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

Natalie Slopen, ScD, Alva Tang, PhD, Charles A. Nelson, PhD, Charles H. Zeanah, MD, Thomas W. McDade, PhD, Katie A. McLaughlin, PhD, and Nathan A. Fox, PhD

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 (β = −0.23 versus 0.08, p = .06), and older age at placement was associated with lower BMI (β = −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

From the Department of Epidemiology and Biostatistics (Slopen), School of Public Health, University of Maryland; Department of Human Development and Quantitative Methodology (Tang, Fox), University of Maryland, College Park; Boston Children’s Hospital (Nelson), Harvard Medical School, Boston; Harvard Graduate School of Education (Nelson), Cambridge, Massachusetts; Tulane University School of Medicine (Zeanah), New Orleans, Louisiana; Department of Anthropology and Institute for Policy Research (McDade), Northwestern University, Evanston, Illinois; and Department of Psychology (McLaughlin), Harvard University, Cambridge, Massachusetts.

Address correspondence to Natalie Slopen, ScD, Epidemiology and Biostatistics, University of Maryland, College Park, MD 20742. E-mail: nslopen@umd.edu

Received for publication April 26, 2018; revision received January 24, 2019.

DOI: 10.1097/PSY.000000000000696

Copyright © 2019 by the American Psychosomatic Society

Psychosomatic Medicine, V 81 • 449-457 449 June 2019

Copyright © 2019 by the American Psychosomatic Society. Unauthorized reproduction of this article is prohibited.
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 (37,38,39), 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 examined 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 Alc (HbAlc), 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 provide verbal assent instead.
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, 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), IL-8 (12.55, 6.23, 4.73), IL-10 (13.45, 6.23, 4.73), and TNF-α (12.55, 6.23, 4.73).

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)

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

M (SD) = mean (standard deviation).
IL-8 (8.69, 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).

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 |
| BMI z-score | −0.04 (1.55) | 0.17 (1.94) | .74 | 0.08 (1.96) | −0.23 (1.08) | .056 |
| BMI, kg/m² | 20.87 (4.83) | 21.33 (5.41) | .77 | 21.38 (6.98) | 20.77 (2.89) | .05 |
| SBP, mm Hg | 110.00 (17.00) | 106.65 (16.00) | .34 | 109.00 (16.00) | 110.00 (17.00) | .92 |
| DBP, mm Hg | 69.00 (13.00) | 70.00 (11.00) | .89 | 70.00 (15.00) | 69.00 (13.00) | .51 |
| HbaA1c, % | 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 (28.45) | 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.

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.

Psychosomatic Medicine, V 81 • 449-457 452 June 2019
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

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>$\beta$</th>
<th>(95% CI)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI z-score$^{a}$</td>
<td>$-0.07$</td>
<td>$(-0.12$ to $-0.01)$</td>
<td>$0.033$</td>
</tr>
<tr>
<td>SBP, mm Hg$^{b,c}$</td>
<td>$-0.53$</td>
<td>$(-1.95$ to $0.85)$</td>
<td>$0.42$</td>
</tr>
<tr>
<td>DBP, mm Hg$^{b,c}$</td>
<td>$-0.90$</td>
<td>$(-2.49$ to $0.49)$</td>
<td>$0.24$</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>$0.03$</td>
<td>$(-0.31$ to $0.15)$</td>
<td>$0.82$</td>
</tr>
<tr>
<td>(log) CRP, mg/ml$^{b}$</td>
<td>$0.01$</td>
<td>$(-0.08$ to $0.09)$</td>
<td>$0.77$</td>
</tr>
<tr>
<td>(log) IL-6, pg/ml$^{b}$</td>
<td>$0.02$</td>
<td>$(-0.05$ to $0.004)$</td>
<td>$0.11$</td>
</tr>
<tr>
<td>(log) IL-8, pg/ml$^{b}$</td>
<td>$0.01$</td>
<td>$(-0.003$ to $0.03)$</td>
<td>$0.24$</td>
</tr>
<tr>
<td>(log) IL-10, pg/ml$^{b}$</td>
<td>$0.02$</td>
<td>$(-0.09$ to $0.07)$</td>
<td>$0.64$</td>
</tr>
<tr>
<td>TNF-α, pg/ml$^{b}$</td>
<td>$0.03$</td>
<td>$(-0.15$ to $0.07)$</td>
<td>$0.56$</td>
</tr>
<tr>
<td>(log) EBV antibody titers, U/ml$^{b}$</td>
<td>$0.01$</td>
<td>$(-0.04$ to $0.06)$</td>
<td>$0.82$</td>
</tr>
</tbody>
</table>

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, ethnicity.

$^e$ Excludes individuals who are on medications to control glucose.
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 different 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.

The authors thank the families and children who participated in this study and the research team and staff in Romania for their support and investment in this project. The authors would like to thank Aaron Miller (Northwestern University) for his technical help with specimen processing.
Early Deprivation and Biomarkers of Disease Risk

Source of Funding and Conflicts of Interest: This study was supported by the John D. and Catherine T. MacArthur Foundation, the Help the Children of Romania, Inc Foundation, the Binder Family Foundation, the Palix Foundation, the Jacobs Foundation, and the National Institute of Mental Health of the National Institutes of Health under Award R01MH091363 (to C.A.N.). The authors report no conflicts of interest.

REFERENCES


