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Association between traumatic stress load, psychopathology, and cognition in the Philadelphia Neurodevelopmental Cohort

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Original Article

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Abstract

Background. Traumatic stressors during childhood and adolescence are associated with psychopathology, mostly studied in the context of post-traumatic stress disorder (PTSD) and depression. We investigated broader associations of traumatic stress exposure with psychopathology and cognition in a youth community sample.

Methods. The Philadelphia Neurodevelopmental Cohort ($N = 9498$) is an investigation of clinical and neurobehavioral phenotypes in a diverse (56% Caucasian, 33% African American, 11% other) US youth community population (aged 8–21). Participants were ascertained through children's hospital pediatric (not psychiatric) healthcare network in 2009–2011. Structured psychiatric evaluation included screening for lifetime exposure to traumatic stressors, and a neurocognitive battery was administered.

Results. Exposure rate to traumatic stressful events was high (none, $N = 5204$; one, $N = 2182$; two, $N = 1092$; three or more, $N = 830$). Higher stress load was associated with increased psychopathology across all clinical domains evaluated: mood/anxiety (standardized $\beta = .378$); psychosis spectrum ($\beta = .360$); externalizing behaviors ($\beta = .311$); and fear ($\beta = .256$) (controlling for covariates, all $p < 0.001$). Associations remained significant controlling for lifetime PTSD and depression. Exposure to high-stress load was robustly associated with suicidal ideation and cannabis use (odds ratio compared with non-exposed 5.3 and 3.2, respectively, both $p < 0.001$). Among youths who experienced traumatic stress ($N = 4104$), history of assaultive trauma was associated with greater psychopathology and, in males, vulnerability to psychosis and externalizing symptoms. Stress load was negatively associated with performance on executive functioning, complex reasoning, and social cognition.

Conclusions. Traumatic stress exposure in community non-psychiatric help-seeking youth is substantial, and is associated with more severe psychopathology and neurocognitive deficits across domains, beyond PTSD and depression.

Introduction

The association between psychopathology and traumatic stressful events (TSE) exposure during childhood and adolescence is evident in clinical psychiatric practice (Wiersma *et al.* 2009). Significant childhood adversities, including TSE occurring during brain development, can derail normative neurodevelopmental trajectories and increase susceptibility to psychiatric (Teicher *et al.* 2006; Shonkoff *et al.* 2009; Lee *et al.* 2014) and other medical conditions (Derry *et al.* 2015; Berens *et al.* 2017). Extensive research documents the association with 'classic' stress-related disorders, such as post-traumatic stress disorder (PTSD) and depression [for reviews (Heim & Binder, 2012; Messman-Moore & Bhuptani, 2017)], with fewer studies on TSE association with other domains of psychopathology (Gilman *et al.* 2015; Carliner *et al.* 2017; McGrath *et al.* 2017; Miller & Brock, 2017).

Most research describing the association of early life traumatic events with psychopathology relies on the adult recollection of childhood adversity, which can be inaccurate (Hardt & Rutter, 2004), especially in psychiatric patients often biased to recall adversities (Newbury *et al.* 2017). Therefore, there is a need for studies conducted in youths ascertained through non-psychiatric services, which integrates data collected from typical and atypical development at young ages (McLaughlin, 2016). An example of such an effort is the National Comorbidity Survey Replication Adolescent Supplement study, conducted in a representative US adolescent population aged 13–17 evaluated between 2001 and 2004 (McLaughlin *et al.* 2012). This study reported an association between childhood adversities

(not limited to traumatic events, i.e. parents' divorce) and lifetime anxiety, depression, behavioral and substance use disorders (Kessler *et al.* 2009).

The Philadelphia Neurodevelopmental Cohort (PNC) is a unique resource with genetic, clinical and neurocognitive data on a large ($N = 9498$) youth (age 8–21) community sample, representative of US urban population (Calkins *et al.* 2015). In addition to anxiety, mood, and externalizing disorders, the clinical phenotyping included psychosis spectrum symptoms and cognitive assessments, which were not previously obtained in large-scale community studies. Importantly, high exposure to TSE in the PNC provides an informative platform for dissecting TSE-developmental psychopathology relationships. In the current study, we evaluated the association of lifetime TSE load with psychopathology domains, gender-specific associations with exposure and psychopathology beyond PTSD and depression, and the association of TSE with cognitive performance.

Methods

Participants

The PNC is a collaboration between the Children's Hospital of Philadelphia and the Brain Behavior Laboratory at the University of Pennsylvania, as previously described (Calkins *et al.* 2014; 2015). Enrollment criteria included (1) age 8–21 years; (2) ambulatory in stable health; (3) proficient in English; (4) physically and cognitively capable of participating in an interview and performing the neurocognitive assessment; and (5) absence of a disorder that impaired motility or cognition (e.g., paresis or palsy, intellectual disability).

Recruitment procedure

Participants were recruited from a pool ($N = 150\,293$) of children previously genotyped as part of a genomic study at the Children's Hospital of Philadelphia healthcare network, which extends to over 30 clinical community sites in the tri-state area of Pennsylvania, New Jersey, and Delaware, in the USA. Participants were not recruited from psychiatric clinics and the sample is not enriched for those seeking mental health services. Based on electronic medical records review or follow-up phone contact, potential participants from this pool were excluded if they were not proficient in English, had significant developmental delays or other conditions that would interfere with their ability to complete study procedures, or could not be contacted. From the remaining pool, 13 598 individuals were invited, 2699 declined, 1401 were excluded, and 9498 youths (age 8–21) were enrolled. The cohort is racially diverse (56% Caucasian, 33% African American and 11% other), with the diverse socioeconomic background (Moore *et al.* 2016).

Clinical assessment

Psychopathology symptoms were evaluated in clinical interviews by trained and supervized assessors using a structured screening interview (GOASSESS) (Calkins *et al.* 2014), based on the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) (Kaufman *et al.* 1997). Psychopathology factors were produced based on item-level data from GOASSESS as previously described (Shanmugan *et al.* 2016). For the current analyses, psychopathology domains were considered significant if sufficient items were endorsed with frequency and duration meeting DSM-IV disorder or episode criteria, accompanied by significant distress or impairment. Comparison of the diagnostic algorithms from this interview with the full criteria using data from the National Comorbidity Survey-Adolescent (Merikangas *et al.* 2009) yielded fair (e.g. eating disorders) to excellent (e.g. ADHD) area under the receiver-operating characteristic curve values for the major classes of disorders (Calkins *et al.* 2015). Computerized algorithms used the endorsement of symptoms, their frequency and duration, and the presence of distress or impairment to approximate DSM-IV criteria of PTSD or depression. Level of function was evaluated by the Children's Global Assessment Scale (C-GAS) (Shaffer *et al.* 1983). Age was regressed out of clinical scores.

Factor analysis

We used itemwise (i.e. symptom-level) psychopathology responses from the GOASSESS across all assessed psychopathology domains to run an exploratory factor analysis (EFA) extracting four factors (using 111 items), as previously described (Shanmugan *et al.* 2016). The items used to calculate the factor scores did *not* include the traumatic stress exposure GOASSESS items (independent variable in the current analysis). This EFA was then used to assign items to factors for a confirmatory factor analysis (CFA). The CFA was estimated using a Bayesian estimator in Mplus, version 7.1. As predicted by theory and supported by initial exploratory models, the four factors primarily represent anxious-misery (mood/anxiety) symptoms, psychosis spectrum symptoms, externalizing behavior symptoms (conduct and ADHD), and fear symptoms (phobias). Factor scores were generated from these four confirmatory correlated-traits factors.

Evaluation of TSE

The GOASSESS TSE screen assessed lifetime exposure to potential traumatic events including situations in which the participant (1) experienced a natural disaster or (2) experienced a bad accident; (3) thought that s/he or someone close to him/her could be killed or hurt badly; (4) witnessed someone getting killed, badly beaten, or die; (5) saw a dead body; or if s/he ever was a victim of one of the following assaults: (6) attacked or badly beaten, (7) threatened with a weapon, or (8) sexually forced (including but not limited to rape). For the visual presentation of data and univariate comparisons, TSE load was categorized into four groups: none, one TSE, two TSEs, and three or more TSEs, as in previous work (McCutcheon *et al.* 2009). In participants with at least 1 TSE ($N = 4104$), we compared two groups based on whether or not they had endorsed having a history of being a victim of assault (badly beaten, threatened with a weapon, or sexually forced). For 190 participants (2% of PNC), GOASSESS sections including TSE screening were missing and therefore they were excluded from analyses.

Neurocognitive assessment

The 1-hour Penn Computerized Neurocognitive Battery includes 14 tests assessing five neurobehavioral domains: executive (abstraction and mental flexibility, attention, working memory), episodic memory (words, faces, shapes), complex cognition (verbal reasoning, nonverbal reasoning, spatial processing), social cognition (emotion identification, emotion intensity

differentiation, age differentiation), and sensorimotor speed (motor, sensorimotor) (Gur *et al.* 2010; Moore *et al.* 2015). The reading subtest of the Wide Range Achievement Test-4th Edition (WRAT4) (Wilkinson, 2006) was administered first to determine participants' ability to complete the battery and to provide an estimate of IQ. In this study, we examined a measure of cognitive efficiency, which combines accuracy and speed of cognitive performance.

Statistical analysis

Univariate comparison among TSE exposure categories (load category, assaultive category) was conducted using Analysis of Variance (ANOVA), *t* Test, or Chi-Square as appropriate. For multivariate analyses, we considered the continuous variable of cumulative TSE count as the key independent variable of interest. Linear regression was conducted for continuous measures (psychopathology factors, functioning scale and cognitive scores) and binary logistic regression for dichotomous measures (lifetime suicidal ideation or cannabis use). We controlled for covariates including age, gender, socioeconomic status (Moore *et al.* 2016), race, and a proxy-measure of parents' separation status (based on a text search from the Timeline section of the GOASSESS). In order to control for lifetime PTSD and depression association with psychopathology factor scores, PTSD and depression were regressed out of both the independent variable (cumulative stress load) and the dependent variable (psychopathology factors).

For all regression models described above, domains of psychopathology were analyzed separately so as to obtain separate coefficients for quantitative and visual comparison. To test statistically whether the relationships of stress with psychopathology differ by psychopathology domain, we performed a mixed model repeated measures (MMRM) analysis treating domain as a within-subject variable. All relevant covariates were included, and the effects of interest were the stress × domain interactions. Significant interaction terms would suggest that the relationship of stress with psychopathology differs across domains. To examine gender by stress and gender by assaultive stress interactions, we conducted linear regression with gender, stress, and gender X stress as independent variables and psychopathology domain as the dependent variable. A two-tailed p value <0.05 was considered statistically significant in all subsequent analyses performed to elucidate significant interactions. Statistical analyses were performed using SPSS Statistics 24 (IBM, Armonk, New York, USA), except for the MMRM ('nlme' package in R (Pinheiro *et al.* 2017)).

Results

Exposure rates

Of the 9498 PNC participants, 4104 (43.2%) endorsed at least one |TSE: 2182 (23%) endorsing a single |TSE, 1092 (11.5%) two TSEs, and 830 (8.7%) three or more TSEs. As can be seen in Table 1, higher TSE load was associated positively with age and parents' separation, and inversely with socioeconomic status and Caucasian race (Table 1). PTSD rates (based on K-SADS) rose from 13% in the 1 TSE group to 27% and 46% in the 2 TSE and 3 + TSE groups, respectively. Regarding the nature of the assault, 1042 participants reported having been a victim of an assault. Specific TSE frequencies and rates are provided in the online supporting information (online Supplementary Table S1).

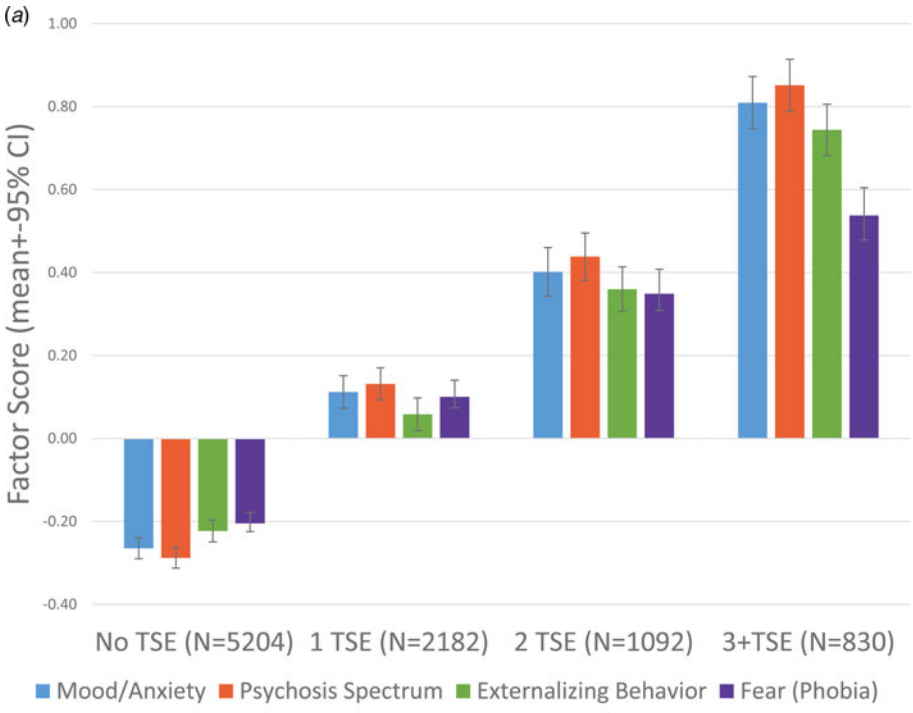
Table 1. Demographic characteristics and exposure rates for traumatic stressful events in PNC participants

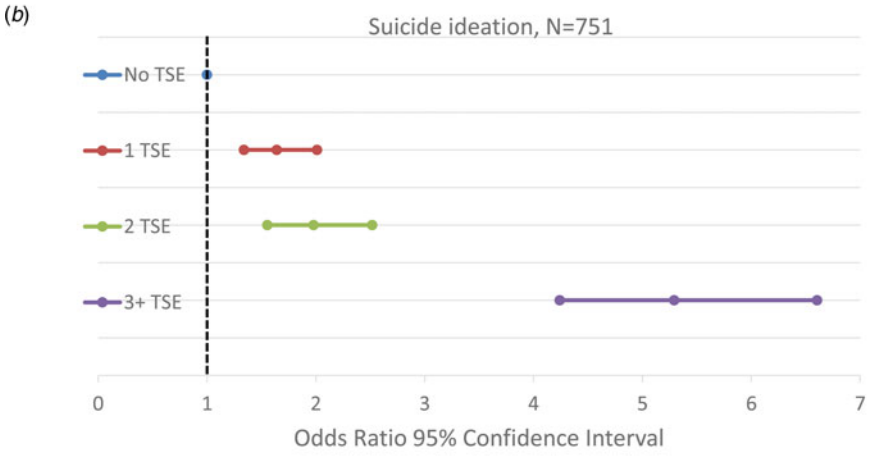
	Total cohort $N = 9498$[a]	0 TSE $N = 5204$	1 TSE $N = 2182$	2 TSE $N = 1092$	3 + TSE $N = 830$	Test result (Pearson χ^2/ ANOVA F), (df)	p
Demographic characteristics							
Age, mean years (s.d.)	14.2 (3.7)	13.4 (3.6)	14.6 (3.5)	15.5 (3.5)	16.6 (3)	F (3, 9304) = 282	<0.001
Gender, N (%) males	4592 (48.3%)	2544 (48.9%)	987 (45.2%)	532 (48.7%)	416 (50.1%)	$\chi^2 = 10$ (3)	0.019
Caucasian, N (%)	5298 (55.8%)	3243 (62.3%)	1222 (56%)	481 (44%)	277 (33.4%)	$\chi^2 = 320$ (3)	<0.001
SES (s.d.)	0.000 (1)	0.1363 (0.95)	−0.0036 (0.99)	−0.2928 (1.04)	−0.5274 (1.02)	F (3, 9304) = 163	<0.001
Parents separated, N (%)	1749 (18.4%)	783 (15.2%)	446 (20.6%)	269 (25%)	240 (29.2%)	$\chi^2 = 134$ (3)	<0.001
Stress related characteristics							
A victim of assault[b], N (%)	1045 (11%)	0 (0%)	219 (10.1%)	273 (25.1%)	550 (66.7%)	$\chi^2 = 1006$ (2)	<0.001
Lifetime PTSD[c], N (%)	997 (10.5%)	1 (0%)	304 (13.9%)	300 (27.5%)	390 (46%)	$\chi^2 = 2112$ (3)	<0.001
Lifetime depression[c], N (%)	1140 (12.2%)	358 (6.9%)	314 (14.4%)	202 (18.5%)	266 (32%)	$\chi^2 = 491$ (3)	<0.001

PNC, Philadelphia Neurodevelopmental Cohort; TSE, traumatic stressful events; s.d., standard deviation of the mean; PTSD, post traumatic stress disorder.
[a]For 190 participants (2% of PNC), clinical sections including TSE screening were missing and therefore they were excluded from analyses.
[b]Assaultive victimization included a history of being attacked or badly beaten, threatened with a weapon, or sexually forced, not limited to but including rape.
[c]Lifetime PTSD or depressive episode were determined based on the DSM-IV criteria, screened using Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) based interview.

Association of exposure with psychopathology and functioning

A history of TSE was associated with higher psychopathology factor scores in all the four domains, in a dose-response pattern (Fig. 1*a*). After controlling for covariates, linear regression revealed that TSE was significantly associated with psychosis-spectrum, mood/anxiety, externalizing and, to a lesser extent, fear (models detailed in Table 2). Associations remained





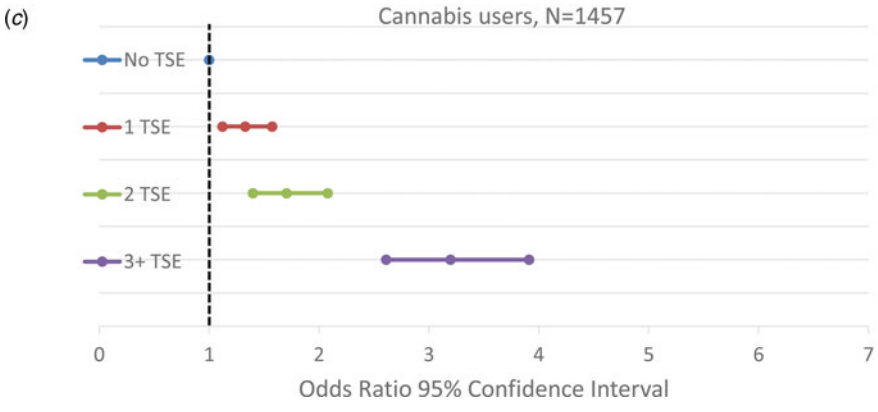


Fig. 1. Association of traumatic stress load with psychopathology in all PNC participants. (*a*) Association with psychopathology factor scores: mood/anxiety (Cohen's $d = 0.4$ for 1TSE, 0.7 for 2TSE, and 1.16 for 3 or more TSE, all values represent effect sizes as compared to no traumatic stress exposure- 0TSE); psychosis spectrum (Cohen's $d = 0.39$ for 1TSE, 0.69 for 2TSE, and 1.16 for 3 or more TSE); externalizing behavior (Cohen's $d = 0.29$ for 1TSE, 0.62 for 2TSE, and 1.03 for 3 or more TSE); fear (phobia) (Cohen's $d = 0.32$ for 1TSE, 0.57 for 2TSE, and 0.76 for 3 or more TSE). (*b*, *c*) Association of childhood traumatic stress load with a history of lifetime (*b*) suicidal ideation and (*c*) cannabis use. Bars represent mean ± 95% confidence interval in Figure *a* and odds ratio ± 95% confidence interval in Figs *b*, *c*. (TSE = traumatic stressful events).

Table 2. Linear regression with cumulative TSE count as independent variable and psychopathology factor of global assessment of function score as dependent variable

	Crude regression			Model A[a]			Model B[b]			Model C[c]		
	B	Beta	p	B	beta	p	B	beta	p	B	beta	p
Mood/Anxiety factor	0.297	0.351	<0.001	0.32	0.378	<0.001	0.323	0.381	<0.001	0.241	0.241	<0.001
Psychosis factor	0.297	0.351	<0.001	0.305	0.360	<0.001	0.307	0.362	<0.001	0.232	0.274	<0.001
Externalizing factor	0.266	0.314	<0.001	0.264	0.311	<0.001	0.269	0.317	<0.001	0.212	0.212	<0.001
Fear factor	0.215	0.253	<0.001	0.217	0.256	<0.001	0.221	0.26	<0.001	0.147	0.122	<0.001
Level of function	−2.608	−0.259	<0.001	−2.34	−0.233	<0.001	−2.367	−0.235	<0.001	−0.143	−0.144	<0.001

[a]Model A controls for age, gender and SES.
[b]Model B controls for age, gender and race (white, black).
[c]Model C controls for age, gender, SES, lifetime PTSD, and lifetime depression.

significant for all psychopathology factors after regressing out lifetime PTSD and depression (model c in Table 2). For the mixed model, treating psychopathology domain as a within-subject variable, all stress × domain interactions were significant ($p < 0.001$), indicating that the stress–psychopathology relationship does indeed differ by domain. The nature of these interactions is apparent in Figure 1*a*. Higher TSE load was negatively associated with the level of function (linear regression controlling for covariates, Table 2). High TSE load was also associated with lifetime history of suicidal ideation and with cannabis use (Fig. 1*b*, *c*, odds ratio compared with non-exposed was 5.3 and 3.2, respectively, both $p < 0.001$).

Gender by traumatic stress exposure interaction in association with psychopathology

Both males and females showed increased psychopathology factor scores in association with increased TSE load (Table 3, see also Fig. S1, available online). There was a significant TSE load by gender interaction in association with fear ($t = 3.661$; $p < 0.001$), and a trend level interaction in association with mood/anxiety ($t = 1.893$; $p = .058$), controlling for lifetime PTSD and depression. In both cases, TSE load in females was associated with higher psychopathology factor scores compared with males (online Supplementary Fig. S1). No TSE load by gender interaction was found in association with psychosis or externalizing psychopathology factors.

Within the group of participants that have experienced at least one TSE, being a victim of assaultive TSE was associated with higher psychopathology and with poorer level of function in all four psychopathology factors compared with victims of non-assaultive TSEs, controlling for covariates including non-assaultive cumulative TSE count (online Supplementary Table S2 and Fig. S2, available online). After controlling for lifetime PTSD and depression, there was a significant gender by assault interaction (Table 3, see also Fig. S3, available online), manifested by increased susceptibility of males to assaultive stress in association with psychosis ($t = 2.139$; $p = .032$) and externalizing factors ($t = 2.359$; $p = .018$). No assault by gender interaction was found with mood/anxiety or fear factors (Table 3).

Association of TSE load with cognitive function

Higher TSE load was associated with poorer overall efficiency in cognitive function, controlling for covariates (Fig. 2, see also Table S3, available online). The strongest negative association was observed with executive function and complex reasoning, whereas for social cognition the negative association with TSE load did not survive controlling for covariates. Episodic memory was the only cognitive domain to show a weak, but the significant positive association with higher TSE load. No significant TSE load by cognitive efficiency interactions were found in association with any of the psychopathology factors (p values > 0.05 for all TSE load X overall cognitive efficiency linear regression analyses predicting psychopathology factors, supporting information in Table S4, available online).

Discussion

We report that traumatic stress load in childhood and adolescence is robustly associated with psychopathology, reduced global function, and poorer cognition in a deeply phenotyped, generalizable,

Table 3. Gender × stress interactions in association with psychopathology factor scores. Significant interactions are marked in bold

		Gender × cumulative stress load interaction[a]			Gender × assault interaction[b]		
		All PNC population $N = 9498$			Participants with trauma history $N = 4104$		
		Beta =	t =	p =	Beta =	t =	p =
Mood/Anxiety	Gender main effect	0.029	2.883	0.004	0.058	1.241	0.215
	Exposure main effect	0.185	5.868	<0.001	0.109	2.264	0.024
	Gender × exposure interaction		1.893	0.058		−0.919	0.358
Psychosis	Gender main effect	−0.083	−8.084	<0.001	−0.009	−0.197	0.843
	Exposure main effect	0.201	6.627	<0.001	0.140	2.911	0.004
	Gender × exposure interaction		1.405	0.16		−2.139	**0.032**
Externalizing	Gender main effect	−0.137	−13.791	<0.001	−0.072	−1.584	0.113
	Exposure main effect	0.247	7.985	<0.001	0.222	4.73	<0.001
	Gender × exposure interaction		−1.206	0.228		−2.359	**0.018**
Fear	Gender main effect	0.101	9.962	<0.001	0.119	2.533	0.011
	Exposure main effect	0.038	1.188	0.235	−0.007	−0.138	0.89
	Gender × exposure interaction		3.661	**<0.001**		−0.236	0.814

[a]Linear regression models controlling for age, socioeconomic status, lifetime PTSD, and depression.
[b]Linear regression controlling for age, socioeconomic status, lifetime PTSD and depression, and cumulative non-assaultive stress load.

US youth community sample. This stress–psychopathology association cuts across diagnostic domains and remains statistically significant after controlling for lifetime PTSD and depression. Particularly, the association of TSE with psychosis factor was comparable in magnitude to that with mood/anxiety factor. Our results indicate that in community youths, stress exposure-psychopathology association is not limited to 'traditional' stress-related disorders. The association had a 'dose-response' pattern in several psychopathology domains, level of function and cognitive efficiency. These findings are consistent with literature describing cumulative traumatic stress as a greater risk factor for psychopathology (Suliman *et al.* 2009; Evans *et al.* 2013; Karam *et al.* 2014), in the presence of elevated allostatic load that confers susceptibility for illness (McEwen, 1998, 2017).

We chose to treat psychopathological phenotypes of the study participants using continuous factor scores that represent various domains of psychopathology (mood/anxiety, psychosis spectrum, externalizing behaviors, and fear). This approach, compared with dichotomous psychiatric disorders, allowed us to obtain a more precise understanding of each participant's psychopathological profile, especially as the study's sample was intentionally *not* enriched for youth with threshold psychiatric symptomatology. That is, most of the study participants did not reach psychiatric threshold symptoms, and analysis using non-continuous scales would have likely resulted in the loss of meaningful data (Markon *et al.* 2011). Nonetheless, even in the non-psychiatric population of this study, we found a dose-response association pattern with the accumulation of TSEs across all the psychopathological domains (small effect size for 1 TSE, medium effect size for 2 TSEs and large effect size for 3 + TSEs). Importantly, the large sample and the deep phenotyping of the participants, coupled with the substantial rate of traumatic stress exposure, enabled us to control for PTSD and depression and show that there is significant association for TSEs beyond these two disorders, for which there is robust literature describing their association with traumatic stress (Heim & Binder, 2012; Messman-Moore & Bhuptani, 2017). This finding shows that in a community youth population, not ascertained to enrich for trauma exposure or significant psychopathology, traumatic stress exposure is associated with psychopathological domains including psychosis and externalizing symptomatology, not accounted for by PTSD or depression.

The strength of the cumulative stress load association with psychopathology, as estimated by the standardized beta coefficients of the regression analyses, varied according to the participant gender and whether they had endured an assaultive trauma. These findings align with the view that cumulative stress by itself can only partly explain the mental health risk attributed to stress exposure (McLaughlin & Sheridan, 2016). We found that females showed higher fear and mood/anxiety (trend level significance) symptoms associated with greater stress load, consistent with reports indicating an increased risk for PTSD and depression in females (MacMillan *et al.* 2001; Bale & Epperson, 2015). Furthermore, in patients with a history of trauma exposure, assaultive TSE was associated with worst psychopathology scores, consistent with previous reports (Ribeiro *et al.* 2013; Liu *et al.* 2017; Lowe *et al.* 2017). Examination of gender by assault interaction revealed that in males, an assault was associated with higher psychosis and externalizing symptoms. Taken together, our results suggest a gender-specific developmental trajectory associated with trauma exposure, as previously suggested in clinical settings (MacMillan *et al.* 2001; Cort *et al.* 2012) and studies with neuroimaging (Everaerd *et al.* 2012; 2016; Elton *et al.* 2014), as well as inflammation (Derry *et al.* 2015; Baldwin *et al.* 2018) related phenotypes.

There is growing interest in understanding the association between early life adversities and poorer cognitive performance

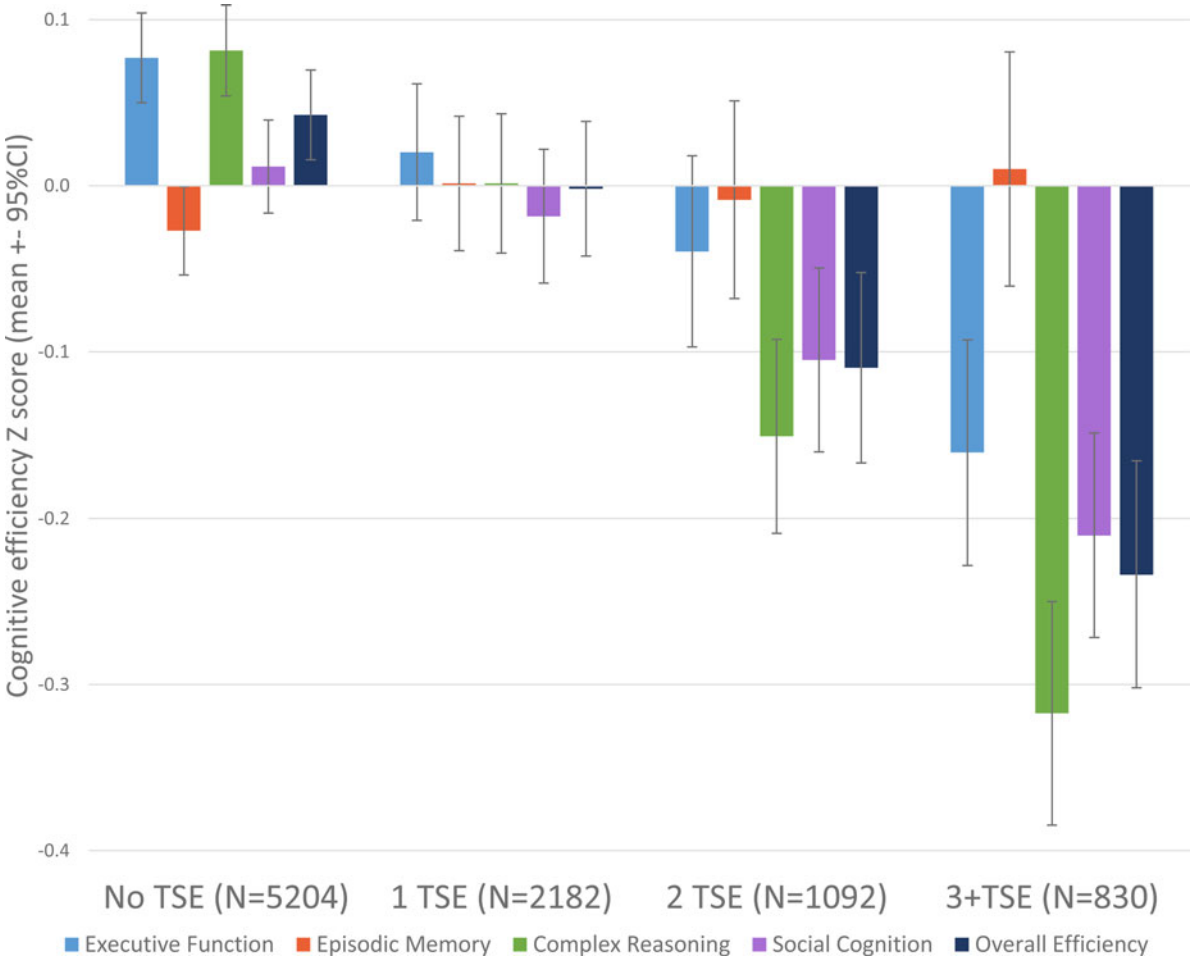


Fig. 2. Association of traumatic stress load with cognitive efficiency. Association of traumatic stress load with performance in executive function (Cohen's $d = -0.06$ for 1TSE, −0.12 for 2TSE, and −0.25 for 3 or more TSE, all values represent effect sizes as compared with no traumatic stress exposure); episodic memory (Cohen's $d = 0.03$ for 1TSE, 0.02 for 2TSE, and 0.04 for 3 or more TSE); complex reasoning (Cohen's $d = -0.08$ for 1TSE, −0.24 for 2TSE, and −0.4 for 3 or more TSE); social cognition (Cohen's $d = -0.03$ for 1TSE, −0.12 for 2TSE, and −0.22 for 3 or more TSE); and general cognitive efficiency (Cohen's $d = -0.05$ for 1TSE, −0.16 for 2TSE, and −0.28 for 3 or more TSE). Bars represent mean ± 95% confidence interval. (TSE = traumatic stressful events).

(Cowell *et al.* 2015). The neurocognitive phenotyping of PNC participants, coupled with substantial TSE exposure, enabled examination of the association between early life traumatic stress load and cognitive performance in a non-clinical population. We report a dose-response of TSEs associated with poorer cognitive efficiency across multiple cognitive domains. Specifically, there was a small effect size association of high traumatic stress exposure (3 + TSEs) with poorer executive function and social cognition and a larger effect size (small to moderate) association of high exposure with poorer abstract reasoning. Judging from these effect sizes, we suggest that in the current study (non-help-seeking sample), the participants require substantial exposure (3 + TSE) to show significantly lower cognitive performance in association with the exposure. This might indicate that cognitive efficiency is somewhat 'spared' compared with the larger effect sizes that we observed in the association of traumatic stress exposure with psychopathology factor scores. Importantly, one should be cautious interpreting directionality from stress to cognition when analyzing cross-sectional data, especially in light of recent evidence suggesting that cognitive deficit itself should be considered a risk factor for victimization (Danese *et al.* 2017).

Examination of cognitive performance in specific domains showed that episodic memory was the only cognitive domain that was not negatively associated with traumatic stress exposure. While unexpected, this finding is in line with a recent meta-analysis examining cognitive correlates of childhood trauma with and without PTSD (Malarbi *et al.* 2017). Specifically, the meta-analysis reported that trauma exposure without known PTSD status was not significantly associated with memory impairment but was associated with poorer cognitive performance in tests measuring complex reasoning and executive function. However, in separate analyses of adolescents with a diagnosis of PTSD, traumatic stress exposure was associated with poorer memory, as well as other cognitive domains (Malarbi *et al.* 2017). Notably, a different meta-analysis of adult PTSD studies examining cognitive functioning reported that studies of help-seeking individuals showed greater memory deficits than studies of community samples (Scott *et al.* 2015), which may partially explain why our non-help-seeking community population did not show associations between increased trauma exposure and poorer memory.

There is growing recognition that a history of childhood adversities, as in the case of people with high TSE load, has critical

clinical implications (Teicher & Samson, 2013; Nemeroff, 2016). These include more severe clinical course (Barnhofer *et al.* 2014; Kelly & Mezuk, 2017) and less favorable response to treatment (Tyrka *et al.* 2013; MacPherson *et al.* 2014; Miller *et al.* 2015). While most studies describing the unfavorable trajectory of early life adversity focused on patients ascertained for depression, here we describe detrimental associations between high TSE load and psychopathology and level of function in a non-psychiatrically ascertained population, with psychopathological associations extending beyond depression. Considering the high rate of stress exposure observed in our study (2 + TSE in almost 20% of the PNC) and a previous population-based study in community youth (Kessler *et al.* 2009), we propose that screening for adversity in clinical settings may help better determine risk, prognosis and treatment plan. Moreover, as we show robust association of TSE with psychopathology and cognition, and as there is evidence of association of trauma exposure with other phenotypes (e.g. imaging (Busso *et al.* 2017), inflammation (Baumeister *et al.* 2016)), screening and controlling for history of early TSE exposure may be warranted in research studies involving children and adolescents.

Our study has several limitations. First, the cross-sectional data of the PNC limit causal inferences from TSE to psychopathology and related outcomes. Most prominently, it is difficult to disentangle the possibility of early sensitization to consequent PTSD and depression following early life adversity associated with later trauma exposure (McLaughlin *et al.* 2017). We tried to address that limitation through conducting a regression model controlling for lifetime PTSD and depression and showing that the association between exposure and psychopathology remains significant. The cross-sectional nature of the study also constrains inferring directionality between stress exposure, psychopathology, and the associated poorer cognitive efficiency we observed, and warrants longitudinal investigation in prospective studies. Another limitation is that TSEs were endorsed from a list of eight events, not allowing evaluation of other forms of early life adversity. As a result, we do not have measures for childhood neglect or chronicity of abuse - factors that significantly affect development (McLaughlin & Sheridan, 2016). Furthermore, in this study 'load' refers to the endorsement across multiple categories and types of TSE, but we cannot account for 'load' wherein an individual may have experienced repeated or ongoing exposures within a category or type of stressor. That we nonetheless found robust clinical associations with load, as defined in this study, may highlight the broad role of traumatic stress during brain development in mental health, cognition, and function.

In conclusion, in a community ascertained, socio-demographically diverse, generalizable US youth population we found that traumatic stress exposure is strongly associated with a broad range of psychopathology domains, lower functional level and poorer cognitive efficiency. The psychopathology profile involved higher symptom burden that extended beyond the well-described stress-related disorders PTSD and depression. The results are relevant to child and adolescent mental health policy, as we show that administration of a short screen for TSE may reveal information that is robustly associated with mental illness in community youth and may identify at risk populations (Asselmann *et al.* 2018). The high exposure rates we and others have observed further underscore the effort required from society to minimize childhood adversities (Shonkoff *et al.* 2009; Walker *et al.* 2011). More research is needed to better understand the biological mechanisms underlying the developing brain's vulnerability to stress and elucidate causative pathways.

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Declaration of interest. Barzilay serves on the scientific board and reports stock ownership in 'Taliaz Health', with no conflict of interest relevant to this work. All other authors declare no potential conflict of interest.

References

Asselmann E, *et al.* (2018) Sociodemographic, clinical, and functional long-term outcomes in adolescents and young adults with mental disorders. *Acta Psychiatrica Scandinavica* **137**, 6–17.

Baldwin JR, *et al.* (2018) Childhood victimization and inflammation in young adulthood: a genetically sensitive cohort study. *Brain, Behavior, and Immunity* **67**, 211–217.

Bale TL and Epperson CN (2015) Sex differences and stress across the lifespan. *Nature Neuroscience* **18**, 1413–1420.

Barnhofer T, *et al.* (2014) A comparison of vulnerability factors in patients with persistent and remitting lifetime symptom course of depression. *Journal of Affective Disorders* **152–154**, 155–161.

Baumeister D, *et al.* (2016) Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. *Molecular Psychiatry* **21**, 642–649.

Berens AE, Jensen SKG and Nelson CA (2017) Biological embedding of childhood adversity: from physiological mechanisms to clinical implications. *BMC Medicine* **15**, 135.

Busso DS, *et al.* (2017) Child abuse, neural structure, and adolescent psychopathology: a longitudinal study. *Journal of the American Academy of Child and Adolescent Psychiatry* **56**, 321–328.e1.

Calkins ME, *et al.* (2015) The Philadelphia Neurodevelopmental Cohort: constructing a deep phenotyping collaborative. *Journal of Child Psychology and Psychiatry* **56**, 1356–1369.

Calkins ME, *et al.* (2014) The psychosis spectrum in a young U.S. Community sample: findings from the Philadelphia Neurodevelopmental Cohort. *World Psychiatry* **13**, 296–305.

Carliner H, *et al.* (2017) Trauma exposure and externalizing disorders in adolescents: results from the national comorbidity survey adolescent supplement. *Journal of the American Academy of Child and Adolescent Psychiatry* **56**, 755–764.e3.

Cort NA, *et al.* (2012) Predictors of treatment outcomes among depressed women with childhood sexual abuse histories. *Depression and Anxiety* **29**, 479–486.

Cowell RA, *et al.* (2015) Childhood maltreatment and its effect on neurocognitive functioning: timing and chronicity matter. *Development and Psychopathology* **27**, 521–533.

Danese A, *et al.* (2017) The origins of cognitive deficits in victimized children: implications for neuroscientists and clinicians. *American Journal of Psychiatry* **174**, 349–361.

Derry HM, *et al.* (2015) Sex differences in depression: does inflammation play a role? *Current Psychiatry Reports* **17**, 78.

Elton A, *et al.* (2014) Childhood maltreatment is associated with a sex-dependent functional reorganization of a brain inhibitory control network. *Human Brain Mapping* **35**, 1654–1667.

Evans GW, Li D and Whipple SS (2013) Cumulative risk and child development. *Psychological Bulletin* **139**, 1342–1396.

Everaerd D, *et al.* (2012) Sex modulates the interactive effect of the serotonin transporter gene polymorphism and childhood adversity on hippocampal volume. *Neuropsychopharmacology* **37**, 1848–1855.

Everaerd D, *et al.* (2016) Childhood abuse and deprivation are associated with distinct sex-dependent differences in brain morphology. *Neuropsychopharmacology* **41**, 1716–1723.

Gilman SE, *et al.* (2015) Contributions of the social environment to first-onset and recurrent mania. *Molecular Psychiatry* **20**, 329–336.

Gur RC, *et al.* (2010) A cognitive neuroscience-based computerized battery for efficient measurement of individual differences: standardization and initial construct validation. *Journal of Neuroscience Methods* **187**, 254–262.

Hardt J and Rutter M (2004) Validity of adult retrospective reports of adverse childhood experiences: review of the evidence. *Journal of Child Psychology and Psychiatry, and Allied Disciplines* **45**, 260–273.

Heim C and Binder EB (2012) Current research trends in early life stress and depression: review of human studies on sensitive periods, gene–environment interactions, and epigenetics. *Experimental Neurology* **233**, 102–111.

Karam EG, *et al.* (2014) Cumulative traumas and risk threshold: 12-month PTSD in the world mental health (WMH) surveys. *Depression and Anxiety* **31**, 130–142.

Kaufman J, *et al.* (1997) Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. *Journal of the American Academy of Child & Adolescent Psychiatry* **36**, 980–988.

Kelly KM and Mezuk B (2017) Predictors of remission from generalized anxiety disorder and major depressive disorder. *Journal of Affective Disorders* **208**, 467–474.

Kessler RC, *et al.* (2009) National comorbidity survey replication adolescent supplement (NCS-A): II. Overview and design. *Journal of the American Academy of Child and Adolescent Psychiatry* **48**, 380–385.

Lee FS, *et al.* (2014) Adolescent mental health–Opportunity and obligation. *Science* **346**, 547–549.

Liu H, *et al.* (2017) Association of *DSM-IV* posttraumatic stress disorder with traumatic experience type and history in the World Health Organization World Mental Health Surveys. *JAMA Psychiatry* **74**, 270.

Lowe SR, *et al.* (2017) Pathways from assaultive violence to post-traumatic stress, depression, and generalized anxiety symptoms through stressful life events: longitudinal mediation models. Cambridge University Press. *Psychological Medicine* **47**, 2556–2566.

MacMillan HL, *et al.* (2001) Childhood abuse and lifetime psychopathology in a community sample. *American Journal of Psychiatry* **158**, 1878–1883.

MacPherson HA, *et al.* (2014) Predictors and moderators in the randomized trial of multifamily psychoeducational psychotherapy for childhood mood disorders. *Journal of Clinical Child & Adolescent Psychology* **43**, 459–472.

Malarbi S, *et al.* (2017) Neuropsychological functioning of childhood trauma and post-traumatic stress disorder: a meta-analysis. *Neuroscience & Biobehavioral Reviews* **72**, 68–86.

Markon KE, Chmielewski M and Miller CJ (2011) The reliability and validity of discrete and continuous measures of psychopathology: a quantitative review. *Psychological Bulletin* **137**, 856–879.

McCutcheon VV, *et al.* (2009) Accumulation of trauma over time and risk for depression in a twin sample. *Psychological medicine* **39**, 431–441.

McEwen BS (1998) Stress, adaptation, and disease: Allostasis and Allostatic Load. Blackwell Publishing Ltd Annals of the New York. *Academy of Sciences* **840**, 33–44.

McEwen BS (2017) Allostasis and the epigenetics of brain and body health over the life course. *JAMA Psychiatry* **74**, 551.

McGrath JJ, *et al.* (2017) The association between childhood adversities and subsequent first onset of psychotic experiences: a cross-national analysis of 23 998 respondents from 17 countries. *Psychological Medicine* **47**, 1230–1245.

McLaughlin KA (2016) Future directions in childhood adversity and youth psychopathology. *Journal of Clinical Child & Adolescent Psychology* **45**, 361–382.

McLaughlin KA, *et al.* (2012) Childhood adversities and first onset of psychiatric disorders in a national sample of US adolescents. *Archives of General Psychiatry* **69**, 1151.

McLaughlin KA, *et al.* (2017) Childhood adversities and post-traumatic stress disorder: evidence for stress sensitisation in the World Mental Health Surveys. *The British Journal of Psychiatry* **211**, 280–288.

McLaughlin KA and Sheridan MA (2016) Beyond cumulative risk: a dimensional approach to childhood adversity. *Current Directions in Psychological Science* **25**, 239–245.

Merikangas K, *et al.* (2009) National comorbidity survey replication adolescent supplement (NCS-A): I. Background and measures. NIH Public Access. *Journal of the American Academy of Child and Adolescent Psychiatry* **48**, 367–369.

Messman-Moore TL and Bhuptani PH (2017) A review of the long-term impact of child maltreatment on posttraumatic stress disorder and its comorbidities: an emotion dysregulation perspective. *Clinical Psychology: Science and Practice* **24**, 154–169.

Miller ML and Brock RL (2017) The effect of trauma on the severity of obsessive-compulsive spectrum symptoms: a meta-analysis. *Journal of Anxiety Disorders* **47**, 29–44.

Miller S, *et al.* (2015) Cognition-childhood maltreatment interactions in the prediction of antidepressant outcomes in major depressive disorder patients: results from the i-SPOT D trial. *Depression and Anxiety* **32**, 594–604.

Moore TM, *et al.* (2016) Characterizing social environment's association with neurocognition using census and crime data linked to the Philadelphia Neurodevelopmental Cohort. *Psychological Medicine* **46**, 599–610.

Moore TM, *et al.* (2015) Psychometric properties of the Penn computerized neurocognitive battery. *Neuropsychology* **29**, 235–246.

Nemeroff CB (2016) Paradise lost: the neurobiological and clinical consequences of child abuse and neglect. *Neuron* **89**, 892–909.

Newbury JB, *et al.* (2017) Measuring childhood maltreatment to predict early-adult psychopathology: comparison of prospective informant-reports and retrospective self-reports. Elsevier. *Journal of Psychiatric Research* **96**, 57–64.

Pinheiro J, *et al.* and RCT (2017) *Linear and Nonlinear Mixed Effects Models*. 3.1-128.

Ribeiro WS, *et al.* (2013) The impact of epidemic violence on the prevalence of psychiatric disorders in Sao Paulo and Rio de Janeiro, Brazil. Ed. U Schmidt. *PLoS ONE* **8**, e63545.

Scott JC, *et al.* (2015) A quantitative meta-analysis of neurocognitive functioning in posttraumatic stress disorder. *Psychological Bulletin* **141**, 105–140.

Shaffer D, *et al.* (1983) A children's global assessment scale (CGAS). *Archives of General Psychiatry* **40**, 1228–1231.

Shanmugan S, *et al.* (2016) Common and dissociable mechanisms of executive system dysfunction across psychiatric disorders in youth. *American Journal of Psychiatry* **173**, 517–526.

Shonkoff JP, Boyce WT and McEwen BS (2009) Neuroscience, molecular biology, and the childhood roots of health disparities: building a new framework for health promotion and disease prevention. *JAMA* **301**, 2252–2259.

Suliman S, *et al.* (2009) Cumulative effect of multiple trauma on symptoms of posttraumatic stress disorder, anxiety, and depression in adolescents. *Comprehensive Psychiatry* **50**, 121–127.

Teicher MH and Samson JA (2013) Childhood maltreatment and psychopathology: a case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. American Psychiatric AssociationArlington, VA. *American Journal of Psychiatry* **170**, 1114–1133.

Teicher MH, Tomoda A and Andersen SL (2006) Neurobiological consequences of early stress and childhood maltreatment: are results from

human and animal studies comparable? *Annals of the New York Academy of Sciences* **1071**, 313–323.

Tyrka AR, *et al.* (2013) The neurobiological correlates of childhood adversity and implications for treatment. *Acta Psychiatrica Scandinavica* **128**, 434–447.

Walker SP, *et al.* (2011) Inequality in early childhood: risk and protective factors for early child development. *The Lancet* **378**, 1325–1338.

Wiersma JE, *et al.* (2009) The importance of childhood trauma and childhood life events for chronicity of depression in adults. Physicians Postgraduate Press, Inc. *The Journal of Clinical Psychiatry* **70**, 983–989.

Wilkinson G (2006) *WRAT 4 : wide range achievement test professional manual*, 4th edn., Lutz, FL: Psychological Assessment Resources Inc.