td>Q2</td>
<td>136</td>
<td>8</td>
<td>5.9</td>
</tr>
<tr>
<td>Q3</td>
<td>144</td>
<td>12</td>
<td>8.3</td>
</tr>
<tr>
<td>Q4</td>
<td>120</td>
<td>15</td>
<td>12.5</td>
</tr>
</tbody>
</table>

Note: CHD = coronary heart disease; ETI = Early Trauma Inventory; Q = quartile.
Table 2
Cumulative Sequential Models of the Relationship Between Early Trauma Exposure and Symptomatic CHD

<table>
<thead>
<tr>
<th>Model</th>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall sample</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Unadjusted (n = 562)</td>
<td>1.48</td>
<td>[1.18, 1.86]</td>
</tr>
<tr>
<td>2</td>
<td>Adjusted for age (n = 562)</td>
<td>1.57</td>
<td>[1.24, 1.98]</td>
</tr>
<tr>
<td>3</td>
<td>Further adjusted for education and behavioral factors&lt;sup&gt;a&lt;/sup&gt; (n = 555)</td>
<td>1.42</td>
<td>[1.12, 1.81]</td>
</tr>
<tr>
<td>4</td>
<td>Further adjusted for psychological factors&lt;sup&gt;b&lt;/sup&gt; (n = 554)</td>
<td>1.37</td>
<td>[1.07, 1.76]</td>
</tr>
<tr>
<td>Within-pair effects&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Unadjusted (n = 562)</td>
<td>1.12</td>
<td>[0.75, 1.65]</td>
</tr>
<tr>
<td>3</td>
<td>Further adjusted for education and behavioral factors&lt;sup&gt;a&lt;/sup&gt; (n = 555)</td>
<td>0.96</td>
<td>[0.62, 1.49]</td>
</tr>
<tr>
<td>4</td>
<td>Further adjusted for psychological factors&lt;sup&gt;b&lt;/sup&gt; (n = 554)</td>
<td>0.96</td>
<td>[0.62, 1.49]</td>
</tr>
<tr>
<td>Between-pair effects&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Unadjusted (n = 562)</td>
<td>1.76</td>
<td>[1.30, 2.40]</td>
</tr>
<tr>
<td>2</td>
<td>Adjusted for Age (n = 562)</td>
<td>1.94</td>
<td>[1.43, 2.64]</td>
</tr>
<tr>
<td>3</td>
<td>Further adjusted for education and behavioral factors&lt;sup&gt;a&lt;/sup&gt; (n = 555)</td>
<td>1.81</td>
<td>[1.31, 2.49]</td>
</tr>
<tr>
<td>4</td>
<td>Further adjusted for psychological factors&lt;sup&gt;b&lt;/sup&gt; (n = 554)</td>
<td>1.76</td>
<td>[1.26, 2.45]</td>
</tr>
</tbody>
</table>

Note: Each model includes all variables in the previous model. Values presented are odds ratios (ORs) of early trauma exposure on coronary heart disease. The ORs describe the increase in odds of outcome for each incremental Early Trauma Inventory (ETI) quartile difference. CHD = coronary heart disease.

<sup>a</sup>Behavioral factors include alcohol and drug abuse, body mass index, smoking status (current/past smoker) and physical activity.

<sup>b</sup>Psychological factors include depression and posttraumatic stress disorder.

<sup>c</sup>For the within-pair effects, the OR describes the increase in odds of CHD per each incremental ETI quartile difference, comparing twins in each pair. Because age does not vary within twin pairs, Step 2 was removed.

<sup>d</sup>For the between-pair effects, the OR describes the increase in odds of CHD for the twin pair (describing the average odds for the two twins in each pair) per each incremental ETI quartile difference, across twin pairs.