

Elevated Inflammation Levels in Depressed Adults With a History of Childhood Maltreatment

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Context: The association between depression and inflammation is inconsistent across research samples.

Objective: To test whether a history of childhood maltreatment could identify a subgroup of depressed individuals with elevated inflammation levels, thus helping to explain previous inconsistencies.

Design: Prospective longitudinal cohort study.

Setting: New Zealand.

Participants: A representative birth cohort of 1000 individuals was followed up to age 32 years as part of the Dunedin Multidisciplinary Health and Development Study. Study members were assessed for history of childhood maltreatment and current depression.

Main Outcome Measures: Inflammation was assessed using a clinically relevant categorical measure of high-sensitivity C-reactive protein (>3 mg/L) and a dimensional inflammation factor indexing the shared variance of continuous measures of high-sensitivity C-reactive protein, fibrinogen, and white blood cells.

Results: Although depression was associated with high levels of high-sensitivity C-reactive protein (relative

risk, 1.45; 95% confidence interval, 1.06-1.99), this association was significantly attenuated and no longer significant when the effect of childhood maltreatment was taken into account. Individuals with current depression and a history of childhood maltreatment were more likely to have high levels of high-sensitivity C-reactive protein compared with control subjects (n=27; relative risk, 2.07; 95% confidence interval, 1.23-3.47). In contrast, individuals with current depression only had a nonsignificant elevation in risk (n=109; relative risk, 1.40; 95% confidence interval, 0.97-2.01). Results were generalizable to the inflammation factor. The elevated inflammation levels in individuals who were both depressed and maltreated were not explained by correlated risk factors such as depression recurrence, low socioeconomic status in childhood or adulthood, poor health, or smoking.

Conclusions: A history of childhood maltreatment contributes to the co-occurrence of depression and inflammation. Information about experiences of childhood maltreatment may help to identify depressed individuals with elevated inflammation levels and, thus, at greater risk of cardiovascular disease.

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MAJOR DEPRESSION IS A multisystemic disorder that affects both brain and bodily functions.¹ Increasing evidence suggests that inflammation may contribute to the link between psychological and somatic symptoms in depressed individuals.² For example, depression and cardiovascular disease often co-occur,^{3,4} and inflammation has been associated with both conditions.^{5,6} However, not all individuals with depression have elevated levels of inflammation.⁵ Those who do could be at highest risk for cardiovascular disease. Evidence that childhood maltreatment, a major risk factor for depression, predicts inflammation in adulthood⁷ led us to test the hypothesis that a history of

maltreatment could help to identify depressed individuals with elevated levels of inflammation.

Inflammation may be related to depression through 2-way neuroimmunoenocrine interactions. On the one hand, brain functioning regulates secretion of glucocorticoid hormones, and glucocorticoids can inhibit inflammation processes.⁸ On the other hand, inflammation reduces glucocorticoid signaling, and reduced glucocorticoid signaling may lead to abnormal brain functioning.⁹ Depressed individuals often have impaired glucocorticoid signaling¹⁰ and may, therefore, be at higher risk of inflammation.¹¹

Inflammation is also related to cardiovascular disease through its involvement in the pathophysiology of atherosclero-

sis.¹² Even mild elevation in inflammation levels seems to predict increased risk of cardiovascular disease in apparently healthy individuals.⁶ Moreover, therapeutic reduction in inflammation levels decreases risk of cardiovascular disease.¹³ For these reasons, a marker of inflammation, high-sensitivity C-reactive protein (hsCRP), has been endorsed as an adjunct to traditional risk factor screening for cardiovascular disease.¹⁴

Inflammation has, therefore, been hypothesized to partly explain the observed comorbidity between depression and cardiovascular disease,² 2 leading causes of disability worldwide. However, studies testing the association between depression and inflammation have reported inconsistent results.⁵ This inconsistency could be due to heterogeneity in the etiologic pathways leading to a diagnosis of depression. For example, it is possible that inflammation could be influenced by etiologic factors associated with depression rather than by depression itself. Consistent with this hypothesis, inflammation persists in individuals with a history of depression even when depressive symptoms are absent.¹⁵ Similarly, poor prognosis of heart disease, which can be influenced by inflammation, persists in individuals with a history of depression even when depressive symptoms have been significantly reduced with treatment.⁴

Initial evidence suggests that depression, inflammation, and cardiovascular disease may share common origins in early-life stress such as childhood maltreatment.^{7,16,17} Experimental research also shows that depressed adults with increased early-life stress have greater inflammatory response to an acute psychosocial stress challenge than nondepressed control individuals, which has been interpreted to suggest that early-life stress might influence long-term inflammation processes in depressed individuals.¹⁸ However, it is unclear whether this experimental finding may translate into clinically relevant changes in inflammation levels.

To better characterize the heterogeneity of inflammation levels in depressed individuals, we tested the hypothesis that childhood maltreatment could predict which depressed adults have clinically relevant levels of inflammation. At age 32 years, study participants were too young to exhibit cardiovascular outcomes; however, levels of inflammation can be used to predict their risk for future cardiovascular disease.¹⁴

METHODS

SAMPLE

Participants were members of the Dunedin Multidisciplinary Health and Development Study. Of infants born in Dunedin, New Zealand, between April 1972 and March 1973, 1037 children (91% of eligible births; 52% male) participated in the first follow-up at age 3 years, constituting the base sample for the longitudinal study. Participants represent the full range of socioeconomic status (SES) in the general population of New Zealand's South Island and are primarily white. Assessments were carried out at ages 3, 5, 7, 9, 11, 13, 15, 18, 21, and 26 years and, most recently, at age 32 years, when we assessed 972 of the 1015 study members (96%) still alive in 2004-2005. The study protocol was approved by the institutional review boards of the participating universities. Study members gave informed consent before participating.

MALTREATMENT IN CHILDHOOD

As previously described,¹⁹ evidence of childhood maltreatment during the first decade of life (age 3-11 years) was ascertained using parental reports, prospective behavioral observations, and retrospective reports by study members once they reached adulthood. First, exposure to maternal rejection (characterizing 14% of study participants) was assessed at age 3 years by observational ratings of mothers' interaction with the study children. Second, exposure to harsh discipline was assessed at ages 7 and 9 years according to parental reports of disciplinary behaviors. Parents scoring in the top decile of the samplewide distribution (10% of participants) were classified as unusually harsh for that time and culture. Third, exposure to disruptive caregiver changes was assessed through age 11 years and was defined by 2 or more changes in the child's primary caregiver (6% of participants). Fourth, exposure to physical abuse through age 11 years (4% of participants) was assessed retrospectively at age 26 years on the basis of study members' reports of severe physical punishment resulting in lasting bruising or injury. Fifth, exposure to sexual abuse (12% of participants) was assessed retrospectively at age 26 years on the basis of study members' reports of unwanted sexual contact through age 11 years. We derived a cumulative exposure index for each child by counting the number of maltreatment indicators during the first decade of life¹⁹: 64% of children experienced no maltreatment, 27% experienced 1 indicator of maltreatment, and 9% experienced 2 or more indicators of maltreatment. We previously reported that only the experience of 2 or more indicators of childhood maltreatment significantly predicted inflammation in adulthood.⁷ We, therefore, compared individuals with 2 or more maltreatment indicators (hereafter, "maltreated") with individuals without such a maltreatment history ("nonmaltreated").

MAJOR DEPRESSION AT AGE 32 YEARS

Clinical interviews for the diagnosis of depression at age 32 years were carried out using the Diagnostic Interview Schedule²⁰ and DSM-IV criteria.²¹ At age 32 years, the past-year depression prevalence in the Dunedin cohort was 16% (62% female), which is comparable to the past-year prevalence of 12% for individuals 15 to 34 years old in the National Comorbidity Survey.²² Study members who were depressed at age 32 years self-reported mean (SD) impairment ratings of 3.57 (0.99) on a scale of 1 (some impairment) to 5 (severe impairment), reflecting the extent to which depression interfered with their lives. Of individuals with a diagnosis of depression at the assessment at age 32 years, 62% said they sought mental health services in the past year and 31% said they took medication for their disorder.

INFLAMMATION AT AGE 32 YEARS

Physical examinations and venipuncture (always between 4:15 and 4:45 PM) were performed at the assessment at age 32 years; 92% of the participants (n=892) provided blood samples. Pregnant women (n=26) were excluded from the reported analyses.

We assessed 3 measures of inflammation, as follows. High-sensitivity C-reactive protein (in milligrams per liter) was measured with an automated analyzer (Hitachi 917; Roche Diagnostics GmbH, Mannheim, Germany) using a particle-enhanced immunoturbidimetric assay. We used the Centers for Disease Control/American Heart Association definition of high cardiovascular risk (hsCRP >3 mg/L) to identify our risk group.¹⁴ Fibrinogen (in grams per liter) was measured with a fully automated cap piercing coagulation analyzer (CA 1500; Sysmex Corp, Mahberg, Germany). White blood cells ($\times 10^9/L$) were measured using an au-

tomated hematology analyzer (XE2100; Sysmex Corp, Kobe, Japan) with flow cytometry using a semiconductor laser.

We report results for the categorical measure of inflammation, high hsCRP level (>3 mg/L), because of its clinically significant predictive value.¹⁴ In addition, we found that the continuous measures of (log-transformed) hsCRP, fibrinogen, and white blood cells at age 32 years were positively correlated (range, $r=0.20-0.63$). A principal-component analysis identified a single inflammation factor accounting for 59% of the variance in the continuous measures of these 3 markers of inflammation.⁷ Given that all 3 inflammatory measures index long-term risk of cardiovascular disease,²³ a common factor takes full advantage of their predictive values while minimizing measurement errors of the single components. Thus, we also report results for this dimensional inflammation factor to ascertain whether findings are generalizable to continuous measurements of inflammation.

CO-OCCURRING RISK FACTORS AND POTENTIAL MEDIATING VARIABLES

It is possible that depressed individuals with a history of maltreatment are also characterized by factors other than maltreatment that could explain their inflammation risk. Therefore, we considered the following 5 alternative explanatory hypotheses. Moreover, we considered the effect of sex and medications in all adjusted analyses.

Recurrent Depression History

According to the depression history hypothesis, depressed individuals with a history of maltreatment may experience earlier onset of depression and more depressive episodes across their lifetime.¹⁶ In turn, repeated depressive episodes might cumulatively affect inflammation risk.²⁴ Therefore, we controlled for history of recurrent depression, defined as the number of study assessments when members met criteria for the diagnosis of depression. As previously described,²⁵ a diagnosis of depression at ages 11, 13, 15, 18, 21, 26, and 32 years was made using the then age-appropriate version of the Diagnostic Interview Schedule^{20,26,27} and the then current version of the DSM.^{21,28,29}

Low SES in Childhood

According to the childhood risk hypothesis, depressed individuals with a history of maltreatment may have experienced socioeconomic disadvantage in childhood,³⁰ and childhood socioeconomic disadvantage could affect adult inflammation.³¹ Therefore, we controlled for SES in childhood as measured repeatedly from birth through age 15 years using a scale that placed parents' occupation into 1 of 6 categories based on educational achievement and income associated with that occupation in data from the New Zealand census.³² The variable used in our analyses is the average across assessments of the highest SES of either parent.

Low SES in Adulthood

According to the adulthood risk hypothesis, depressed individuals with a history of maltreatment may grow up to be exposed to more socioeconomic disadvantage in adulthood,³⁰ and adult socioeconomic disadvantage could lead to elevated inflammation levels.³³ Therefore, we controlled for SES at the assessment at age 32 years. Study members' current or most recent occupation was coded using a 6-point scale for occupations in New Zealand; homemakers and those not working were rated on the basis of their educational achievement according to criteria included in the New Zealand Socio-economic Index 1996.³⁴

Cardiovascular Risk Cluster

According to the health risk hypothesis, depressed individuals with a history of maltreatment may have poorer health in adulthood,³⁵ and the increase in inflammation levels could reflect a cluster of health risks rather than an influence of maltreatment specifically on inflammation. Therefore, we controlled for a cluster of cardiovascular risk factors. As previously described,⁷ health risk factor clustering was assessed by measuring 6 biomarkers including overweight, high blood pressure, high total cholesterol concentration, low high-density lipoprotein cholesterol concentration, high glycated hemoglobin level, and low maximum oxygen consumption adjusted for body weight. Study members were clustered if they had at least 3 of these risk factors.

Smoking

According to the health behavior hypothesis, depressed individuals with a history of maltreatment are more likely to engage in unhealthy lifestyles, such as smoking,³⁶ which may, in turn, affect their inflammatory risk. Therefore, we controlled for smoking habits by classifying study members as nonsmokers, light smokers (≤ 10 cigarettes per day), moderate smokers (11-20 cigarettes per day), and heavy smokers (> 20 cigarettes per day) according to their self-reports at age 32 years.

Medications

On the day of the assessment at age 32 years, study members were assessed for their use of medications, including antidepressant agents and drugs with anti-inflammatory effect such as systemic corticosteroids, respiratory corticosteroids, nonsteroidal anti-inflammatory drugs, prophylactic aspirin, antigout medications, antirheumatic medications, statins, and estrogens.

STATISTICAL ANALYSIS

To estimate the relative contribution of childhood maltreatment and depression to inflammation in adulthood, we assigned study members to 1 of 4 groups, as follows: control group, with no current depression and no history of maltreatment; depressed-only group, with current depression and no history of maltreatment; maltreated-only group, with no current depression and history of maltreatment; and depressed and maltreated group, with current depression and history of maltreatment. The control group included individuals who were not depressed at age 32 years, when inflammation was measured, although they could have been depressed in the past.

We tested the association between the study groups and categorical high hsCRP measure with Cox regression analysis with constant time of follow-up and robust variance, and the association between the study groups and the continuous inflammation factor with ordinary least-squares regression analysis. The regression models were expanded to include other covariates to test alternative explanations for the association between study groups and inflammation. Sex and medication use were controlled for in all adjusted analyses.

RESULTS

ASSOCIATION OF DEPRESSION WITH INFLAMMATION

Depression was associated with markers of inflammation (high hsCRP level: relative risk [RR], 1.45; 95% confi-

dence interval [CI], 1.06-1.99; inflammation factor: $b=0.18$; 95% CI, 0.00-0.36). However, childhood maltreatment was more common in depressed compared with nondepressed individuals (RR, 2.40; 95% CI, 1.58-3.63), and maltreated individuals had elevated levels of inflammation markers (high hsCRP level: RR, 1.71; 95% CI, 1.22-2.41; inflammation factor: $b=0.36$; 95% CI, 0.14-0.59). Therefore, we tested whether a history of childhood maltreatment could explain the co-occurrence of depression and inflammation. Once the effect of maltreatment history was taken into account, the association between depression and inflammation markers was attenuated and no longer significant (high hsCRP level: RR, 1.35; 95% CI, 0.98-1.86; inflammation factor: $b=0.14$; 95% CI, -0.04 to 0.32). The Sobel-Goodman test confirmed a statistically significant attenuation of the association between depression and inflammation markers after adjustment for maltreatment history (reduction of 19.2% for hsCRP level, $z=2.277$, $P=.02$; reduction of 22.2% for the inflammation factor, $z=2.451$, $P=.01$). As a further test of this observation, we hypothesized that if childhood maltreatment had an important role in explaining the heterogeneity of inflammation levels in depressed individuals, elevated inflammation levels would be present in depressed individuals with a history of maltreatment but not in those without a history of maltreatment.

A SUBGROUP OF DEPRESSED INDIVIDUALS EXHIBITS ELEVATED INFLAMMATION LEVELS

Table 1 gives the descriptive statistics for inflammatory markers stratified by the 4 study groups: control group, depressed-only group, maltreated-only group, and depressed and maltreated group. Individuals in the depressed and maltreated group and, to a lesser extent, the maltreated-only group were more likely to have high hsCRP levels and higher mean levels of the inflammation factor compared with individuals in the control group. In contrast, individuals in the depressed-only group had a nonsignificant elevation in inflammatory markers (**Figure**).

DIFFERENCES BETWEEN DEPRESSED AND MALTREATED INDIVIDUALS AND DEPRESSED-ONLY INDIVIDUALS

We tested whether, within depressed individuals, those with a history of maltreatment had higher inflammatory risk than individuals without a history of maltreatment. This test was compromised by low power because it involved comparing 27 depressed and maltreated individuals with 109 depressed-only individuals. Nevertheless, results are instructive. Individuals with depression who were maltreated were 1.48 times (95% CI, 0.82-2.68) more likely to have high hsCRP levels and had higher mean levels of the inflammation factor (0.48 vs 0.07; $F=2.88$; $P=.09$) than were individuals with depression only, with effect sizes of Cohen $d=0.26$ and $d=0.35$, respectively.

We also tested whether depressed and maltreated individuals differed from depressed-only individuals in their depressive symptoms profile. We found no systematic difference in symptom presentation (**Table 2**), which suggests that it is impossible to infer maltreatment history from the depressive symptoms profile alone.

ROLE OF OTHER KNOWN RISK FACTORS FOR INFLAMMATION

Consistent with the depression history hypothesis, depressed and maltreated individuals were more likely to have experienced multiple depressive episodes (Table 1). In turn, individuals with recurrent depression showed nonsignificant elevation in risk for high hsCRP (RR, 1.11; 95% CI, 0.94-1.31) and significantly elevated mean levels of the inflammation factor ($b=0.09$; 95% CI, 0.00-0.17). However, after controlling for recurrent depression history, depressed and maltreated individuals showed significant elevation in inflammation markers (**Table 3**, model 3).

Consistent with the childhood risk hypothesis, depressed and maltreated individuals were more likely to have grown up in families with low SES (Table 1). In turn, low SES in childhood was associated with elevated inflammation in adulthood (high hsCRP level: RR, 1.36; 95% CI, 1.09-1.68; inflammation factor: $b=0.26$; 95% CI, 0.15-0.37). However, after controlling for the effect of SES in childhood, depressed and maltreated individuals showed significant elevation in the inflammation markers (Table 3, model 4).

Consistent with the adulthood risk hypothesis, depressed and maltreated individuals were more likely to have low SES in adulthood (Table 1). In turn, low SES in adulthood was associated with elevated inflammation in adulthood (high hsCRP: RR, 1.17; 95% CI, 1.00-1.38; inflammation factor: $b=0.13$; 95% CI, 0.05-0.21). However, after controlling for the effects of SES in adulthood, depressed and maltreated individuals showed significant elevation in the inflammation markers (Table 3, model 5).

Turning to the health risk hypothesis, we found that the prevalence of the cardiovascular risk cluster did not differ across study groups (Table 1). The cardiovascular risk cluster was associated with elevated inflammation in adulthood (high hsCRP: RR, 2.39; 95% CI, 1.84-3.10; inflammation factor: $b=0.87$; 95% CI, 0.70-1.04). After controlling for cardiovascular risk clustering, depressed and maltreated individuals showed significant elevation in inflammation markers (Table 3, model 6).

Consistent with the health-behavior hypothesis, depressed and maltreated individuals were more likely to smoke (Table 1). In turn, smoking was associated with elevated mean levels of the inflammation factor ($b=0.13$; 95% CI, 0.06-0.20) but was not associated with the risk for high hsCRP levels (RR, 0.98; 95% CI, 0.84-1.13). After controlling for smoking, depressed and maltreated individuals showed significant elevation in inflammation markers (Table 3, model 7).

CONCLUSIONS

This study addressed the possible developmental origins of heterogeneity in inflammation markers' levels among depressed individuals. The results suggest that a history of maltreatment has a significant role in explaining the co-occurrence of depression and inflammation

Table 1. Descriptive Statistics and Association Analysis for Inflammation Markers and Potential Intervening Variables Stratified by the 4 Study Groups

Variable	No. (%) of Individuals				Differences Between the 4 Groups
	Control Group (n=673)	Depressed-Only Group (n=109)	Maltreated-Only Group (n=56)	Depressed and Maltreated Group (n=27)	
Inflammation Markers					
C-reactive protein > 3 mg/L	120 (17.9)	27 (25.0)	17 (30.4)	10 (37)	$\chi^2=12.05$, $P=.007$
<i>Differences between study groups and control group^a</i>	...	$\chi^2=3.05$, $P=.08$	$\chi^2=5.23$, $P=.02$	$\chi^2=6.26$, $P=.01$...
Inflammation factor, mean (SE)	-0.06 (0.04)	0.07 (0.10)	0.25 (0.15)	0.48 (0.24)	$F=4.17$, $P=.006$
<i>Differences between study groups and control group</i>	...	$F=1.51$, $P=.22$	$F=5.33$, $P=.02$	$F=7.90$, $P=.005$...
Potential Intervening Variables					
Depression recurrence, No. of episodes					
0	454 (67.5)	0	38 (67.9)	0	$\chi^2=259.22$, $P<.001$
1	146 (21.7)	48 (44.0)	9 (16.1)	7 (25.9)	
≥2	73 (10.9)	61 (56.0)	9 (16.1)	20 (74.1)	
<i>Differences between study groups and control group</i>	...	$\chi^2=203.84$, $P<.001$	$\chi^2=2.02$, $P=.36$	$\chi^2=96.54$, $P<.001$...
SES in Childhood					
Low	112 (16.7)	27 (24.8)	22 (40.0)	9 (33.3)	$\chi^2=24.91$, $P<.001$
Medium	449 (67.1)	61 (56.0)	25 (45.5)	15 (55.6)	
High	108 (16.2)	21 (19.3)	8 (14.6)	3 (11.1)	
<i>Differences between study groups and control group</i>	...	$\chi^2=5.71$, $P=.06$	$\chi^2=18.58$, $P<.001$	$\chi^2=5.04$, $P=.08$...
SES in Adulthood					
Low	187 (27.8)	45 (41.7)	24 (42.9)	10 (37.0)	$\chi^2=20.20$, $P=.003$
Medium	234 (34.8)	37 (34.3)	14 (25.0)	13 (48.2)	
High	252 (37.4)	26 (24.1)	18 (32.1)	4 (14.8)	
<i>Differences between study groups and control group</i>	...	$\chi^2=10.72$, $P=.005$	$\chi^2=5.90$, $P=.05$	$\chi^2=5.74$, $P=.06$...
Cardiovascular Risk					
Cardiovascular risk cluster	111 (16.5)	18 (16.5)	10 (17.9)	5 (18.5)	$\chi^2=0.14$, $P=.99$
<i>Differences between study groups and control group</i>	...	$\chi^2=0.00$, $P=.99$	$\chi^2=0.07$, $P=.80$	$\chi^2=0.08$, $P=.78$...
Smoking					
Cigarettes, No. per d					
0	410 (60.9)	62 (57.4)	21 (37.5)	9 (33.3)	$\chi^2=39.84$, $P<.001$
≤10	118 (17.5)	22 (20.4)	12 (21.4)	3 (11.1)	
11-20	117 (17.4)	21 (19.4)	16 (28.6)	9 (33.3)	
>20	28 (4.2)	3 (2.8)	7 (12.5)	6 (22.2)	
<i>Differences between study groups and control group</i>	...	$\chi^2=1.28$, $P=.73$	$\chi^2=16.27$, $P=.001$	$\chi^2=25.02$, $P<.001$...
Other Variables					
Male sex	377 (56.0)	43 (39.5)	25 (44.6)	12 (44.4)	$\chi^2=12.84$, $P=.005$
<i>Differences between study groups and control group</i>	...	$\chi^2=10.36$, $P=.001$	$\chi^2=2.70$, $P=.10$	$\chi^2=1.41$, $P=.24$...
Medication use	218 (32.7)	25 (23.2)	11 (20.4)	5 (18.5)	$\chi^2=8.71$, $P=.03$
<i>Differences between study groups and control group</i>	...	$\chi^2=3.93$, $P=.05$	$\chi^2=3.49$, $P=.06$	$\chi^2=2.39$, $P=.12$...

Abbreviations: SES, socioeconomic status; ellipses, not applicable.

^aItalicized entries indicate analysis.

in adulthood. Information about experiences of childhood maltreatment may help to identify depressed individuals with elevated inflammation levels and, thus, greater risk of cardiovascular disease.

These new findings should be evaluated along with several study limitations. First, findings from this New Zealand cohort require replication in other studies and in different ethnic groups. However, given the consis-

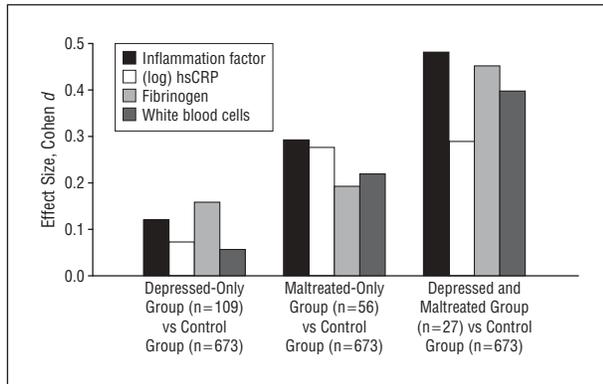


Figure. Differences in effect size (Cohen *d*) units resulting from a priori defined contrasts between control and other study groups. Effect sizes are commonly interpreted as small when equal to 0.2, moderate when equal to 0.5, and large when equal to 0.8. Comparisons between depressed-only individuals vs control individuals showed effect sizes of $d=0.12$ for the inflammation factor, $d=0.07$ for (log) high-sensitivity C-reactive protein (hsCRP), $d=0.16$ for fibrinogen, and $d=0.06$ for white blood cells (WBCs). Comparisons between maltreated-only individuals vs control individuals showed effect sizes of $d=0.29$ for the inflammation factor, $d=0.28$ for (log) hsCRP, $d=0.19$ for fibrinogen, and $d=0.22$ for WBCs. Comparisons between depressed and maltreated individuals vs control individuals showed effect sizes of $d=0.48$ for the inflammation factor, $d=0.29$ for (log) hsCRP, $d=0.45$ for fibrinogen, and $d=0.40$ for WBCs.

Table 2. Descriptive Psychopathology of the Current Depressive Episode in Depressed-Only and Depressed and Maltreated Individuals

Depressive Symptoms	No. (%) of Individuals		Differences Between Groups
	Depressed-Only Group (n=109)	Depressed and Maltreated Group (n=27)	
Depressed mood	102 (94)	21 (78)	$\chi^2=6.25$, $P=.01$
Diminished interest	81 (74)	24 (89)	$\chi^2=2.61$, $P=.11$
Appetite/weight changes			
Decreased appetite/weight loss	75 (69)	18 (67)	$\chi^2=0.05$, $P=.83$
Increased appetite/weight gain	36 (33)	9 (33)	$\chi^2=0.00$, $P=.98$
Sleep changes			
Sleep deficit	83 (76)	25 (93)	$\chi^2=3.58$, $P=.06$
Sleep excess	34 (31)	8 (30)	$\chi^2=0.02$, $P=.88$
Psychomotor changes	87 (80)	25 (93)	$\chi^2=2.43$, $P=.12$
Fatigue	101 (93)	25 (93)	$\chi^2=0.00$, $P=.99$
Guilt/worthlessness	64 (59)	24 (89)	$\chi^2=8.63$, $P=.003$
Concentration problems	103 (95)	25 (93)	$\chi^2=0.14$, $P=.71$
Thoughts of death	49 (45)	16 (59)	$\chi^2=1.77$, $P=.18$

tent effect of childhood maltreatment in explaining depression heterogeneity with regard to other stress biomarkers,³⁷⁻⁴⁰ there is reason to believe that our results may be replicated in other settings. Second, lacking measures of inflammation markers before the onset of de-

Table 3. Group Differences in Predicting Risk of High hsCRP and Inflammation Factor Levels

Variable (Model No. ^a)	Regression Coefficients (95% Confidence Interval)		
	Depressed-Only Group (n=109)	Maltreated-Only Group (n=56)	Depressed and Maltreated Group (n=27)
C-reactive protein > 3 mg/L^b			
(1) Unadjusted	1.40 (0.97 to 2.01)	1.69 (1.10 to 2.60)	2.07 (1.23 to 3.47)
(2) Sex and medication use	1.34 (0.93 to 1.92)	1.61 (1.03 to 2.50)	2.06 (1.21 to 3.51)
(3) Depression recurrence ^c	1.52 (1.00 to 2.34)	1.62 (1.04 to 2.53)	2.41 (1.31 to 4.43)
(4) SES in childhood ^c	1.31 (0.91 to 1.87)	1.52 (0.98 to 2.35)	1.92 (1.12 to 3.29)
(5) SES in adulthood ^c	1.30 (0.90 to 1.87)	1.57 (1.01 to 2.44)	1.97 (1.16 to 3.37)
(6) Cardiovascular risk cluster ^c	1.32 (0.93 to 1.87)	1.56 (1.02 to 2.38)	2.00 (1.21 to 3.32)
(7) Smoking ^c	1.35 (0.94 to 1.94)	1.64 (1.05 to 2.55)	2.13 (1.24 to 3.66)
Inflammation factor^d			
(1) Unadjusted	0.12 (-0.08 to 0.33)	0.31 (0.04 to 0.58)	0.53 (0.15 to 0.91)
(2) Sex and medication use	0.10 (-0.10 to 0.30)	0.27 (0.00 to 0.55)	0.52 (0.14 to 0.90)
(3) Depression recurrence ^c	0.10 (-0.13 to 0.33)	0.27 (0.00 to 0.55)	0.52 (0.12 to 0.92)
(4) SES in childhood ^c	0.09 (-0.11 to 0.29)	0.22 (-0.05 to 0.49)	0.47 (0.10 to 0.85)
(5) SES in adulthood ^c	0.07 (-0.13 to 0.27)	0.26 (-0.02 to 0.53)	0.49 (0.11 to 0.86)
(6) Cardiovascular risk cluster ^c	0.10 (-0.09 to 0.29)	0.25 (0.00 to 0.51)	0.50 (0.14 to 0.85)
(7) Smoking ^c	0.09 (-0.11 to 0.29)	0.21 (-0.06 to 0.48)	0.42 (0.04 to 0.80)

Abbreviations: hsCRP, high-sensitivity C-reactive protein;

SES, socioeconomic status.

^aModel 1 shows the unadjusted analysis. Model 2 shows the analysis adjusted for sex and use of anti-inflammatory medications. Model 3 indexes the depression history hypothesis. Model 4 indexes the childhood risk hypothesis. Model 5 indexes the adulthood risk hypothesis. Model 6 indexes the health risk hypothesis. Model 7 indexes the health behavior hypothesis.

^bCox regression analysis with constant time of follow-up and robust variance. Control individuals (ie, nondepressed nonmaltreated individuals; n=673) were considered the reference group.

^cAdjusted analyses also include sex and medications covariates.

^dOrdinary least-squares regression analysis. Control individuals (ie, nondepressed nonmaltreated individuals; n=673) were considered the reference group.

pression, we were unable to test the direction of the effect. Future research should address this issue. Third, although childhood maltreatment seemed to predict elevated inflammation levels in depressed individuals, some depressed individuals with elevated inflammation levels had not been maltreated. Further studies are needed to discover other factors contributing to the heterogeneity of inflammation marker levels in depression. Nevertheless, the current results may have implications for research, psychiatric nosology, and clinical practice.

With regard to research implications, our findings help to reconcile previous puzzling evidence about the rela-

Table 4. Summary of Brain Imaging, Neuroendocrine, and Immunologic Differences Among Study Groups Compared With the Control Group^a

Variable	Depressed-Only Group	Maltreated-Only Group	Depressed and Maltreated Group
Brain imaging			
Hippocampal volume ⁴⁰	=	?	↓
Psychosocial stress challenge			
Corticotropin ³⁷	=	↑	↑
Cortisol ³⁷	=	=	↑
CRF stimulation test			
Corticotropin ³⁸	↓	↑	↓
Cortisol ³⁸	↓	↓	↓
Corticotropin stimulation test			
Cortisol ³⁸	↓	↓	↓
Dexamethasone (0.5-mg) suppression test			
Corticotropin ³⁹	=	=	↓
Cortisol ³⁹	=	=	↓
Inflammation (present study)			
hsCRP > 3 mg/L	=	↑	↑
Inflammation factor	=	↑	↑

Abbreviations: CRF, corticotropin-releasing factor; hsCRP, high-sensitivity C-reactive protein.

^aAdapted from Newport et al.³⁹ Symbols indicate whether values of different biological markers in study groups are equal (=), increased (↑), or decreased (↓) compared with the control group or whether comparisons are missing (?). Biological differences between depressed and maltreated and depressed-only individuals suggest the existence of a developmental-stress subtype of depression with abnormal stress response and increased risk of medical comorbidity.

tionship between depression and inflammation such as the inconsistency of this association across samples and the persistence of inflammation and cardiovascular disease risk in individuals with a history of depression but no current depression.^{4,5,15} We showed that current depression diagnosis alone is less likely to be related to inflammation risk, but current depression and maltreatment history combined seem to be good predictors of inflammation levels. Moreover, even in the absence of a current diagnosis of depression, maltreatment history alone still confers increased risk of clinically relevant inflammation levels (Table 1 and Figure). This suggests that previous inconsistencies across studies could be owing to variation in the prevalence of childhood maltreatment in different samples. Results also suggest that elevated inflammation levels and cardiovascular disease risk observed in individuals with a history of depression but no current depression may be due to the long-term effect of childhood maltreatment.^{7,17}

With regard to implications for psychiatric nosology, our study adds to a growing body of research that suggests that childhood maltreatment can identify a subgroup of depressed individuals characterized by multiple markers of abnormal stress response. **Table 4** summarizes findings from 3 lines of research. First, reduced volume of the hippocampus, a brain region that regulates the extinction of the stress response, has been reported in depressed and maltreated individuals compared with control individuals but not in depressed-

only individuals.⁴⁰ Second, greater neuroendocrine response to a psychosocial stress test and insufficient glucocorticoid signaling have been reported in depressed and maltreated individuals compared with control individuals but not in depressed-only individuals.³⁷⁻³⁹ Third, consistent with previous experimental evidence,¹⁸ in the present study we report that depressed and maltreated individuals are twice as likely to have clinically relevant levels of hsCRP compared with control individuals while depressed-only individuals exhibit a nonsignificant increase in the risk of high hsCRP. It is possible that a subgroup of depressed individuals with stressful developmental experiences is at highest risk of future disease. Further studies are needed to better characterize individuals with this developmental stress subtype of depression.

With regard to implications for clinical practice, our results support the importance of collecting information about childhood maltreatment from depressed individuals. In our cohort, the information conveyed by maltreatment history was not captured by information about symptom presentation during the depressive episode (Table 2). Moreover, we showed that other commonly assessed factors with potential influence on inflammation processes do not account for the effect of childhood maltreatment on inflammation in adult depressed individuals (Table 3). For these reasons, we suggest that routine assessment of maltreatment history could provide clinicians with necessary information to identify depressed individuals with elevated risk of inflammation and potentially poor health. In turn, the early recognition of the health risk associated with maltreatment history might help to address pressing needs for the care of depressed individuals such as the reduction of the effect of depression on comorbid medical illness.¹

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Incorrect Formatting of Tables 1 and 3. In the article titled "Elevated Inflammation Levels in Depressed Adults With a History of Childhood Maltreatment," by Danese et al, published in the April issue of the *Archives* (2008;65[4]:409-416) Tables 1 and 3 were formatted incorrectly. Table 1, on page 413, should have read as follows:

Table 1. Descriptive Statistics and Association Analysis for Inflammation Markers and Potential Intervening Variables Stratified by the 4 Study Groups

Variable	No. (%) of Individuals				Differences Between the 4 Groups
	Control Group (n=673)	Depressed-Only Group (n=109)	Maltreated-Only Group (n=56)	Depressed and Maltreated Group (n=27)	
Inflammation Markers					
C-reactive protein >3 mg/L	120 (17.9)	27 (25.0)	17 (30.4)	10 (37)	$\chi^2=12.05$, $P=.007$
<i>Differences between study groups and control group^a</i>	...	$\chi^2=3.05$, $P=.08$	$\chi^2=5.23$, $P=.02$	$\chi^2=6.26$, $P=.01$...
Inflammation factor, mean (SE)	-0.06 (0.04)	0.07 (0.10)	0.25 (0.15)	0.48 (0.24)	$F=4.17$, $P=.006$
<i>Differences between study groups and control group</i>	...	$F=1.51$, $P=.22$	$F=5.33$, $P=.02$	$F=7.90$, $P=.005$...
Potential Intervening Variables					
Depression recurrence, No. of episodes					
0	454 (67.5)	0	38 (67.9)	0	$\chi^2=259.22$, $P<.001$
1	146 (21.7)	48 (44.0)	9 (16.1)	7 (25.9)	
≥ 2	73 (10.9)	61 (56.0)	9 (16.1)	20 (74.1)	
<i>Differences between study groups and control group</i>	...	$\chi^2=203.84$, $P<.001$	$\chi^2=2.02$, $P=.36$	$\chi^2=96.54$, $P<.001$...
SES in childhood					
Low	112 (16.7)	27 (24.8)	22 (40.0)	9 (33.3)	$\chi^2=24.91$, $P<.001$
Medium	449 (67.1)	61 (56.0)	25 (45.5)	15 (55.6)	
High	108 (16.2)	21 (19.3)	8 (14.6)	3 (11.1)	
<i>Differences between study groups and control group</i>	...	$\chi^2=5.71$, $P=.06$	$\chi^2=18.58$, $P<.001$	$\chi^2=5.04$, $P=.08$...
SES in adulthood					
Low	187 (27.8)	45 (41.7)	24 (42.9)	10 (37.0)	$\chi^2=20.20$, $P=.003$
Medium	234 (34.8)	37 (34.3)	14 (25.0)	13 (48.2)	
High	252 (37.4)	26 (24.1)	18 (32.1)	4 (14.8)	
<i>Differences between study groups and control group</i>	...	$\chi^2=10.72$, $P=.005$	$\chi^2=5.90$, $P=.05$	$\chi^2=5.74$, $P=.06$...
Cardiovascular risk cluster	111 (16.5)	18 (16.5)	10 (17.9)	5 (18.5)	$\chi^2=0.14$, $P=.99$
<i>Differences between study groups and control group</i>	...	$\chi^2=0.00$, $P=.99$	$\chi^2=0.07$, $P=.80$	$\chi^2=0.08$, $P=.78$...
Smoking, cigarettes per day					
0	410 (60.9)	62 (57.4)	21 (37.5)	9 (33.3)	$\chi^2=39.84$, $P<.001$
≤ 10	118 (17.5)	22 (20.4)	12 (21.4)	3 (11.1)	
11-20	117 (17.4)	21 (19.4)	16 (28.6)	9 (33.3)	
>20	28 (4.2)	3 (2.8)	7 (12.5)	6 (22.2)	
<i>Differences between study groups and control group</i>	...	$\chi^2=1.28$, $P=.73$	$\chi^2=16.27$, $P=.001$	$\chi^2=25.02$, $P<.001$...
Other Variables					
Male sex	377 (56.0)	43 (39.5)	25 (44.6)	12 (44.4)	$\chi^2=12.84$, $P=.005$
<i>Differences between study groups and control group</i>	...	$\chi^2=10.36$, $P=.001$	$\chi^2=2.70$, $P=.10$	$\chi^2=1.41$, $P=.24$...
Medication use	218 (32.7)	25 (23.2)	11 (20.4)	5 (18.5)	$\chi^2=8.71$, $P=.03$
<i>Differences between study groups and control group</i>	...	$\chi^2=3.93$, $P=.05$	$\chi^2=3.49$, $P=.06$	$\chi^2=2.39$, $P=.12$...

Abbreviations: SES, socioeconomic status; ellipses, not applicable.

^a Italicized entries indicate analysis.

In Table 3, on page 414, column 1, the top section of the column under the subheading "C-reactive protein >3 mg/L^b," entries 1 through 7 should have aligned with entries 1 through 7 in the bottom section, under the subheading "Inflammation factor^d."