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Adverse Experience in Childhood as a Developmental Risk Factor for Altered Immune Status in Adulthood

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Compelling evidence is now available that adverse childhood experiences are associated with adult pathology. However, understanding of the pathways and mechanisms underlying these associations is limited. Participants in the European Prospective Investigation into Cancer and Nutrition in Norfolk, UK (EPIC-Norfolk), aged 40 to 80 years, provided an opportunity to investigate the hypothesis that adverse experience in childhood is associated with peripheral leukocyte count in adulthood in the context of a large-scale population-based cohort study. White blood cell counts were available from 11,367 participants and, after a mean interval of 44 months, from 11,857 at a second health check. A self-completion questionnaire that included the assessment of adverse experience during childhood was administered during the interval between health checks. Associations were observed between early adverse experiences and lymphocyte counts at both health checks. Lifestyle factors accounted for about half of this association. Caution is needed in the interpretation of

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these findings that require replication but they may be seen to aid understanding of the mechanisms through which early environmental exposures act.

Key words: abuse, adversity, childhood, cohort studies, immunity, leukocytes

Compelling evidence, gained through clinical and epidemiological studies, has accumulated over the past 20 years for an association between exposure to adverse experience during childhood and an increased likelihood of health impairment in adulthood. Psychopathological outcomes that include alcohol and drug dependence, anxiety, bulimia nervosa, depression, panic and posttraumatic stress disorder, substance abuse, and suicidal behaviors have been most commonly studied (Bifulco, Brown, Moran, Ball, & Campbell, 1998; Bifulco & Moran, 1998; Dinwiddie et al., 2000; Dube et al. 2001; Hope, Power, & Rodgers, 1998; Kendler et al., 1996, 2000; Kendler, Neale, Kessler, Heath, & Eaves, 1992; MacMillan et al., 2001; Molnar, Buka, & Kessler, 2001b; Mullen, King, & Tonge, 2000; Mullen, Martin, Anderson, Romans, & Herbison, 1993, 1996; Nelson et al., 2002; Romans, Martin, Anderson, Oshea, & Mullen, 1995). Other work has revealed associations between adverse childhood experience and physical health risk behaviors and outcomes in adulthood that include current smoking, severe obesity, physical inactivity, fractures, heart disease, and cancer (Felitti et al., 1998; McCauley et al., 1997; Walker et al., 1999). Such associations have most often been established through retrospective recall of single measures of loss through parental death or separation, of deprivation and of family disharmony, of parental psychopathology, and of interpersonal trauma, or most commonly, measures of physical and sexual abuse. Recent evidence from a large-scale retrospective survey of the United States household population (Kessler, Davis, & Kendler, 1997; Molnar et al., 2001b; Molnar, Berkman, & Buka, 2001a) where participants were asked about their exposure to multiple adverse experiences during childhood, provided evidence of strong clustering of these experiences and of additivity in their effects in relation to adult psychiatric disorder. Such evidence of exposure clustering supported by other work (Dube et al., 2001), however, underlined the need for caution expressed by the authors concerning the apparent unique and specific health effects in adulthood of particular adverse experiences in childhood reported in the literature.

Improvement in understanding of the pathways through which early adverse experience may influence the development of adult disease is now thought to depend upon consideration of the interrelationship between psychosocial and biological factors—ideally within a life-course perspective (Cicchetti & Walker, 2001; Kuh, Power, Blane, & Bartley, 1997; Power & Hertzman, 1997, 1999; Power & Matthews, 1998; Power, Matthews, & Manor, 1998). However, given limitations in the availability of such comprehensive data needed to achieve such

objectives within individual studies, evidence is accumulating through animal "models" and through clinical studies of early adverse experience.

Evidence from rodent and primate models of adverse early experience (that include maternal separation or loss, abuse or neglect, and social deprivation) has provided support for the conclusion that such experiences are associated with long-term behavioral, neuroendocrine, and immunological abnormalities together with alterations in brain morphology (Caldji et al., 2001; Coe, 1993, 1999; Sanchez, Ladd, & Plotsky, 2001). These and other studies, for example, (Liu et al., 1997; Sapolsky, 1997) support the conclusion that early maternal behavior and early stress experience serve to program neurobiological development of the hypothalamic–pituitary–adrenal (HPA) axis response in those offspring subject to these circumstances. Study of cell-mediated immunity and survival of adult rhesus monkeys (Lewis, Gluck, Petitto, Hensley, & Ozer, 2000), according to whether they had experienced social deprivation during their first year of life, has also shown mortality to be raised significantly among those who had experienced early social deprivation as compared to those without such experience and associations with differences in cell-mediated immune status.

Study of human brain maturation, available through longitudinal study, has provided evidence that the volume of limbic system structures (septal area, hippocampus, amygdala) continues to increase until around age 16 years and myelination increases to continue into the third decade (Giedd et al., 1999). Use of MRI technology, employed to assess differences in brain morphology between children with chronic posttraumatic stress disorder secondary to maltreatment (that included sexual abuse and being a witness to domestic violence) compared to a group of healthy controls (De Bellis et al., 1999; De Bellis, 2001) has provided findings interpreted as childhood maltreatment having "global and adverse influences on brain development that may be cumulative" (De Bellis, 2001, p. 552) and evidence that men may be more vulnerable than women to the effects of adverse experience on brain structures. An autopsy study of Japanese children (Fukunaga et al., 1992) has provided evidence that adverse experience in childhood can modify immune function. A significant decrease in thymus weight (the organ where T cells mature) was found among children who had been abused or neglected compared to a control group of children (who had died as a result of accident or other cause but without a history of abuse).

These findings contribute to an emerging scientific consensus that early developmental experiences can have pervasive and enduring effects on developmental health through "biological embedding" (Hertzman, 1999; Keating, & Hertzman, 1999) that have been associated with early sexual and physical abuse in childhood (Heim et al. 2000; Heim & Nemeroff, 2001; Heim, Newport, Bonsall, Miller, & Nemeroff, 2001). With this perspective has come an improved understanding of the neurobiology of adverse event interpretation—particularly concerning the role of the hippocampus in storing and recalling episodic memory—and how HPA

activation impacts upon the immune system (Coe 1999; Dhabhar & McEwen, 2001; McEwen, 2001; Spencer, Kalman & Dhabhar, 2001).

Evidence now suggests that stressful experience serves to disturb physiological homeostasis and may result in either immunosuppressive or enhancing effects according to exposure context. Meta-analytic reviews of the relationship between adult stress exposures and immunological assays have shown adult stress exposures to be positively related to the number of circulating white blood cells (Herbert & Cohen, 1993; Zorrilla et al., 2001). Population-based studies have implicated markers of inflammation in the progression of (and mortality from) coronary heart disease and total mortality (Brown, Giles, & Croft, 2001; Elkind, Cheng, Boden-Albala, Paik, & Sacco, 2001; Ernst, Hammerschmidt, Bagge, Matrai, & Dormandy, 1987; James, Knuiman, Divitini, Musk, & Ryan, 1999; Kannel, Anderson, & Wilson, 1992; Lee et al., 2001; Ross, 1999; Sweetnam, Thomas, Yarnell, Baker, & Elwood, 1997; Weiss, Segal, Sparrow, & Wager, 1995). Strong dose–response relationships have been found between adverse childhood experience and immune-mediated endpoints that include heart disease and cancer (Felitti et al., 1998); maltreatment during childhood among a random sample of women has also been found to be significantly associated with increased rates of physician diagnosed minor infectious diseases (Walker et al., 1999). However, investigation of a possible association between early adverse experience and markers of immune system status in adulthood does not appear to have been undertaken. Recently some authors (Dhabhar & McEwen, 2001) have suggested that neurobiological consequences of stress may have a critical evolutionary adaptive role—acting to prepare the immune system for immunological challenge. According to this perspective we might expect an association between adverse experience during childhood and peripheral leukocyte counts in adulthood.

Data collected from participants in the European Prospective Investigation into Cancer and Nutrition in Norfolk (EPIC-Norfolk) (Day et al., 1999; Khaw et al., 2001), a population-based cohort study designed to advance understanding of nutritional and other determinants of chronic disease development, now provide an opportunity for the assessment of the association between measures of adverse experience (including abuse, reported by adults as having occurred before age 16) and enumerative measures of peripheral leukocytes. This article aims to investigate the hypothesis that adverse exposures during childhood are associated with peripheral leukocyte counts in adulthood and whether, if found, the association persists after adjustment for social circumstances, lifestyle factors, psychosocial factors (including adverse event exposures during adulthood), and other known correlates of leukocyte counts (Nieto, Szklo, Folsom, Rock, & Mercuri, 1992; Schwartz & Weiss, 1991). The availability of leukocyte data from two health checks provides an important (within-study) replication and test of consistency.

METHODS

Participants

During 1993–1997 EPIC-Norfolk recruited, through general practice age–sex registers, 30,414 men and women (then) aged 40 to 74 years and resident in East Anglia, UK, when a baseline questionnaire survey was completed. All participants were asked to complete details of their educational qualifications and medical history, including whether a doctor had ever confirmed to them a diagnosis of any of a range of conditions that included cancer, diabetes, heart attack, and stroke. Subsequently, 25,637 participants attended a first, and on average 44 months later, 15,786 attended a second health check. During 1996–2000 an assessment of social and psychological circumstances, based upon the Health and Life Experiences Questionnaire (HLEQ) (Surtees, Wainwright, & Brayne, 2000) and designed according to principles advocated by (Dillman, 1978), was completed by a total of 20,921 participants, representing a response rate of 73.2% of the total eligible EPIC sample. As part of this assessment, details of current (or prior employment) were obtained enabling standard social class allocation according to CASOC (Computer-Assisted Standard Occupational Coding; Elias, Halstead, & Prandy, 1993). Of those participants who completed the HLEQ, 18,248 attended the first and 14,112 attended the second health check, with leukocyte counts available respectively on 12,818 and 13,241 participants.

Adverse Experiences, Mood State, and Hostility

The participants were requested to endorse which of the following circumstances they recalled experiencing prior to age 17: separation from their mother for more than 1 year; hospital stay for more than 2 weeks; parental divorce; prolonged parental unemployment; an experience that was so frightening as to be thought about for years following its occurrence; being sent away from home because of doing something wrong; parental alcohol or drug use sufficient to cause family problems, and experience of physical abuse by someone close to them. These questions were designed to represent areas commonly included in both questionnaire and interviewer-based assessments of childhood adverse experience. They were influenced by items included in the National Comorbidity Survey assessments (NCS; Kessler et al., 1994), the Midlife Development Inventory (MIDI, developed by the MacArthur Foundation Research Network on Successful Midlife Development, Rossi, 2001) and in questions included in the Childhood Experience of Care and Abuse (semistructured) interview (CECA; Bifulco, Brown, & Harris, 1994) (see Wainwright & Surtees, 2002, for further details). Assessment of lifetime adverse event experience was restricted to those incidents considered most likely to be remembered reliably over an extended period, namely, serious

illnesses, injuries or assaults, relationship events (separation, divorce, termination of pregnancy), work events (retirement, redundancy or being sacked), and loss experiences (of first degree relatives), see Surtees, & Wainwright (2000) for further details. Event selection was based upon those developed for the questionnaire version of the List of Threatening Experiences (LTE-Q) (Brugha, Bebbington, Tennant, & Hurry, 1985). Concurrent validity of the LTE-Q assessed against the Life Events and Difficulties Schedule (LEDS; Brown, & Harris, 1978) has shown both high specificity and sensitivity (Brugha & Cragg, 1990). The participants also completed a revised form of the Personality Deviance Scales (PDS-R) (Deary, Bedford, & Fowkes, 1995) that included an 8-item measure of hostility comprising questions concerned with hostile thoughts and acts. All items were prefaced by "most of my life." Four categories of response were available for each scale item; very often/nearly always, often, seldom, never. Individual scale items were scored (in the range 1–4) and summed (with a resulting scale range of 8–32). A low-scale score is indicative of increased hostility (see Surtees et al. (in press)). A structured self-assessment approach to psychiatric symptoms representative of selected Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (APA, 1994) criteria for major depressive disorder was also included in the HLEQ (see Surtees et al., 2000, for further details) providing identification of those participants thought likely to have met putative depressive diagnoses at any time in their lives.

Assays and Other Measurements

Non-fasting blood samples were taken by venepuncture and collected in EDTA, citrated, and plain Monovettes. Citrated and plain blood samples were stored overnight in a refrigerator at 4 to 7°C, and the EDTA samples were stored at room temperature. The following day white blood cell (WBC) counts and leukocyte differentiation counts were measured from EDTA samples using a quantitative automated Coulter MD Series (MicroDiff 18) hematology analyzer (Coulter Corporation, Miami, FL) located in the EPIC laboratory providing enumerative measures of total WBC, granulocyte, lymphocyte, and monocyte counts expressed in thousands of leukocytes per microliter of whole blood. Daily quality control procedures were followed through the Coulter scheme and, in addition through adoption of the Haematology Department of Addenbrooke's Hospital (Cambridge, UK) Quality Control Scheme. Plasma ascorbic acid (vitamin C) concentration (in μmol/L) was estimated with a fluorometric assay from citrated plasma within 1 week of sampling using a Monarch centrifugal analyzer (Khaw et al., 2001; Vuilleumier & Keck, 1989). Serum triglyceride was measured (mmol/L) with the RA 1000 (Bayer Diagnostics, Basingstoke, UK). Blood pressure was measured (mmHg) twice at each health check with an Accutorr noninvasive monitor by trained nurses after each participant had been seated for 5 min. Analysis was then

based upon the mean of the two readings. Forced expiratory volume of gas (in liters) in 1 s (FEV_1) was measured by trained observers, while each participant was standing and looking straight ahead, using a turbine spirometer (Micro Medical Instruments, Rochester, UK). Two measurements were taken on each participant. Instrument monitoring procedures were implemented to maintain measurement accuracy. Expected FEV_1 values were determined from sex-specific reference algorithms for forced ventilatory flows for non-smoking adults of European descent aged 18 to 70 years that took account of each participant's age and height (Quanjer et al., 1993). Analysis was then based upon adjusted FEV_1 values (observed minus expected). Height was measured (with shoes removed) to the nearest 0.1 cm using a stadiometer. Weight was measured (wearing light clothing) to the nearest 100 g using Salter scales. The participants provided a record of their average consumption of alcohol over the past year through use of a semi-quantitative food frequency questionnaire, with intake subsequently converted to grams per day through use of food tables (Bingham et al., 2001; Day et al., 1999). Current and lifetime smoking behavior were assessed through self-report.

Statistical Analysis

After exclusion of those with prevalent conditions at EPIC baseline (cancer, stroke, diabetes mellitus, or previous myocardial infarction), the sample available for analysis included data from 15,049 participants. This included 11,367 participants with data from the first and 11,857 with data from the second health check. The participants were classified into groups according to whether they reported 0, 1, or ≥ 2 of a maximum of 7 childhood problems assessed (hospital stay for more than 2 weeks was excluded from these analyses). A log transformation was applied to all WBC counts for all analyses (as the distributions of these data were found to be skewed to the right). Adjusted associations between leukocyte counts and childhood problems are displayed as (geometric) mean values obtained (back-transformed) from multiple linear regression models. All models include adjustment for age (in 5-year bands), sex, age–sex interaction, and calendar month of leukocyte assay. As the analysis was performed with respect to total WBC and the three leukocyte subsets, multiple testing is an issue and Bonferroni adjustments are discussed. Further measures considered for the analysis were representative of social circumstances (educational attainment and social class), lifestyle factors (smoking history [current vs. former vs. never] and alcohol intake [grams per day]), psychosocial factors (hostility, lifetime depression, and the experience during adulthood of stressful events [expressed as a rate and not including events concerning illness or injury to self]), and other known correlates of leukocyte counts (BMI [weight in kilograms divided by height in meters squared], triglycerides, SBP, adjusted FEV_1, and plasma vitamin C). Additional covariates were included for smoking behavior (represented by cigarette use in total pack years—1 pack

year equivalent to 20 cigarettes a day for 1 year—and years since giving up smoking, for former smokers). Smoking history and behavior, alcohol use, BMI, and all blood based assessments were obtained contemporaneously with leukocyte assays. The analysis was performed in SPlus version 5.0.

RESULTS

Table 1 shows the number of study participants who reported each adverse experience during their childhood (for the second health check sample) and the bivariate clustering of these experiences. From this sample (n = 11,857) a total of 6,418 problems were reported (a rate of 0.54 per person) with 7,481 (63.1%) of the sample reporting none, 2,925 (24.7%) reporting 1, and 1,451 (12.2%) more than 1. The most commonly reported problems were the experience of a frightening event (reported by 18% of the sample) and being separated from mother (13%). Abuse was reported by 4% of the sample and the least commonly reported experience was being sent away from home (0.5%). In addition, there was considerable clustering of these circumstances with more than half of those reporting each experience also reporting at least one other. This clustering was even greater for childhood abuse and being sent away from home, with four out of five of those reporting these events also reporting at least one other.

TABLE 1
Numbers of EPIC-Norfolk HLEQ Participants Reporting Specific Adverse Experiences to age 16 and (Bivariate) Clustering of Such Experiences (Second Health Check Sample)

Adverse Experience	*n*	*Sep*	*Div*	*Emp*	*Fri*	*Sen*	*Dri*	*Abu*	*Not Shared*
		1,542	498	924	2,142	60	742	510	
Separated from mother (Sep)	1,542	—	201	175	460	34	155	128	797
Parental divorce (Div)	498		—	69	164	14	74	63	172
Parental employment problems (Emp)	924			—	283	12	123	71	457
Experience of frightening event (Fri)	2,142				—	29	284	334	1,105
Sent away from home (Sen)	60					—	14	19	10
Parental drink/drug problems (Dri)	742						—	135	284
Physical abuse (Abu)	510							—	100
Total	6,418								2,925

Association Between Adverse Childhood Experiences and Leukocyte Counts

Table 2 shows mean (*SD*) leukocyte counts from both health checks according to the number of adverse experiences reported in childhood. A positive association was observed for lymphocyte counts at both health checks and for total WBC at the first health check only. No associations were observed for either granulocytes or monocytes. The associations with lymphocyte counts were robust to Bonferroni corrections for multiple testing (adjusted *p*-values for 4 tests; .0002 and .008).

Table 3 shows age–sex adjusted associations between childhood adverse experiences and lymphocyte counts at both health checks and when stratified according to age and sex. Adjusted associations were observed at both health checks. There was a 2.5% increase in lymphocyte count for those who reported ≥ 2 adverse experiences in childhood as compared to those who reported none (a difference of $0.05 \times 10^3/\mu L$, $p = .0003$) at the first health check and a 2.5% increase ($0.05 \times 10^3/\mu L$, $p = .005$) at the second health check. No differences were observed by sex (*p*-values for sex interactions were .71 and .18 at the first and second health check, respectively). In addition, these associations were generally consistent by age.

Table 4 shows age–sex adjusted associations for specific adverse experiences. Although the magnitude of associations varied, the direction of association was maintained across all childhood circumstances. The magnitude of association was greatest for being sent away from home and for physical abuse. As the number of participants who reported being sent away from home was small, we conclude that

TABLE 2
Mean (*SD*) Leukocyte Counts ($10^3/\mu L$) at Two Health Checks According to the Number of Reported Adverse Childhood Experiences

	Number of Reported Adverse Childhood Experiences						
	0		*1*		*≥2*		
	M	*SD*	*M*	*SD*	*M*	*SD*	*p value*[a]
First health check							
Total WBC	6.44	1.72	6.55	1.84	6.54	1.71	0.004
Granulocytes	3.93	1.35	3.97	1.42	3.98	1.35	0.1
Lymphocytes	1.99	0.73	2.05	0.82	2.05	0.73	<0.0001
Monocytes	0.52	0.36	0.53	0.36	0.50	0.36	0.5
Second health check							
Total WBC	6.42	1.76	6.42	1.76	6.49	1.81	0.2
Granulocytes	3.83	1.36	3.80	1.33	3.85	1.38	0.9
Lymphocytes	2.00	0.83	2.03	0.85	2.05	0.97	0.002
Monocytes	0.59	0.45	0.59	0.44	0.60	0.47	0.2

[a]Test of trend.

TABLE 3
Mean Lymphocyte Counts (10^3/μL, Adjusted for Age and Sex) According to the Number of Reported Adverse Experiences in Childhood, at Two Health Checks, and Stratified by Age and Sex

	Childhood Adverse Experience					
	First Health Check			*Second Health Check*		
	0	*1*	*≥2*	*0*	*1*	*≥2*
All	1.97	2.02	2.02‡	1.98	2.01	2.03†
Men	1.96	2.01	2.02*	1.93	1.98	1.99†
Women	1.98	2.03	2.02†	2.04	2.05	2.06
Age						
40–55	1.89	1.93	1.94*	1.95	1.97	1.99
56–65	1.97	2.02	2.00	1.96	2.00	2.03†
66–80	1.94	1.99	1.99*	1.95	1.97	1.96

*$p < .05$. †$p < .01$. ‡$p < .001$ for test of trend according to number of adverse experiences.

TABLE 4
Mean Lymphocyte Counts (10^3/μL, Adjusted for Age and Sex) According to Absence/Presence of Specific Adverse Experiences During Childhood at Two Health Checks

	First Health Check		*Second Health Check*	
	No	*Yes*	*No*	*Yes*
Adverse experience				
Separated from mother	1.98	2.03*	1.99	2.01
Parental divorce	1.99	2.01	2.00	2.03
Parental employment problems	1.99	2.03*	2.00	2.02
Experience of frightening event	1.99	2.00	2.00	2.02
Sent away from home	1.99	2.13	2.00	2.16
Parental drink/drug problems	1.99	2.02	2.00	2.01
Physical abuse	1.99	2.09‡	2.00	2.06*

*$p < .05$. †$p < .01$. ‡$p < .001$ for test of difference by absence/presence of adverse experience.

a major component of the combined childhood–lymphocyte association is due to the contribution of physical abuse.

Mediating Factors

Table 5 displays measures of social and educational circumstances, lifestyle, psychosocial factors, and other known correlates of leukocyte counts according to the

TABLE 5
Biological, Lifestyle, Social, and Psychosocial Correlates of Reported Adverse Experiences in Childhood

	Adverse Experiences in Childhood						
	0[a]		*1*[b]		≥*2*[c]		
Covariates[d]	*M*	*SD*	*M*	*SD*	*M*	*SD*	*p-value*[e]
Continuous variables							
Triglycerides[§]	1.85	1.06	1.87	1.06	1.91	1.15	0.15
SBP (mmHg)[§]	135	18	135	18	134	19	0.1
Adjusted FEV_1[§]	–0.21	0.5	–0.20	0.5	–0.23	0.5	0.4
Vitamin C[§]	63.6	23.9	63.9	23.4	63.4	23.2	0.7
BMI (kg/m)[§]	26.5	3.9	26.7	4.0	26.9	4.1	0.001
Alcohol intake (grams/day)	8.8	12.7	8.7	12.5	8.8	13.2	0.09
Hostility[§]	25.2	3.3	24.7	3.4	23.9	3.5	<0.0001
Event rate (/10 years)	1.00	0.49	1.08	0.50	1.15	0.55	<0.0001
Age started smoking	18.2	4.34	18.1	4.59	18.1	5.06	0.6
Total pack years smoked[§,f]	15.7	15.0	17.0	16.3	18.3	16.6	<0.0001
Years since gave up smoking[§,g]	21.1	11.6	21.5	11.8	19.7	10.8	0.06
Categorical variables (% [*n*])							
Current smokers[§]	7.6	570	8.3	244	9.6	139	0.009
Lifetime smokers[§]	47.6	3,559	51	1,491	55.7	808	<0.0001
Lifetime depression[‡]	13.4	1,004	17.1	500	22.7	330	<0.0001
Education (tertiary vs. other)[h]	15.4	1,149	14.4	421	13.1	190	0.02
Social class (I or II vs. III, IV, or V)[h]	41.5	3,105	41.6	1,218	40.8	592	0.7

[a]$n = 7,481$. [b]$n = 2,925$. [c]$n = 1,451$. [d]Test of association with lymphocyte count: *$p < .05$. †$p < .01$. ‡$p < .001$. §$p < .0001$. [e]Test of trend according to number of adverse experiences. [f]Lifetime smokers. [g]Ex-smokers. [h]Tests of association with lymphocyte count across all categories of education and social class.

number of adverse experiences reported in childhood. In addition, the degree of association between these factors and lymphocyte counts (at the second health check) is indicated. Of the factors considered, BMI, smoking (including pack years smoked), hostility, and lifetime depression were strongly associated with childhood adverse experiences and with lymphocyte counts. Only these factors were considered for inclusion in further multiple regression analysis.

Table 6 shows the relative effect size of the association between adverse experiences in childhood and lymphocyte counts after successive adjustments. This gives an indication of the extent to which the association is accounted for by these factors. Lifestyle factors (largely due to smoking behavior) and psychosocial factors (largely due to hostility) were important in accounting for the association. Considered separately, lifestyle factors accounted for 45 to 50% of the association at both health checks and psychosocial factors accounted for 20 to 40%. Considered together, lifestyle factors were most

TABLE 6
Relative Effect Size ($\beta \times 10^3$ Coefficient) for the Association Between Reported Adverse Experiences in Childhood and Lymphocyte Counts ($10^3/\mu L$) in Adulthood Following Successive Adjustment for BMI, Smoking, Hostility, and Lifetime Depression, at Two Health Checks

Association With Adverse Experiences in Childhood	*First Health Check*		*Second Health Check*	
	$\beta \times 10^3$	*95% CI*	$\beta \times 10^3$	*95% CI*
Baseline adjustment[a]	15	7–23	11	3–19
Further adjustment for				
A: Lifestyle correlates				
BMI	13	5–21	9	2–17
Smoking[b]	9	1–17	7	–1–15
Both	8	0–15	6	–2–13
B: Psychosocial correlates				
Hostility	12	4–20	8	0–16
Lifetime depression	14	6–22	10	2–18
Both	12	4–20	7	–1–15
C: Lifestyle and psychosocial correlates	7	0–15	4	–4–12

[a]Adjusted for age, sex, and calendar month. [b]Lifetime smoking status and total pack years.

important, with psychosocial factors resulting in only a small additional reduction in effect size.

DISCUSSION

We believe this study to be the first to investigate the relationship between reports of adverse experience in childhood and measures of immune status in adulthood. This study has provided evidence for a positive association with lymphocyte counts, but not for total WBC, granulocytes or monocytes. Lymphocytes are responsible for acquired immunity (Goldsby, Kindt, & Osborne, 2000) and an explanation of this finding could lie in the extended mature cell life span of some lymphocyte subsets as compared to the much shorter life span of granulocytes (Sothern & Roitman-Johnson, 2001). However, we acknowledge as have others (Crowell & Samet, 1995), the difficulty in interpretation of leukocyte differentiation counts. The effect size observed in this study was modest although measurement error may have resulted in some attenuation (Breslow & Day, 1987; Wong, Day, Bashir, & Duffy, 1999a). In addition, this association was shown to be consistent across the entire range of individual adverse childhood experiences, with physical abuse perhaps the dominant source of the association. Consideration of lifestyle factors, that included smoking behavior and BMI, revealed these to be most important in explaining this association, accounting for about 50% of the effect size at both health checks.

A number of methodological issues merit further comment. Firstly, associations were investigated for total WBC and three leukocyte subsets and therefore multiple testing is an issue. However, these associations were robust to Bonferroni correction at both health checks. In addition, the (within-study) replication of associations based upon data obtained at two health checks (on average 44 months apart, both prior to and following HLEQ assessment) provides further protection against chance findings. Secondly, the range of data available from the EPIC-Norfolk study (that included known correlates of leukocyte counts [BMI, triglycerides, SBP, FEV, plasma vitamin C, smoking history, alcohol use, depression, hostility, adult stress exposures, social class, and educational attainment]) allowed extensive statistical adjustment to be undertaken. Of these factors, smoking behavior and hostility were found to be most important in accounting for the association between adverse experiences in childhood and lymphocyte count in adulthood. In addition, those participants with known prevalent major conditions at baseline were also excluded from analysis. However, the possibility remains that our findings may still be due to residual confounding, arising from limitations in the measures (e.g., the self-assessment of smoking behavior and of lifetime event experience), the effects of intermediate variables not considered, and of the failure to exclude those with more minor (but immune-related) conditions. It is important therefore that these findings are replicated.

Investigation of the effects of childhood adverse experience on adult health and biology presents considerable challenges. Not the least, is the extent to which errors of measurement arise through use of self-report accounts of adverse experience histories recalled many decades following their occurrence, that may impact on adverse exposure prevalence estimation, on the specification of correlates and their sequelae (Brewin, Andrews, & Gotlib, 1993; Fergusson, Horwood, & Woodward, 2000; Maughan & Rutter, 1997). Such evidence has concluded that single retrospective reports of specific exposures (e.g., child abuse) are likely to underestimate the true prevalence of such experiences. However, other evidence has pointed to the strong clustering of a range of experiences and the need to consider this in analysis.

The idea that early experience may shape neuroimmune and neuroendocrine response to adverse exposures at the individual level that can then show up later as population effects—the process by which psychosocial factors embed themselves in human health (Keating & Hertzman, 1999; Kelly, Hertzman, & Daniels, 1997)—remains controversial with limited understanding of the biological processes that may be involved. Changes in immunocompetence across the life span, for example, immune system immaturity in childhood and immunosenescence in old age, are reflected in life stage specific differences in disease prevalence. Adverse exposures that occur during a time of neurodevelopmental system maturation may therefore have the potential to cast a "biological shadow" across the life span particularly if such exposures endure for extended periods as with child abuse or maltreatment (Putnam & Trickett, 1997). The results of this study

provide the first suggestion that adverse exposures in childhood are associated with lymphocyte count in adulthood. A major component of this association was due to factors that related to adult lifestyle. Whether the remainder of this association reflects neuroimmunological scars or is due to unmeasured factors should be the focus of further research that includes investigation of relationships with incident autoimmune disorders, infectious illnesses, and cancer.

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