The Consequences of Foster Care Versus Institutional Care in Early Childhood on Adolescent Cardiometabolic and Immune Markers: Results From a Randomized Controlled Trial

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ABSTRACT

Objective: Children exposed to institutional rearing often exhibit problems across a broad array of developmental domains. We compared the consequences of long-term, high-quality foster care versus standard institution-based care, which began in early childhood on cardiometabolic and immune markers assessed at the time of adolescence.

Methods: The Bucharest Early Intervention Project is a longitudinal investigation of children institutionalized during early childhood (ages 6 to 30 months at baseline) who were subsequently randomized to either high-quality foster care or continued institutional care. At the age of 16 years, 127 respondents participated in a biomarker collection protocol, including 44 institutionalized children randomly assigned to receive care as usual, 41 institutionalized children randomized to be removed from institutional care and placed in high-quality foster care in infancy, and a control group of 42 demographically matched children raised in biological families. Outcomes included body mass index (BMI), systolic and diastolic blood pressure, C-reactive protein, interleukin (IL)-6, IL-8, IL-10, tumor necrosis factor α, glycosylated hemoglobin A1c, and Epstein-Barr virus antibody titers.

Results: Early institutional rearing was not associated with differences in cardiometabolic or immune markers. Randomization to foster care and age of placement into foster care were also unrelated to these markers, with the exception of BMI z-score, where children assigned to care as usual had lower BMI z-scores relative to children assigned to foster care (−0.23 versus 0.08, $p = .06$), and older age at placement was associated with lower BMI ($\beta = -0.07$, $p = .03$).

Conclusions: The impact of institutional rearing on measures of cardiometabolic health and immune system functioning is either absent or not evident until later in development. These findings provide new insights into the biological embedding of adversity and how it varies developmentally and across regulatory systems and adversity type.

Clinical Trial Registration: NCT00747396

Key words: cardiovascular, children, deprivation, immune, inflammation, institutional rearing, metabolic.

INTRODUCTION

Childhood adversity is an important determinant of chronic diseases in adulthood (1,2), including cardiometabolic diseases, which have their origins early in life (3,4). Institutional rearing is a severe form of childhood adversity often characterized by extreme psychosocial deprivation (5,6). The Bucharest Early Intervention Project (BEIP) (5–7) and other studies of children with histories of institutional care (8–14) have provided insight into brain and behavioral abnormalities associated with early psychosocial deprivation and the advantages of foster care over institutional care across many developmental domains (5). Harmful effects of early psychosocial deprivation have been documented for a vast array of developmental outcomes, including growth (15,16), cognition and language ability (7,17), neural structure (18) and function (19), social and emotional functioning (20,21), motor outcomes (22), and psychopathology (11,12,23–25). However, the extent to which early psychosocial deprivation affects key biological processes involved in the development of chronic diseases in adulthood is unknown. Examining the links between early deprivation and biomarkers of chronic

BEIP = Bucharest Early Intervention Project, **BMI** = body mass index, **CAUG** = care as usual group, **CRP** = C-reactive protein, **DBP** = diastolic blood pressure, **EBV** = Epstein-Barr virus, **FCG** = foster care group, **HbA1c** = glycosylated hemoglobin a1c, **IL-6** = interleukin-6, **IL-8** = interleukin-8, **IL-10** = interleukin-10, **ITT** = intent-to-treat, **NIG** = never-institutionalized group, **SBP** = systolic blood pressure, **TNF-α** = tumor necrosis factor alpha

SDC Supplemental Content

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disease (i.e., predisease processes or conditions) before adulthood—and whether placement into foster care attenuates these associations—can shed light on early-life determinants of chronic disease risk and the potential for enriched social environments to mitigate this risk. The objective of this study is to examine the long-term effects of early institutional rearing and subsequent randomization into foster care on cardiometabolic and immune markers in adolescence.

Extensive research has documented biomarkers in adulthood that may serve as mechanisms (26–29) linking childhood adversity to chronic diseases in adulthood (30–32). Fewer studies have examined the biological consequences of adversity on inflammation (33–35), metabolic abnormalities (27,36,37), or immune system functioning (38–41) that are evident during childhood and adolescence, and systematic reviews on this topic show mixed results across studies (36,42). Given that measures of cardiometabolic function, such as blood pressure (BP) (43,44), body mass index (BMI) (44,45), glucose metabolism (46,47), and C-reactive protein (CRP) (48) track from childhood into adulthood, it is important to identify when dysregulation in response to childhood adversity begins (49). Emerging evidence suggests that different forms of childhood adversity may have distinct influences on neural development (50,51). Childhood neglect—the most frequent form of childhood maltreatment (52), shown to be associated with brain structure (53,54) and function (16,55) and psychopathology (24,56)—is frequently combined with physical and sexual abuse within research studies (52). However, because research on the biological consequences of child maltreatment has advanced, increasing evidence suggests that neglect may have a unique impact on neural structure and functioning relative to other forms of maltreatment (51,57), which could result in distinct effects on downstream regulatory systems as well (58,59). Related institutional rearing is often associated with nutritional deprivation (60) that may have a distinct influence on cardiometabolic risk relative to the influence of other types of adversity. Finally, evidence from the BEIP (7,61) and other cohorts (62) shows that earlier placement into foster care is protective for neurodevelopmental outcomes; however, to our knowledge, no prior studies have examine whether cardiometabolic or immune markers are related to age of placement into foster care.

In this study, we investigated differences in cardiometabolic and immune markers in the BEIP at the age of 16 years. Based on the extreme impact of institutionalization for other developmental outcomes, combined with prior observational studies that show a positive association between childhood maltreatment and cardiometabolic and immune-related risk in youth (34,63,64) and adults (27,65–67), including a study of previously institutionalized children (39), we hypothesized that adolescents with a history of institutional rearing would display elevated levels of cardiometabolic—CRP, interleukin (IL)-6, IL-8, tumor necrosis factor alpha (TNF-α), glycosylated hemoglobin A1c (HbA1c), systolic and diastolic BP, and BMI z-score—and immune (Epstein-Barr virus [EBV] antibody titers) biomarkers, compared with demographically matched children raised in biological families. Of note, EBV antibody titers can be used as an indirect measure of cell-mediated immune function, because once an individual is infected, it remains (asymptomatically) in the body for life and adequate cell-mediated immune function is required to maintain EBV in a latent state (68,69). We predicted that IL-10 would be lower among previously institutionalized children in comparison with the never-institutionalized group (NIG), given that IL-10 is an anti-inflammation marker (70,71). We expected that institutionalized children randomly assigned to foster care would display lower levels of these markers (and higher IL-10) compared with children randomized to care as usual. Finally, based on prior studies (7,61,62), we hypothesized that earlier placement in foster care would produce lower cardiometabolic and immune risk across outcomes.

METHODS

Procedure

The BEIP is a longitudinal, randomized controlled trial of children who were raised in institutions from early infancy (6). Children in institutional care were recruited from institutions for young children in Bucharest, Romania. A total of 187 children in institutional care were screened for eligibility, and 51 were deemed ineligible because of medical reasons (Figure 1). Accordingly, 136 children (aged 6 to 30 months) were recruited into the institutional care sample. Children in this group had lived in an institution for at least half of their life, and most had spent their entire life in an institution. At baseline, half of these children were randomly assigned to high-quality foster care that was developed and monitored by the BEIP team (i.e., foster care group [FCG]; $n = 68$). The other children remained in institutional care (*i.e.*, care as usual group [CAUG]; $n = 68$). The randomization procedure and intervention have been described in detail elsewhere (6). Foster parents were paid a salary according to Romanian law. In addition, they received support from social workers that were a part of the BEIP team. At the time of randomization to foster care, 43 families received 1 child, 6 received 2 (unrelated) children each, and 4 families received 2 siblings (placed together) (72). A sample of age- and sex-matched typically developing children was recruited from pediatric clinics (i.e., NIG; $n = 72$), and additional children from the community have been included at subsequent follow-ups. At baseline, there were no differences in sex, birth weight, age, or percent of life spent in an institution between the FCG and CAUG.

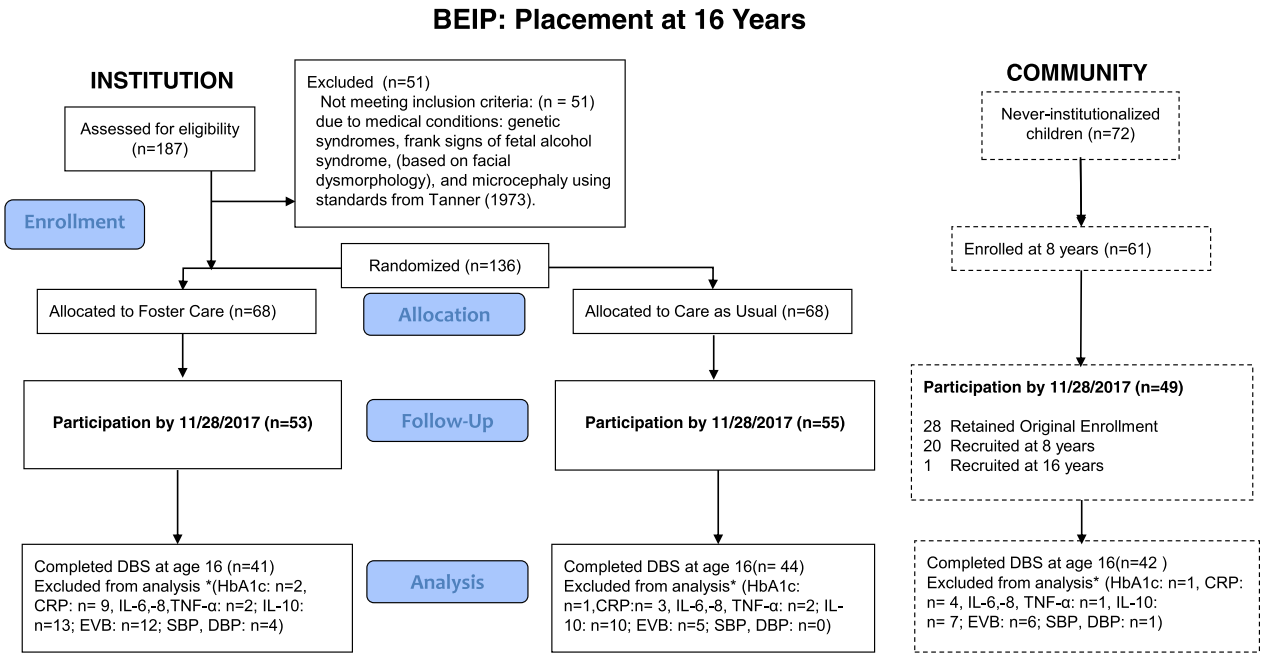
The BEIP was initiated in collaboration with the Institute of Maternal and Child Health of the Romanian Ministry of Health, and there were extensive procedures to ensure its ethical integrity (73–75). The study protocol was approved by an ethical committee with appointees from Bucharest University and several government departments, the local commissions on child protection in Bucharest, and the institutional review boards at three home institutions of the primary investigators (C.H.Z., C.A.N., and N.A.F.).

During follow-up, some of the FCG children moved away from their BEIP foster care placement and some of the CAUG children moved out of institutions. Among the 53 FCG children who participated in the age 16 follow-up, 24 were in BEIP foster care, 2 were adopted, 11 returned to their biological families, 6 were in government foster care, and 10 were in institutional care. Among the 55 CAUG in the age 16 follow-up, 23 were in institutional care, 4 were adopted, 20 returned to their biological families, and 8 were in government foster care.

Participants

In adolescence (age range: 15.49–17.97 years), 127 children provided blood samples ($n = 127$: 44 CAUG, 41 FCG, 42 NIG, see Table 1 for participant characteristics and Figure 1 for CONSORT diagram). Thirteen participants who completed other components of the age 16 follow-up declined to participate in blood collection. There were no differences between CAUG and FCG children who provided blood samples compared with those who did not on sex ($p = .97$), ethnicity, ($p = .08$), birth weight ($p = .49$), baseline BMI ($p = .32$), and baseline age ($p = .56$). We excluded one participant who was pregnant and one participant who was breastfeeding from all analyses.

Each child's legal guardian provided informed consent, and each child provided written assent, unless the child had an intellectual disability, in which case the child to provided verbal assent instead.



*Exclusion from blood spot analysis at age16 is due to assay results below the limit of detection, insufficient quantity of sample or missing data.

FIGURE 1. Participant flow diagram. Color image is available only in online version (www.psychosomaticmedicine.org).

Biological Measures

Height, weight, and BP were measured by a trained research assistant before blood samples were drawn. We calculated age- and sex-standardized BMI z-scores according to the World Health Organization reference values (76). BP was obtained three times using an automated monitor (Omron 7 Series) following a standardized protocol, and we calculated the average of the second and third readings for analyses.

Blood was collected following a standardized noninvasive protocol (77). Trained research assistants cleaned the participant's middle or ring finger and then pricked it with a micro-lancet. The first drop of blood was wiped away and discarded. The second drop was collected using a microcuvette and was analyzed immediately using a point-of-care device to measure glycated hemoglobin (HbA1c; HemoCue Hb 501 analyzer) (78). HbA1c is reported as a percent, reflecting the average blood glucose levels in the preceding 2 to 3 months (79).

Four or five subsequent drops of blood of approximately 50 μL each were applied to filter paper and air-dried for a minimum of 4 hours. After drying, each specimen was stored in a resealable bag and placed in a −20°C freezer until it was shipped by courier service on dry ice to the Laboratory of Human Biology Research in Evanston, Illinois, for processing. Five inflammation markers (CRP, IL-6, IL-8, IL-10, TNF-α) and one immune biomarker (EBV antibody titers) were assayed according to procedures developed and validated for DBS. CRP was measured using a high-sensitivity assay developed at the Laboratory of Human Biology Research (80). IL-6 was measured using a modification of the R&D Systems Quantikine HS Human IL-6 (Kit# HS600B) (81). IL-8, IL-10, and TNF-α were measured using a modified version of the Meso Scale Discovery V-PLEX Custom Human Cytokine electrochemiluminescent assay (Kit# K151A0H-1) (82). The between-assay coefficients of variability (%CV) for low, mid, and high control samples were as follows: CRP (12.35, 4.23, 6.98), IL-6 (12.75, 6.97, 4.77),

TABLE 1. Comparison of Children in Institutional Care Randomly Assigned to Usual Care and Foster Care, and Children Without Histories of Institutional Care ($N = 127$)

Child Characteristic		Care as Usual ($n = 44$)	Foster Care ($n = 41$)	Never Institutionalized ($n = 42$)
Sex	Male, *n* (%)	22 (50%)	20 (48.8%)	18 (43.9%)
Ethnicity	Romanian, *n* (%)	21 (47.7%)	23 (56.1%)	39 (92.7%)
	Roma, unknown, or other, *n* (%)	23 (52.3%)	18 (43.9%)	3 (7.3%)
Any medication	Yes, *n* (%)	6 (13.6%)	10 (24.4%)	9 (22.0%)
Hypertension medication	Yes, *n* (%)	0 (0.0%)	2 (4.9%)	0 (0.0%)
Glucose medication	Yes, *n* (%)	1 (2.5%)	0 (0.0%)	1 (2.3%)
Body temperature, M (SD), °C		36.64 (0.06)	36.69 (0.06)	36.63 (0.06)
Age at 16-y assessment, M (SD), mo		202.05 (1.20)	200.58 (1.11)	200.50 (0.92)
Age at entry to institution, M (SD), mo		2.90 (4.03)	2.95 (4.23)	—
Months of institutionalization before baseline assessment, M (SD)		17.45 (8.50)	16.56 (7.47)	—

M (SD) = mean (standard deviation).

IL-8 (9.69, 3.32, 8.19), IL-10 (32.46, 10.01, 6.74), and TNF-α (37.00, 14.13, 6.34). The between-assay CVs for low and high EBV antibody controls were 9.35 and 7.67, respectively. CRP, IL-6, IL-8, IL-10, and EBV were not normally distributed and were log transformed in some analyses.

Age of Foster Care Placement

We used a continuous measure for age of foster care placement in months for FCG participants (range = 6.81–33.01).

Covariates

Age, use of medications, and body temperature (degree Celsius, assessed twice using an infrared thermometer and averaged) were recorded. Temperature was included as a covariate for outcomes that can be expected to vary based on body temperature (i.e., measures of inflammation and immune system functioning, and blood pressure outcomes).

Statistical Analyses

We compared unadjusted medians and marginal means (and 95% confidence intervals, estimated using generalized linear models with 1000 bootstrapped permutations) for each cardiometabolic and immune biomarker to test differences between (*a*) institutionalized and never-institutionalized children and (*b*) previously institutionalized children randomized to the FCG compared with CAUG. Consistent with prior BEIP studies (5,24), we used an intent-to-treat (ITT) analysis.

Adjusted comparisons of inflammation and immune system functioning (i.e., CRP, IL-6, IL-8, IL-10, TNF-α, EBV antibodies) controlled for BMI z-score, temperature, age, sex, ethnicity, and medication use. Group differences in HbA1c excluded two individuals taking drugs to control glucose levels, and the adjusted comparison controlled for BMI z-score, age, sex, and ethnicity. Group differences in SBP and DBP excluded two individuals taking medications for hypertension, and controlled for BMI z-score, temperature, age, sex, ethnicity, and any medication use. The adjusted model for BMI z-score controlled only for ethnicity (given that ethnic minorities are overrepresented among the children with institutional care).

Finally, to examine whether earlier placement in foster care was associated with the outcomes among FCG children, we regressed each outcome on age at foster care placement.

RESULTS

Institutional Rearing Effects

Children reared in institutions did not differ from NIG children on any of the biological measures, in both unadjusted median and mean comparisons and adjusted mean comparisons (Table 2 and Table S2, Supplemental Digital Content 2, http://links.lww.com/PSYMED/A558). In Table S1, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A557, we display the univariate distributions for each biomarker for the total sample.

Randomization to Foster Care

Among the children with a history of institutional rearing, children randomized to foster care did not differ from the CAUG on any biological measures, in median or mean comparisons (Table 2 and Table S3, Supplemental Digital Content 3, http://links.lww.com/PSYMED/A559), other than BMI z-score for the mean comparison only. FCG children had a higher BMI z-score relative to CAUG children, although the average BMI z-scores for both groups were within the healthy range according to World Health Organization reference values (76).

Timing Effects

Among the FCG children, we do not observe any associations between age at placement into foster care and the biological measures, for bivariate or adjusted associations, with the exception of BMI z-score. As shown in Table 3, an older age at foster care placement

TABLE 2. Median Values (and Interquartile Ranges) for Biomarkers of Chronic Disease Risk at the Age of 16 Years

	Children in Institutional Care at Baseline	Children With No History of Institutionalized Care	*p*	Children in Institutional Care at Baseline		*p*
				Foster Care	Care as Usual	
BMI z-score	−0.04 (1.55)	0.17 (1.94)	.74	0.08 (1.96)	−0.23 (1.08)	.056
BMI, kg/m^2	20.87 (4.83)	21.33 (5.41)	.77	21.38 (6.98)	20.77 (2.89)	.050
SBP, mm Hg[a]	110.00 (17.00)	106.65 (16.00)	.34	109.00 (16.00)	110.00 (17.00)	.92
DBP, mm Hg[a]	69.00 (13.00)	70.00 (11.00)	.89	70.00 (15.00)	69.00 (13.00)	.51
HbA1c, %[b]	5.10 (0.40)	5.00 (0.45)	.36	5.10 (0.60)	5.10 (0.40)	.74
CRP, mg/l	0.40 (0.77)	0.45 (1.43)	.84	0.46 (0.93)	0.32 (0.74)	.44
IL-6, pg/ml	1.83 (0.69)	1.23 (0.82)	.44	1.29 (0.67)	1.30 (0.71)	.99
IL-8, pg/ml	80.36 (28.8)	72.27 (37.99)	.25	73.14 (24.51)	84.68 (30.76)	.27
IL-10, pg/ml	0.69 (0.45)	0.85 (0.55)	.22	0.61 (0.40)	0.72 (0.54)	.77
TNF-α, pg/ml	2.98 (0.89)	3.15 (0.90)	.41	2.85 (0.87)	3.00 (0.94)	.93
EBV antibody titers, U/ml	87.88 (133.76)	133.19 (178.16)	.20	94.88 (84.02)	75.59 (186.92)	.76

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; HbA1c = glycosylated hemoglobin a1c; CRP = C-reactive protein; IL-6 = interleukin-6; IL-8 = interleukin-8; IL-10 = interleukin-10; TNF-α = tumor necrosis factor alpha; EBV = Epstein-Barr virus.

p values were obtained from Mann-Whitney *U* test.

For comparison 1, BMI: $n = 124$; SBP: $n = 122$; DBP $n = 122$; HbA1c: $n = 122$; CRP: $n = 111$; IL-6: $n = 123$ and: $n = 122$; IL-8: $n = 123$ and: $n = 122$; IL-10: $n = 97$ and: $n = 96$; TNF-α: $n = 123$ and: $n = 122$; EBV antibody titers: $n = 104$. For comparison 2, BMI: $n = 83$; SBP: $n = 81$; DBP: $n = 81$; HbA1c: $n = 82$; CRP: $n = 73$; IL-6: $n = 81$; IL-8: $n = 81$; IL-10: $n = 62$; TNF-α: $n = 81$; EBV antibody titers: $n = 68$.

[a] Excludes individuals who are on medications for hypertension.

[b] Excludes individuals who are on medications to control glucose. Samples sizes are slightly different due to medication exclusions for certain outcomes, assay results below the limit of detection, insufficient quantity of sample, or missing data.

TABLE 3. Age of Foster Care Placement and Cardiometabolic and Immune Biomarkers at Age 16 Among Participants Assigned to Foster Care

Outcome	β	(95% CI)	*p*
BMI z-score[a]	−0.07	(−0.12 to −0.01)	.033
SBP, mm Hg[b,c]	−0.53	(−1.95 to 0.85)	.42
DBP, mm Hg[b,c]	−0.90	(−2.49 to 0.49)	.24
HbA1c, %[d,e]	0.03	(−0.31 to 0.15)	.82
(log) CRP, mg/ml[b]	−0.01	(−0.08 to 0.09)	.77
(log) IL-6, pg/ml[b]	−0.02	(−0.05 to 0.004)	.11
(log) IL-8, pg/ml[b]	0.01	(−0.003 to 0.03)	.24
(log) IL-10, pg/ml[b]	−0.02	(−0.09 to 0.07)	.64
TNF-α, pg/ml[b]	−0.03	(−0.15 to 0.07)	.56
(log) EBV antibody titers, U/ml[b]	0.01	(−0.04 to 0.06)	.82

CI = confidence interval; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; HbA1c = glycosylated hemoglobin a1c; CRP = C-reactive protein; IL-6 = interleukin-6; IL-8 = interleukin-8; IL-10 = interleukin-10; TNF-α = tumor necrosis factor alpha; EBV = Epstein-Barr virus.

Samples sizes are slightly different due to medication exclusions for certain outcomes, assay results below the limit of detection, insufficient quantity of sample or missing data: BMI: $n = 39$; SBP: $n = 39$; DBP: $n = 39$; HbA1c: $n = 39$; CRP: $n = 32$; IL-6: $n = 39$; IL-8: $n = 39$; IL-10: $n = 28$; TNF-α: $n = 39$; EBV antibody titers: $n = 39$.

[a] Adjusted for ethnicity.

[b] Adjusted for BMI z-score, temperature, age, sex, ethnicity, and any medication use.

[c] Excludes individuals who are on medications for hypertension.

[d] Adjusted for BMI z-score, age, sex, and ethnicity.

[e] Excludes individuals who are on medications to control glucose.

is associated with lower BMI z-score in adolescence ($p = .03$). Of note, duration of institutionalization before study baseline was unrelated to any biological measure (data not shown).

DISCUSSION

This study examined the impact of early psychosocial deprivation and randomization to foster care on a set of cardiometabolic health and immune markers in a sample of adolescents in Bucharest, Romania. Our study has three distinct strengths. First, this study included a diverse and validated assortment of biological measures that are known to track into adulthood and predict future chronic disease risk. Second, the study used a randomized design to examine the potential impact of foster care, which minimizes confounds by facilitating a strong counterfactual comparison group. Third, our participants were adolescents; younger samples (i.e., compared with samples in mid adulthood) may offer superior ability to detect biological dysregulation as a direct consequence of childhood adversity, because there is less heterogeneity in behavioral factors at earlier ages (e.g., tobacco use) that could introduce variation in these measures (83).

We observed no significant differences in measures of cardiometabolic health or immune system functioning for comparisons between (*a*) children with a history of institutional rearing and a community-matched sample of children reared in biological families or (*b*) children randomly assigned to a foster care intervention in infancy and children randomized to remain in institutional care, with the exception of BMI z-score, which was higher among the children assigned to foster care. Furthermore, the timing of placement into foster care among those who received the intervention was not associated with any biological measure, other than BMI z-score. To our knowledge, this is most comprehensive analysis to date on the effect of early institutional rearing and foster care intervention on blood-based biological measures of chronic disease risk during adolescence.

We found no evidence to support the hypothesis that institutional rearing influences cardiometabolic and immune markers. This contrasts with extensive evidence for harmful effects of institutional rearing across behavioral, cognitive, and neurological domains (7,11,12,15–25), as well as clear benefits of foster care intervention across many outcomes in the current cohort (5,84). Our results contrast with a case-control study finding that internationally adopted Romanian children ($n = 40$) had elevated HSV-1 antibody levels relative to demographically similar controls ($n = 80$), and with numerous studies of other forms of childhood adversity that report associations with dysregulation of inflammatory processes (33–35,85,86), cell-mediated immune response to latent viruses (38–41), and cardiometabolic abnormalities (27,36,37) during childhood and adolescence. However, literature on this topic is inconsistent and numerous studies do not find an association between early adversity and cardiometabolic risk factors in youth (see (27,36,42) for systematic reviews).

Potential Explanations for Null Results

Our findings raise questions about how the biological embedding of adverse childhood experiences might vary across regulatory systems and adversity type. Before addressing these, we considered several methodologic features that represent possible limitations and that could have falsely produced null results.

First, sample size is a concern. Although our sample size is small, other studies with similar sample sizes have documented associations between childhood adversity and immune inflammation markers in children and adolescents (e.g., TNF-α, $n = 112$ (85); CRP, $n = 69$ (86), HSV-1 antibody titers, $n = 155$ (39); antibody response to meningococcal serotype C vaccine, $n = 164$ (87)), and cardiometabolic markers (e.g., SBP and DBP, $n = 45$ (88)). If our null results are entirely a symptom of insufficient power, we would expect to observe patterns of group differences that align with our hypotheses but fall short of statistical significance, but that is not the case.

Second, considering our subset of outcomes derived from blood samples, we opted to collect finger-prick blood rather than a venous blood draw, because finger pricks are less invasive and could be expected to maximize participation (77). Although the assays used here have previously been validated as proxies for serum values, there may be variability in finger-prick blood (89). Notably, however, the laboratory that conducted our assays has validated drop-to-drop variability for all assays and obtained patterns of variability that are comparable with serum assays. Furthermore, other studies of childhood adversity and CRP (i.e., bullying, $n = 1420$ (90); maltreatment, $n = 174$ (34); perceived discrimination, $n = 42$ (88)) have used the similar finger-prick methodology and detected associations (34,90), which argues against finger-prick blood as an explanation for false null results. Relatedly, the between-assay CVs for the lowest tertiles of IL-10 and TNF-α are more than 10%. Thus, low precision of the assay results for the lower values on these two outcomes could be introducing random error into group comparisons. In post hoc sensitivity analyses, we confirmed that

our conclusions for IL-10 and TNF-α are unchanged if we conduct logistic regression analyses with each outcome dichotomized at the top quartile (Table S4, Supplemental Digital Content 4, http://links.lww.com/PSYMED/A560). We are not aware of validation studies of the assays used in our research, specific to child or adolescent populations; although there is no obvious reason to assume that the assays would function differently based on age, we suggest this as a direction for future research.

Third, specific to the null results for randomization to foster care, our comparison of FCG and CAUG used an ITT approach, which provides a conservative estimate of the treatment effect given that many children in CAUG eventually moved out of institutional settings (91). However, all prior studies on the main effect of BEIP have used ITT, and many have documented between group differences (5).

There is also a potential biological explanation for the lack of differences between the FCG and CAUG. The FCG has elevated BMI relative to the CAUG, which suggests greater nutritional deprivation in the CAUG, contributing to lower BMI. Indeed, the CAUG exhibited greater growth stunting at earlier assessments than the FCG (15). Lower BMI is expected to be associated with lower inflammation, HbA1c, and lower BP (92,93), and this pattern is opposite to the expected patterns of association with other forms of childhood adversity (27,31,36,42). It is possible that nutritional deprivation is masking the effects of psychosocial deprivation in the CAUG. Indeed, early childhood malnutrition is associated with neurodevelopmental and behavioral deficits (94–96), consistent with those observed in the CAUG children in BEIP (5,7,24). Although controlling for BMI should help reveal these associations, BMI is a crude measure of body composition (97,98), and adjustment may not be sufficient to reveal group differences. Unfortunately, we do not have information on nutritional status of the children across their lives, which may be a key element for understanding the results.

Future Directions

Our failure to support any of the study hypotheses raises a number of questions for future research. First, increasing evidence suggests that early exposure to deprivation has distinct consequences for neurobiological development as compared with other forms of adversity characterized by threat or socioeconomic disadvantage (50,51,57,99). To date, little research has examined the possibility of differential effects on cardiometabolic and immune markers across distinct types of early adversity (1,33,36). Institutional rearing may not impact cardiometabolic and immune markers in a manner similar to that observed for other adverse childhood exposures. For example, prior research on children with histories of institutional care (14,100) has not found evidence for earlier pubertal onset, which is consistently observed among children exposed to adversities characterized by threat (e.g., violence, abuse) (101–104). This distinction suggests that although some forms of adversity may accelerate processes linked to aging (e.g., pubertal timing (101–104), accelerated telomere erosion (105,106), and elevated inflammation (34)), institutionalization may be associated with delayed or atypical neurobiological development as the result of nutritional insufficiencies and growth hormone deficiencies (15,60,107), which could influence synaptic development (108), and thus a range of downstream outcomes. Indeed, delayed development across multiple biological systems has recently been observed among US children exposed to deprivation (58).

Alternatively, it is possible that psychosocial deprivation influences cardiometabolic health and the immune system, but not until later stages of development. As displayed in Table S1, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A557, the average levels of many of the risk of the biological measures were low (reflecting healthy profiles), with little variability around the means as indicated by the small standard deviations. Physiological systems and homeostatic processes tend to be more effective and efficient earlier in the lifespan (109), and this low variability may be why we did not detect links between early institutionalization and the study outcomes. Some existing studies suggest that biological dysregulation in response to early adversity may be observable in adolescents only within a stress-reactivity study, or ex vivo stimulation in a laboratory, but not under typical conditions. For example, female adolescents from harsh family climates had a larger ex vivo cytokine response to lipopolysaccharide stimulation relative to those from supportive families, but a difference was not evidence for basal levels of inflammatory activity (i.e., circulating IL-6) (110). Similarly, in a study of autonomic nervous system function in BEIP children at the age of 12 years using the Trier Social Stress Test (84), children randomized to CAUG had blunted autonomic nervous system stress responses relative to the FCG children and NIG children, yet there were no group differences in basal levels of heart rate, SBP, DBP, respiratory sinus arrhythmia, or markers of hypothalamic pituitary adrenal axis function. It is possible that group differences may emerge later, as the result of either (*a*) prolonged excess activation of the HPA axis, which eventually weakens regulatory systems (31,111–113), or (*b*) differences in health behaviors that have a cumulative impact on health as individuals age, such as poorer sleep, diet quality, and substance use, all of which are associated with chronic disease risk (114–116). In future research, it will be important to examine whether and when group differences emerge for trajectories of each outcome into adulthood, closer to the typical age of onset for common chronic diseases, and also the potential role of diet.

Finally, this study focused on the "main effects" of institutional rearing and foster care; potential differences may involve interactions with psychiatric symptoms (34,117,118) or other social factors, which represents another direction for research.

CONCLUSIONS

We find no evidence that early institutional rearing is associated with cardiometabolic or immune markers in adolescence or that earlier placement into foster care is associated with any of the outcomes, besides BMI z-score, which had an association in the direction opposite to our hypothesis. The impact of institutional rearing on cardiometabolic health and measures of immune system functioning may be minimal or not emerge until later in development. These findings raise questions about the biological embedding of adversity and how it varies developmentally and across regulatory systems and adversity type.

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REFERENCES

1. Suglia SF, Koenen KC, Boynton-Jarrett R, Chan PS, Clark CJ, Danese A, Faith MS, Goldstein BI, Hayman LL, Isasi CR. Childhood and adolescent adversity and cardiometabolic outcomes: a scientific statement from the American Heart Association. Circulation 2017;137:e15–28.
2. Shonkoff JP, Garner AS. The lifelong effects of early childhood adversity and toxic stress. Pediatrics 2012;129:E232–46.
3. Barr DA. The childhood roots of cardiovascular disease disparities. Mayo Clin Proc 2017;92:1415–21.
4. Laitinen TT, Pahkala K, Venn A, Woo JG, Oikonen M, Dwyer T, Mikkila V, Hutri-Kahonen N, Smith KJ, Gall SL, Morrison JA, Viikari JS, Raitakari OT, Magnussen CG, Juonala M. Childhood lifestyle and clinical determinants of adult ideal cardiovascular health: The Cardiovascular Risk in Young Finns Study, the Childhood Determinants of Adult Health Study, the Princeton Follow-up Study. Int J Cardiol 2013;169:126–32.
5. Zeanah CH, Humphreys KL, Fox NA, Nelson CA. Alternatives for abandoned children: insights from the Bucharest Early Intervention Project. Curr Opin Psychol 2017;15:182–8.
6. Zeanah CH, Nelson CA, Fox NA, Smyke AT, Marshall P, Parker SW, Koga S. Designing research to study the effects of institutionalization on brain and behavioral development: The Bucharest Early Intervention Project. Dev Psychopathol 2003;15:885–907.
7. Nelson CA, Zeanah CH, Fox NA, Marshall PJ, Smyke AT, Guthrie D. Cognitive recovery in socially deprived young children: The Bucharest early intervention project. Science 2007;318:1937–40.
8. Gunnar MR, Frenn K, Wewerka SS, Van Ryzin MJ. Moderate versus severe early life stress: associations with stress reactivity and regulation in 10-12-year-old children. Psychoneuroendocrinology 2010;35:326.
9. Gunnar MR, Frenn K, Wewerka SS, Van Ryzin MJ. Moderate versus severe early life stress: associations with stress reactivity and regulation in 10–12-year-old children. Psychoneuroendocrinology 2009;34:62–75.
10. Gunnar MR, Morison SJ, Chisholm K, Schuder M. Salivary cortisol levels in children adopted from Romanian orphanages. Dev Psychopathol 2001;13: 611–28.
11. Gunnar MR, Van Dulmen MH, Int Adoption Project Team. Behavior problems in postinstitutionalized internationally adopted children. Dev Psychopathol 2007; 19:129–48.
12. Kreppner JM, Rutter M, Beckett C, Castle J, Colvert E, Groothues C, Hawkins A, O'Connor TG, Stevens S, Sonuga-Barke EJ. Normality and impairment following profound early institutional deprivation: a longitudinal follow-up into early adolescence. Dev Psychol 2007;43:931–46.
13. Pollak SD, Nelson CA, Schlaak MF, Roeber BJ, Wewerka SS, Wiik KL, Frenn KA, Loman MM, Gunnar MR. Neurodevelopmental effects of early deprivation in postinstitutionalized children. Child Dev 2010;81:224–36.
14. Reid BM, Miller BS, Dorn LD, Desjardins C, Donzella B, Gunnar M. Early growth faltering in post-institutionalized youth and later anthropometric and pubertal development. Pediatr Res 2017;82:278–84.
15. Johnson DE, Guthrie D, Smyke AT, Koga SF, Fox NA, Zeanah CH, Nelson CA. Growth and associations between auxology, caregiving environment, and cognition in socially deprived Romanian children randomized to foster vs ongoing institutional care. Arch Pediatr Adolesc Med 2010;164: 507–16.
16. McLaughlin KA, Fox NA, Zeanah CH, Sheridan MA, Marshall P, Nelson CA. Delayed maturation in brain electrical activity partially explains the association between early environmental deprivation and symptoms of attention-deficit/hyperactivity disorder. Biol Psychiatry 2010;68:329–36.
17. Rutter M. Developmental catch-up, and deficit, following adoption after severe global early privation. English Romanian Adoptees (ERA) Study Team. J Child Psychol Psychiatry Allied Discip 1998;39:465–76.
18. Eluvathingal TJ, Chugani HT, Behen ME, Juhasz C, Muzik O, Maqbool M, Chugani DC, Makki M. Abnormal brain connectivity in children after early severe socioemotional deprivation: a diffusion tensor imaging study. Pediatrics 2006;117:2093–100.
19. Marshall PJ, Reeb BC, Fox NA, Nelson CA 3rd, Zeanah CH. Effects of early intervention on EEG power and coherence in previously institutionalized children in Romania. Dev Psychopathol 2008;20:861–80.
20. Zeanah CH, Smyke AT, Koga SF, Carlson E. Attachment in institutionalized and community children in Romania. Child Dev 2005;76:1015–28.
21. Ghera MM, Marshall PJ, Fox NA, Zeanah CH, Nelson CA, Smyke AT, Guthrie D. The effects of foster care intervention on socially deprived institutionalized children's attention and positive affect: results from the BEIP study. J Child Psychol Psychiatry 2009;50:246–53.
22. Levin AR, Zeanah CH, Fox NA, Nelson CA. Motor outcomes in children exposed to early psychosocial deprivation. J Pediatr 2014;164:123–9.e1.
23. Rutter ML, Kreppner JM, O'Connor TG, English Romanian Adoptees study team. Specificity and heterogeneity in children's responses to profound institutional privation. Br J Psychiatry 2001;179:97–103.
24. Zeanah CH, Egger HL, Smyke AT, Nelson CA, Fox NA, Marshall PJ, Guthrie D. Institutional rearing and psychiatric disorders in Romanian preschool children. Am J Psychiatry 2009;166:777–85.
25. Stevens SE, Sonuga-Barke EJ, Kreppner JM, Beckett C, Castle J, Colvert E, Groothues C, Hawkins A, Rutter M. Inattention/overactivity following early severe institutional deprivation: presentation and associations in early adolescence. J Abnorm Child Psychol 2008;36:385–98.
26. Baumeister D, Akhtar R, Ciufolini S, Pariante C, Mondelli V. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. Mol Psychiatry 2016;21:642–9.
27. Danese A, Tan M. Childhood maltreatment and obesity: systematic review and meta-analysis. Mol Psychiatry 2014;19:544–54.
28. Non AL, Rewak M, Kawachi I, Gilman SE, Loucks EB, Appleton AA, Roman JC, Buka SL, Kubzansky LD. Childhood social disadvantage, cardiometabolic risk, and chronic disease in adulthood. Am J Epidemiol 2014;180:263–71.
29. Pollitt RA, Kaufman JS, Rose KM, Diez-Roux AV, Zeng D, Heiss G. Early-life and adult socioeconomic status and inflammatory risk markers in adulthood. Eur J Epidemiol 2007;22:55–66.
30. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, Koss MP, Marks JS. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med 1998;14:245–58.
31. Danese A, McEwen BS. Adverse childhood experiences, allostasis, allostatic load, and age-related disease. Physiol Behav 2012;106:29–39.
32. Miller GE, Chen E, Parker KJ. Psychological stress in childhood and susceptibility to the chronic diseases of aging: moving toward a model of behavioral and biological mechanisms. Psychol Bull 2011;137:959–97.
33. Slopen N, Kubzansky LD, Koenen KC. Childhood adversity and immune and inflammatory biomarkers associated with cardiovascular risk in youth: a systematic review. Brain Behav Immun 2011;26:239–50.
34. Danese A, Caspi A, Williams B, Ambler A, Sugden K, Mika J, Werts H, Freeman J, Pariante CM, Moffitt TE, Arseneault L. Biological embedding of stress through inflammation processes in childhood. Mol Psychiatry 2011;16:244–6.
35. Slopen N, Kubzansky LD, McLaughlin KA, Koenen KC. Childhood adversity and inflammatory processes in youth: a prospective study. Psychoneuroendocrinology 2013;38:188–200.
36. Slopen N, Goodman E, Koenen KC, Kubzansky LD. Socioeconomic and other social stressors and biomarkers of cardiometabolic risk in youth: a systematic review of less studied risk factors. PLoS One 2013;8:e64418.
37. Nygren M, Carstensen J, Koch F, Ludvigsson J, Frostell A. Experience of a serious life event increases the risk for childhood type 1 diabetes: the ABIS population-based prospective cohort study. Diabetologia 2015; 58:1188–97.
38. Dowd JB, Palermo TM, Aiello AE. Family poverty is associated with cytomegalovirus antibody titers in U.S. Children. Health Psychol 2012;31:5–10.
39. Shirtcliff EA, Coe CL, Pollak SD. Early childhood stress is associated with elevated antibody levels to herpes simplex virus type 1. Proc Natl Acad Sci U S A 2009;106:2963–7.
40. Caserta MT, O'Connor TG, Wyman PA, Wang H, Moynihan J, Cross W, Tu X, Jin X. The associations between psychosocial stress and the frequency of illness, and innate and adaptive immune function in children. Brain Behav Immun 2008;22:933–40.
41. Wyman PA, Moynihan J, Eberly S, Cox C, Cross W, Jin X, Caserta MT. Association of family stress with natural killer cell activity and the frequency of illnesses in children. Arch Pediatr Adolesc Med 2007;161:228–34.
42. Slopen N, Koenen KC, Kubzansky LD. Childhood adversity and immune and inflammatory biomarkers associated with cardiovascular risk in youth: a systematic review. Brain Behav Immun 2012;26.
43. Chen X, Wang Y. Tracking of blood pressure from childhood to adulthood: a systematic review and meta-regression analysis. Circulation 2008;117: 3171–80.
44. Juhola J, Magnussen CG, Viikari JS, Kähönen M, Hutri-Kähönen N, Jula A, Lehtimäki T, Åkerblom HK, Pietikäinen M, Laitinen T, Jokinen E, Taittonen L, Raitakari OT, Juonala M. Tracking of serum lipid levels, blood pressure, and body mass index from childhood to adulthood: the cardiovascular risk in Young Finns study. J Pediatr 2011;159:584–90.
45. Singh AS, Mulder C, Twisk JW, van Mechelen W, Chinapaw MJ. Tracking of childhood overweight into adulthood: a systematic review of the literature. Obes Rev 2008;9:474–88.
46. Hofer SE, Raile K, Fröhlich-Reiterer E, Kapellen T, Dost A, Rosenbauer J, Grulich-Henn J, Holl RW. Tracking of metabolic control from childhood to young adulthood in type 1 diabetes. J Pediatr 165:956–61.e2.

47. Nguyen QM, Srinivasan SR, Xu J-H, Chen W, Kieltyka L, Berenson GS. Utility of childhood glucose homeostasis variables in predicting adult diabetes and related cardiometabolic risk factors: the Bogalusa Heart Study. Diabetes Care 2010;33:670–5.
48. Juonala M, Viikari JS, Ronnemaa T, Taittonen L, Marniemi J, Raitakari OT. Childhood C-reactive protein in predicting CRP and carotid intima-media thickness in adulthood: The Cardiovascular Risk in Young Finns Study. Arterioscler Thromb Vasc Biol 2006;26:1883–8.
49. Garner AS, Shonkoff JP, Siegel BS, Dobbins MI, Earls MF, McGuinn L, Pascoe J, Wood DL, Comm Psychosocial Aspects Child F, Comm Early Childhood Adoption D, Sect Dev Behav P. Early childhood adversity, toxic stress, and the role of the pediatrician: translating developmental science into lifelong health. Pediatrics 2012;129:E224–31.
50. McLaughlin KA. Future directions in childhood adversity and youth psychopathology. J Clin Child Adolesc Psychol 2016;45:361–82.
51. McLaughlin KA, Sheridan MA. Beyond cumulative risk: a dimensional approach to childhood adversity. Curr Dir Psychol Sci 2016;25:239–45.
52. Gilbert R, Widom CS, Browne K, Fergusson D, Webb E, Janson S. Burden and consequences of child maltreatment in high-income countries. The lancet 2009; 373:68–81.
53. McLaughlin KA, Sheridan MA, Winter W, Fox NA, Zeanah CH, Nelson CA. Widespread reductions in cortical thickness following severe early-life deprivation: a neurodevelopmental pathway to attention-deficit/hyperactivity disorder. Biol Psychiatry 2014;76:629–38.
54. De Bellis MD. The psychobiology of neglect. Child Maltreat 2005;10:150–72.
55. Vanderwert RE, Marshall PJ, Nelson CA III, Zeanah CH, Fox NA. Timing of intervention affects brain electrical activity in children exposed to severe psychosocial neglect. PLoS One 2010;5:e11415.
56. Sonuga-Barke EJ, Kennedy M, Kumsta R, Knights N, Golm D, Rutter M, Maughan B, Schlotz W, Kreppner J. Child-to-adult neurodevelopmental and mental health trajectories after early life deprivation: the young adult follow-up of the longitudinal English and Romanian Adoptees study. Lancet 2017; 389:1539–48.
57. McLaughlin KA, Sheridan MA, Nelson CA. Neglect as a violation of species-expectant experience: neurodevelopmental consequences. Biol Psychiatry 2017; 82:462–71.
58. Sumner JA, Colich NL, Uddin M, Armstrong D, McLaughlin KA. Early experiences of threat, but not deprivation, are associated with accelerated biological aging in children and adolescents. Biol Psychiatry 2019;85:268–78.
59. Busso DS, McLaughlin KA, Sheridan MA. Dimensions of adversity, physiological reactivity, and externalizing psychopathology in adolescence: deprivation and threat. Psychosom Med 2017;79:162–71.
60. Johnson DE, Gunnar MR. IV. Growth failure in institutionalized children. Monogr Soc Res Child Dev 2011;76:92–126.
61. Fox SE, Levitt P, Nelson CA. How the timing and quality of early experiences influence the development of brain architecture. Child Dev 2010;81:28–40.
62. O'Connor TG, Rutter M. Attachment disorder behavior following early severe deprivation: extension and longitudinal follow-up. English and Romanian Adoptees Study Team. J Am Acad Child Adolesc Psychiatry 2000;39:703–12.
63. Gooding HC, Milliren CE, Austin SB, Sheridan MA, McLaughlin KA. Child abuse, resting blood pressure, and blood pressure reactivity to psychosocial stress. J Pediatr Psychol 2016;41:5–14.
64. Shin SH, Miller DP. A longitudinal examination of childhood maltreatment and adolescent obesity: results from the National Longitudinal Study of Adolescent Health (AddHealth) Study. Child Abuse Negl 2012;36:84–94.
65. Danese A, Moffitt TE, Harrington H, Milne BJ, Polanczyk G, Pariante CM. Adverse childhood experiences and adult risk factors for age-related disease: depression, inflammation, and clustering of metabolic risk markers. Arch Pediatr Adolesc Med 2009;163:1135–43.
66. Wegman HL, Stetler C. A meta-analytic review of the effects of childhood abuse on medical outcomes in adulthood. Psychosom Med 2009;71:805–12.
67. Midei AJ, Matthews KA, Chang YF, Bromberger JT. Childhood physical abuse is associated with incident metabolic syndrome in mid-life women. Health Psychol 2013;32:121–7.
68. Jones JF, Straus SE. Chronic Epstein-Barr virus infection. Annu Rev Med 1987; 38:195–209.
69. Glaser R, Pearson GR, Jones JF, Hillhouse J, Kennedy S, Mao H, Kiecoltglaser JK. Stress-related activation of Epstein-Barr virus. Brain Behav Immun 1991;5: 219–32.
70. Smith EM, Cadet P, Stefano GB, Opp MR, Hughes TK Jr. IL-10 as a mediator in the HPA axis and brain. J Neuroimmunol 1999;100:140–8.
71. Voorhees JL, Tarr AJ, Wohleb ES, Godbout JP, Mo X, Sheridan JF, Eubank TD, Marsh CB. Prolonged restraint stress increases il-6, reduces il-10, and causes persistent depressive-like behavior that is reversed by recombinant il-10. PLoS One 2013;8:e58488.
72. Nelson CA. Romania's Abandoned Children. Harvard University Press; 2014.
73. Zeanah CH, Koga SF, Simion B, Stanescu A, Tabacaru CL, Fox NA, Nelson CA, Grp BC. Ethical considerations in international research collaboration: The Bucharest Early Intervention Project. Infant Ment Health J 2006;27:559–76.
74. Miller FG. The randomized controlled trial as a demonstration project: an ethical perspective. Am J Psychiatry 2009;166:743–5.
75. Millum J, Emanuel EJ. Ethics - The ethics of international research with abandoned children. Science 2007;318:1874–5.
76. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ 2007;85:660–7.
77. McDade TW, Williams S, Snodgrass JJ. What a drop can do: dried blood spots as a minimally invasive method for integrating biomarkers into population-based research. Demography 2007;44:899–925.
78. Andersson A, Lindh J, Eriksson A. Evaluation of the HemoCue HbA1c 501 system in primary care settings. Point of Care 2017;16:128–30.
79. Woerle HJ, Neumann C, Zschau S, Tenner S, Irsigler A, Schirra J, Gerich JE, Göke B. Impact of fasting and postprandial glycemia on overall glycemic control in type 2 diabetes: importance of postprandial glycemia to achieve target HbA1c levels. Diabetes Res Clin Pract 2007;77:280–5.
80. McDade TW, Burhop J, Dohnal J. High-sensitivity enzyme immunoassay for C-reactive protein in dried blood spots. Clin Chem 2004;50:652–4.
81. Miller EM, McDade TW. A highly sensitive immunoassay for interleukin-6 in dried blood spots. Am J Hum Biol 2012;24:863–5.
82. McDade TW, Funk WE. Quantification of inflammatory cytokines in dried blood spot samples. In: Presented at the NIA Biomarker Network, editor. Cambridge, MA: Population Association of America 2013.
83. Copeland WE, Shanahan L, Worthman C, Angold A, Costello EJ. Cumulative depression episodes predict later C-reactive protein levels: a prospective analysis. Biol Psychiatry 2012;71:15–21.
84. McLaughlin KA, Sheridan MA, Tibu F, Fox NA, Zeanah CH, Nelson CA. Causal effects of the early caregiving environment on development of stress response systems. Proc Natl Acad Sci U S A 2015;112:5637–42.
85. Dixon D, Meng H, Goldberg R, Schneiderman N, Delamater A. Stress and body mass index each contributes independently to tumor necrosis factor-[alpha] production in prepubescent Latino children. J Pediatr Nurs 2009; 24:378–88.
86. Fuligni AJ, Telzer EH, Bower J, Cole SW, Kiang L, Irwin MR. A preliminary study of daily interpersonal stress and C-reactive protein levels among adolescents from Latin American and European backgrounds. Psychosom Med 2009;71:329–33.
87. O'Connor TG, Wang H, Moynihan JA, Wyman PA, Carnahan J, Lofthus G, Quataert SA, Bowman M, Burke AS, Caserta MT. Observed parent-child relationship quality predicts antibody response to vaccination in children. Brain Behav Immun 2015;48:265–73.
88. Goosby BJ, Malone S, Richardson EA, Cheadle JE, Williams DT. Perceived discrimination and markers of cardiovascular risk among low-income African American youth. Am J Hum Biol 2015: n/a-n/a.
89. Goosby BJ, Malone S, Richardson E, Cheadle JE, Williams D. Perceived discrimination and markers of cardiovascular risk among low-income African American youth. Am J Hum Biol 2015;27:546–52.
90. Copeland WE, Wolke D, Lereya ST, Shanahan L, Worthman C, Costello EJ. Childhood bullying involvement predicts low-grade systemic inflammation into adulthood. Proc Natl Acad Sci 2014;111:7570–5.
91. Heritier SR, Gebski VJ, Keech AC. Inclusion of patients in clinical trial analysis: the intention-to-treat principle. Med J Aust 2003;179:438–40.
92. Garnett SP, Baur LA, Srinivasan S, Lee JW, Cowell CT. Body mass index and waist circumference in midchildhood and adverse cardiovascular disease risk clustering in adolescence. Am J Clin Nutr 2007;86: 549–55.
93. Lambert M, Delvin EE, Paradis G, O'Loughlin J, Hanley JA, Levy E. C-reactive protein and features of the metabolic syndrome in a population-based sample of children and adolescents. Clin Chem 2004;50:1762–8.
94. Galler JR, Barrett LR. Children and famine: long-term impact on development. Ambul Child Health 2001;7:85–95.
95. Galler JR, Koethe JR, Yolken RH. Neurodevelopment: the impact of nutrition and inflammation during adolescence in low-resource settings. Pediatrics 2017;139:S72–84.
96. Galler JR, Ramsey F, Solimano G, Lowell WE. The influence of early malnutrition on subsequent behavioral development: II. Classroom behavior. J Am Acad Child Psychiatry 1983;22:16–22.
97. Ellis KJ. Selected body composition methods can be used in field studies. J Nutr 2001;131:1589s–5.
98. Wells J. A critique of the expression of paediatric body composition data. Arch Dis Child 2001;85:67–72.
99. McLaughlin KA, Sheridan MA, Lambert HK. Childhood adversity and neural development: deprivation and threat as distinct dimensions of early experience. Neurosci Biobehav Rev 2014;47:578–91.
100. Le Mare L, Audet K. A longitudinal study of the physical growth and health of postinstitutionalized Romanian adoptees. Paediatr Child Health 2006;11: 85–91.
101. Mendle J, Ryan RM, McKone KM. Early childhood maltreatment and pubertal development: replication in a population-based sample. J Res Adolesc 2016;26: 595–602.
102. Mendle J, Leve LD, Van Ryzin M, Natsuaki MN, Ge X. Associations between early life stress, child maltreatment, and pubertal development among girls in foster care. J Res Adolesc 2011;21:871–80.

103. Belsky J, Steinberg LD, Houts RM, Friedman SL, DeHart G, Cauffman E, Roisman GI, Halpern-Felsher BL, Susman E. Family rearing antecedents of pubertal timing. Child Dev 2007;78:1302–21.
104. Noll JG, Trickett PK, Long JD, Negriff S, Susman EJ, Shalev I, Li JC, Putnam FW. Childhood sexual abuse and early timing of puberty. J Adolesc Health 2017;60:65–71.
105. Theall KP, Shirtcliff EA, Dismukes AR, Wallace M, Drury SS. Association between neighborhood violence and biological stress in children. JAMA Pediatr 2017;171:53–60.
106. Shalev I, Moffitt TE, Sugden K, Williams B, Houts RM, Danese A, Mill J, Arseneault L, Caspi A. Exposure to violence during childhood is associated with telomere erosion from 5 to 10 years of age: a longitudinal study. Mol Psychiatry 2013;18:576–81.
107. Kroupina MG, Eckerle JK, Fuglestad AJ, Toemen L, Moberg S, Himes JH, Miller BS, Petryk A, Johnson DE. Associations between physical growth and general cognitive functioning in international adoptees from Eastern Europe at 30 months post-arrival. J Neurodevelop Dis 2015;7:36.
108. Riikonen R. Insulin-like growth factor delivery across the blood-brain barrier. Potential use of IGF-1 as a drug in child neurology. Chemotherapy 2006;52:279–81.
109. McEwen BS. Stress, adaptation, and disease. Allostasis and allostatic load. Ann N Y Acad Sci 1998;840:33–44.
110. Miller GE, Chen E. Harsh family climate in early life presages the emergence of a proinflammatory phenotype in adolescence. Psychol Sci 2010; 21:848–56.
111. McEwen B, Stellar E. Stress and the individual: mechanisms leading to disease. Arch Intern Med 1993;153:2093–101.
112. McEwen BS. Early life influences on life-long patterns of behavior and health. Ment Retard Dev Disabil Res Rev 2003;9:149–54.
113. McEwen BS. Understanding the potency of stressful early life experiences on brain and body function. Metabolism 2008;57(Suppl 2):S11–5.
114. Danese A, Baldwin JR. Hidden wounds? Inflammatory links between childhood trauma and psychopathology. Annu Rev Psychol 2017;68:517–44.
115. Danese A, Lewis JS. Psychoneuroimmunology of early-life stress: the hidden wounds of childhood trauma? Neuropsychopharmacol 2017;42:99–114.
116. Miller G, Chen E, Cole SW. Health psychology: developing biologically plausible models linking the social world and physical health. Annu Rev Psychol 2009;60:501–24.
117. Miller GE, Cole SW. Clustering of depression and inflammation in adolescents previously exposed to childhood adversity. Biol Psychiatry 2012;72:34–40.
118. Danese A, Moffitt TE, Pariante CM, Ambler A, Poulton R, Caspi A. Elevated inflammation levels in depressed adults with a history of childhood maltreatment. Arch Gen Psychiatry 2008;65:409–15.