



Caregiving Disruptions Affect Growth and Pubertal Development in Early Adolescence in Institutionalized and Fostered Romanian Children: A Randomized Clinical Trial

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Objectives To determine the effects of foster care vs institutional care, as well as disruptions in the caregiving environment on physical development through early adolescence.

Study design This was a randomized controlled trial of 114 institutionalized, though otherwise healthy, children from 6 orphanages and 51 never institutionalized control children living in birth families (family care group) in Bucharest, Romania. Children were followed from baseline (21 months, range 5-31) through age 12 years for caregiving disruptions and growth trajectories and through age 14 years for pubertal development.

Results Children randomized to the foster care group showed greater rates of growth in height, weight, and body mass index (BMI) through age 12 years than institutionalized group. Tanner development was delayed in institutionalized group boys compared with foster care group and family care group boys at 12 but not 14 years. There were no differences in Tanner development and age of menarche among foster care group, institutionalized group, and family care group girls at ages 12 and 14 years. More disruptions in caregiving between 30 months and 12 years moderated decreases in growth rates of height in foster care group and weight in foster care group and institutionalized group across age. Institutionalized group boys with ≥ 2 disruptions showed lower Tanner scores at age 12 vs institutionalized group and foster care group boys with < 2 disruptions. Foster care group girls with ≥ 2 disruptions had higher Tanner scores at age 14 vs foster care group girls with < 2 disruptions. Age of menarche was not affected by caregiving disruptions.

Conclusions For children who experienced early institutionalization, stable placement within family care is essential to ensuring the best outcomes for physical developmental. (*J Pediatr* 2018;203:345-53).

Trial registration clinicaltrials.gov: NCT00747396.

Determining the effects of institutional care in early life on physical development is important, because growth failure and alterations in pubertal onset and tempo are associated with later health problems including obesity, cardiovascular disease, and metabolic syndrome.¹⁻⁹ Profound growth failure is a hallmark of institutional care in early childhood.¹⁰⁻¹² Many studies have documented catch-up growth over the short term in children placed in more nurturing environments,¹⁰⁻¹² 3 longitudinal studies have tracked physical growth through late childhood or adolescence.¹³⁻¹⁵ Less is known about how early institutionalization influences pubertal development with reports of delays,¹⁶ accelerations,^{10,14,17,18} and null^{15,19} effects on various markers of pubertal development in boys and girls.

In this study, we examined trajectories of physical development through age 14 years among Romanian adolescents in a randomized, controlled study of foster vs institutional care, the Bucharest Early Intervention Project (BEIP; clinicaltrials.gov NCT00747396). This study offers an opportunity to identify factors that alter growth as well as timing and pace of puberty in a cohort of children from similar backgrounds who experienced a comparable mix of adverse experiences within institutional care early in life followed either by continued institutional care (institutionalized group) or foster care (foster care group). There were 3 goals. The first was to evaluate the effect of randomization to foster care on physical growth trajectories of height, weight, body mass index (BMI), and head circumference among previously institutionalized children using repeated measures of growth from baseline through age 12 years. This work extends our earlier findings on the physical growth effects of foster care through 42 months of age²⁰ by applying

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Supported by the John D. and Catherine T. MacArthur Foundation (Research Network on Early Experience and Brain Development); the Binder Family Foundation; and National Institute of Mental Health (R01MH091363 [to C.N.]). The study sponsors had no role in study design; the collection, analysis and interpretation of data; the writing of the report; and the decision to submit the manuscript for publication. The authors declare no conflicts of interest.

BEIP Bucharest Early Intervention Project
BMI Body mass index

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<https://doi.org/10.1016/j.jpeds.2018.07.027>

longitudinal analyses of growth trajectories through early adolescence. The second goal was to examine the timing and pace of pubertal development in institutionalized group and foster care group compared with same-sex never institutionalized adolescents living with their birth families (family care group) at ages 12 and 14 years using self-report and biological measures, including the Tanner pubertal stages, age of menarche, and salivary testosterone. The third goal was to examine whether caregiving stability moderated physical growth trajectories and pubertal development among institutionalized group and foster care group girls and boys.

Methods

Care as Usual (Institutionalized) and Foster Care Groups

Trial design and subject selection has been discussed in detail in past publications but will be summarized briefly.²¹⁻²³ All children <32 months of age living in institutions for infants in all 6 sectors of Bucharest, other than those scheduled for adoption, were included ($n = 187$). Children ($n = 51$) with serious handicapping conditions (eg, fetal alcohol syndrome, severe cerebral palsy) were excluded. Following identification and baseline assessment of the initial institutionalized cohort ($n = 136$), equal numbers were randomly assigned to receive continued institutional care (institutionalized group) or to a foster care group. Randomization was implemented by assigning each child a number (1-136) written on a piece of paper, which were then placed in a hat and then drawn at random. The first number pulled from the hat was assigned to the institutionalized group, the next randomly drawn number was assigned to the foster care group, and so on, until all children had been assigned to the institutionalized group or the foster care group. The 2 sets of twins in the study were each on the same piece of paper and, thus, placed together. Because government sponsored foster care in Bucharest did not exist when our study commenced, we created our own foster care program.^{23,24} Children randomized to institutionalized group were deinstitutionalized over time at the discretion of Romanian child protection officials. However, irrespective of changes in the caregiving environment over the duration of the study, an intent-to-treat approach was followed, whereby all analyses we report are based on children's original group assignments. Thus, our findings represent a conservative estimate of the response to intervention. Enrollment, group assignments, and follow-up of subjects through age 12 years are illustrated in **Figure 1** (available at www.jpeds.com).

Never-Institutionalized Group (Family Care Group)

Fifty-one children, of which 28 were retained from baseline, were recruited from community pediatric clinics and were born at the same hospitals as the institutionalized children. At 8 years of age, the original control group was supplemented by an addition of 30 age-matched children recruited from 2 local schools, of which 23 participated at 12 years. All control subjects lived with their birth families with no history of institutional care.

Procedures

Study procedures were approved by the Ministry of Health and the National Authority of Child Protection in Romania as well as the Commission for Child Protection for the Sector/County in which each child resided. Study procedures were also approved by an ad hoc Ethics Committee composed of academics and government officials familiar with child development and child protection issues. The study was approved and overseen by the institutional review boards of the home institutions of the 3 principal investigators. Consent to participate was obtained from each child's legal guardian, as determined by Romanian law, at the time of enrollment. At the request of the National Authority on Child Protection consent was obtained from all birth parents whom we could locate ($n = 29$) for children to be randomized into foster care. Consent to participate was obtained from each child's legal guardian at each subsequent assessment and assent was obtained from children in middle childhood and adolescent assessments. All consent was conducted using procedures outlined by the Romanian government authorities. Complete descriptions of procedures employed to ensure ethical integrity have been published previously.^{21,23,25-28}

Measures

Growth was assessed in institutionalized group and foster care group at baseline (21.0 ± 7.4 [SD], range 5-32 months), 30 (30.6 ± 0.9) months, 42 (42.3 ± 0.4) months, 8 (8.5 ± 0.4) years, and 12 (12.6 ± 0.6) years. As previously reported,²⁰ supine length (<24 m) or height (≥ 24 m), weight, weight-for-length/height (baseline, 30 months henceforth included in the term BMI), and BMI (42 months and 8 and 12 years) were converted to age- and sex-standardized scores (z scores) based on Center for Disease Control 2000 data.²⁹ Occipital frontal circumference (OFC) z scores were calculated using the standardized data (0-18 years of age) of Roche et al.³⁰

Visual examination solely to determine Tanner stages³¹ was deemed unjustifiable in this vulnerable population. Instead, participants were given the option to complete a self-report puberty assessment scale³² at ages 12 and 14 years. There were no significant differences in age by group (institutionalized group 12.6, [$n = 53$, CI 12.5, 12.8] and 14.4 [$n = 46$, CI 14.1, 14.6]; foster care group 12.6, [$n = 51$, CI 12.4, 12.7] and 14.3, [$n = 43$, CI 14.1, 14.5]; family care group 12.7 [$n = 50$, CI 12.6, 12.8] and 14.4 [$n = 44$, CI 14.2, 14.6]) or sex (female, 12.6 [$n = 81$, CI 12.5, 12.8] and 14.3 [$n = 67$, CI 14.2, 14.5]; male, 12.6 [$n = 73$, CI 12.5, 12.8] and 14.4 [$n = 70$, CI 14.2, 14.5]) at either time point. Participants were shown a series of pictures depicting different Tanner stages of physical development in breasts/genitalia, and pubic hair and asked to circle the picture that best resembled their current appearance. The 2 Tanner scores were averaged to yield a mean breast/genitalia and pubic hair score that were used in analyses. In addition, girls were asked their age of menarche. The mean age was used in situations in which girls reported 2 ages of menarche in the 12- and 14-year surveys ($n = 30$, mean reported difference 0.15 ± 0.8 years SD). Testosterone levels, which increase as puberty progresses,³³ were used to corroborate self-assessed

Tanner stages at a group level. Saliva samples were obtained as previously described.³⁴ Samples were assayed for testosterone by using commercially available luminescence immunoassay kits. Intra-assay (2.74%) and inter-assay (11.24%) coefficients of variance were acceptable.

Following randomization, all placement decisions for children were made by local Romanian authorities. Some children were adopted, some were returned to parents or extended families, and others were placed in government foster care that did not exist at the outset of the study. The sources and procedures used to obtain this information are described elsewhere in detail.³⁵ The numbers of caregiver changes experienced by the child that were intended to be permanent were documented at each time point (baseline, 30 months, 42 months, 8 years, and 12 years). Because the mean age of placement into foster care was 24.6 ± 5.9 months (SD), range 9–33 months, only disruptions between 30 months and 12 years were used in analyses. The majority of children in both institutionalized group (94%) and foster care group (68%) experienced 1 or more disruptions during this period of time.

Statistical Analyses

Trajectories of height, weight, BMI, and head circumference z scores were separately estimated using growth curve analysis (also known as mixed linear modeling, hierarchical linear modeling) in SPSS (SPSS Inc, Chicago, Illinois).^{36,37} In this analysis, repeated measures of an outcome (eg, height) are regressed on the timing of assessments (ie, participant age from baseline to age 12 years) to estimate variability at baseline (ie, intercept variance) and rates of change for individuals (ie, slope variance). The first step in this analysis is to identify the optimal growth function of each outcome across groups. The second step is to expand on the correct growth model by including covariate interactions to understand how the covariates moderate growth patterns. Accordingly, unconditional models including a random intercept and fixed slope testing linear, quadratic, and cubic functions of age (ie, age, age², and age³) were performed across the entire sample. The -2 log likelihood was compared across the polynomial models for each outcome, with lower values indicating a better fit. Full information maximum likelihood estimation was used to handle missing data and obtain unbiased estimates. The initial unconditional models demonstrated best fit for a cubic growth pattern for height, and a quadratic growth pattern for weight, BMI, and head circumference. To examine the effect of foster care intervention on growth trajectories from baseline to age 12 years, age by group (institutionalized group = reference group, foster care group) interactions were added to the best fitting unconditional model. To further examine the effect of disruptions on growth trajectories, age by group by disruption (ie, number of disruptions from 30 months to 12 years) interactions were added.

One-way ANOVAs were performed to examine differences in mean Tanner scores for genital/breast and pubic hair development and the age of onset of menarche among the 3 groups (institutionalized group, foster care group, and family care group) in each sex separately. We then examined group

differences in mean Tanner scores among the ever institutionalized adolescents (institutionalized group + foster care group) (ever institutionalized group) with different levels of disruptions in stable caregiving (ie, institutionalized group with <2 disruptions, institutionalized group with ≥ 2 disruptions, foster care group with <2 disruptions, foster care group with ≥ 2 disruptions) in each sex separately. All analyses examining pubertal stages accounted for age at time of the puberty survey and BMI z-score at age 12 years, given that higher BMI and age are related to later pubertal stages.^{38,39} Bonferroni correction was applied to multiple pair-wise comparisons; 5000 bootstrap resamples were performed to obtain bootstrapped estimates of the mean and 95% CIs to ensure reliability.

Results

Subjects were enrolled from February through June 2001. Compared with the institutionalized group, the foster care group showed greater rates of growth for height, weight, and BMI from baseline to age 12 years (**Figure 2**). For height z scores, foster care group showed faster rate of linear increase ($b = .63$, CI .27, .98), a slower rate of deceleration ($b = -.08$, CI $-.14$, $-.03$) and steeper cubic slope ($b = .003$, CI .001, .006). For weight z scores, foster care group showed faster rate of linear increase and slower deceleration (linear slope: $b = .31$, CI .16, .45; quadratic slope: $b = -.02$, CI $-.03$ to $-.01$). Likewise, for BMI z scores, foster care group showed a faster rate of linear increase and a slower rate of deceleration (linear slope: $b = .25$, CI .09, .41; quadratic slope: $b = -.015$, CI $-.03$, $-.004$). However, no group difference in the growth rate of head circumference z scores emerged between baseline and age 12 years (linear slope: $b = .01$, CI .02, .21; quadratic slope: $b = -.01$, CI $-.01$, .00). Descriptive statistics of mean z score differences at each age are provided in the **Table** (available at www.jpeds.com). In terms of stature and weight at age 12 years, foster care group ($n = 54$) exceeded institutionalized group ($n = 53$) in mean height (156.1 cm, CI 153.7, 158.5 vs 152.6 cm, CI 150.5, 154.6) and mean weight (47.5 kg, CI 44.7, 50.3 vs 43.0 kg, CI 40.9, 45.1), $P < .05$.

Disruption Effect on Growth among Ever-Institutionalized Adolescents

Disruptions from 30 months to 12 years of age were greater in institutionalized group; (2.10, [CI 1.67, 2.52], range 0–6, $n = 52$) vs foster care group (.96, [CI .61, 1.31], range 0–4, $n = 47$). There was a 3-way interaction among group \times number of disruptions from 30 months to 12 years \times age, $b = -.39$ (CI $-.74$, $-.04$) (**Figure 3**). Within foster care group, each additional disruption was associated with a $-.31$ unit decline (CI $-.62$, $-.01$) in the linear slope of height z-scores across age. In contrast, within institutionalized group, the number of disruptions did not influence the rate of change in height across age (linear slope: $b = -.10$, CI $-.67$, .48; quadratic slope: $b = .004$, CI $-.08$, .09; cubic slope: $b = .004$, CI $-.004$, .004).

There were no significant 3-way interactions observed for the growth rate of weight, but a main effect of the number of disruptions emerged, suggesting disruptions had the same effect

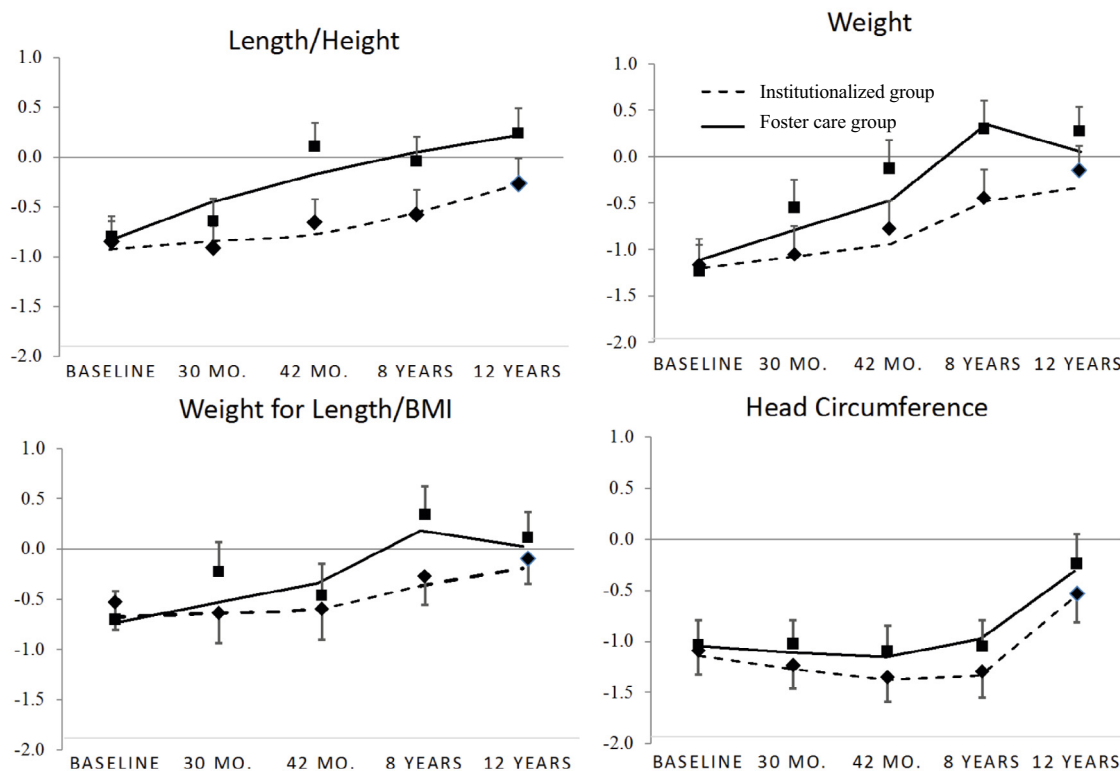


Figure 2. Fitted trajectories and observed means for height, weight, BMI, and head circumference z scores across foster care group and institutionalized group. Error bars are 95% CI for the actual means.

on weight z scores across foster care group and institutionalized group: Each disruption from 30 months to 12 years was associated with a -0.11 unit decline (CI $-0.16, -0.06$) in the linear slope of weight z-scores and a slower acceleration of the quadratic slope ($b = .01$, CI $.003, .01$) across age in both groups (Figure 3). Although disruption was analyzed as a continuous variable, the interactions are visualized in Figure 3 showing the foster care group with 2 or more vs those with less than 2 disruptions. Disruptions in stable caregiving did not moderate growth rates of BMI and head circumference z scores across age.

Pubertal Development

At 12 years of age, growth and hormonal parameters varied in the directions expected from the puberty survey responses. Height and weight were greater in subjects ($n = 148$) reporting full entry into puberty (combined Tanner score ≥ 4) with mean differences in z scores of 0.68 , (CI $0.22, 1.15$) for height and 0.44 (CI $.003, 0.87$) for weight. Salivary testosterone levels were positively correlated with the mean Tanner stages in both girls (Pearson $\rho = .282$, $n = 67$, $P = .021$) and boys (Pearson $\rho = .381$, $n = 65$, $P = .002$).

Effects of Institutionalization and Foster Care on Tanner Development

Figure 4 shows the mean Tanner genital/ breast and pubic hair development for each sex and group at ages 12 and 14 years.

Mean Tanner scores were different among boys at age 12, $F(2,62) = 9.41$, $P < .001$, $\eta^2 = .23$. Institutionalized group boys showed lower Tanner scores compared with foster care group (mean difference $= -1.00$; CI $-1.57, -.46$) and family care group (mean difference $= -1.00$; CI $-1.54, -.49$) boys. Foster care group and family care group boys had comparable Tanner scores (mean differences $= 0.00$; CI $-.57, .56$). At age 14 years, there were no difference among boys in Tanner stages, $F(2,62) = 1.31$, $P = .28$, $\eta^2 = .04$. Among girls, there were no differences in Tanner stages at age 12 years, $F(2,76) = 1.97$, $P = .15$, $\eta^2 = .05$, or age 14 years, $F(2,62) = .67$, $P = .51$, $\eta^2 = .02$.

Effects on Menarche

Of the 81 girls who participated in the puberty surveys, 65 (80%) reported age of menarche by age 14 years, Figure 5 (available at www.jpeds.com). Mean ages of menarche were similar among the 3 groups; institutionalized group 12.2 years ($n = 19$, CI $11.8, 12.6$), foster care group 11.9 years ($n = 21$, CI $11.5, 12.3$), and family care group 12.2 years ($n = 25$, CI $11.8, 12.5$) ($F(2,61) = 0.674$, $P = .513$, $\eta^2 = .022$). Reported age of menarche was < 10 years of age in 2 participants (institutionalized group = 1, foster care group = 1) and < 11 years of age in 7 participants (institutionalized group = 1, foster care group = 4, and family care group = 2). The relative risk for early menarche (< 11 years of age) was not greater in foster care group vs family care group (OR 2.38 , CI

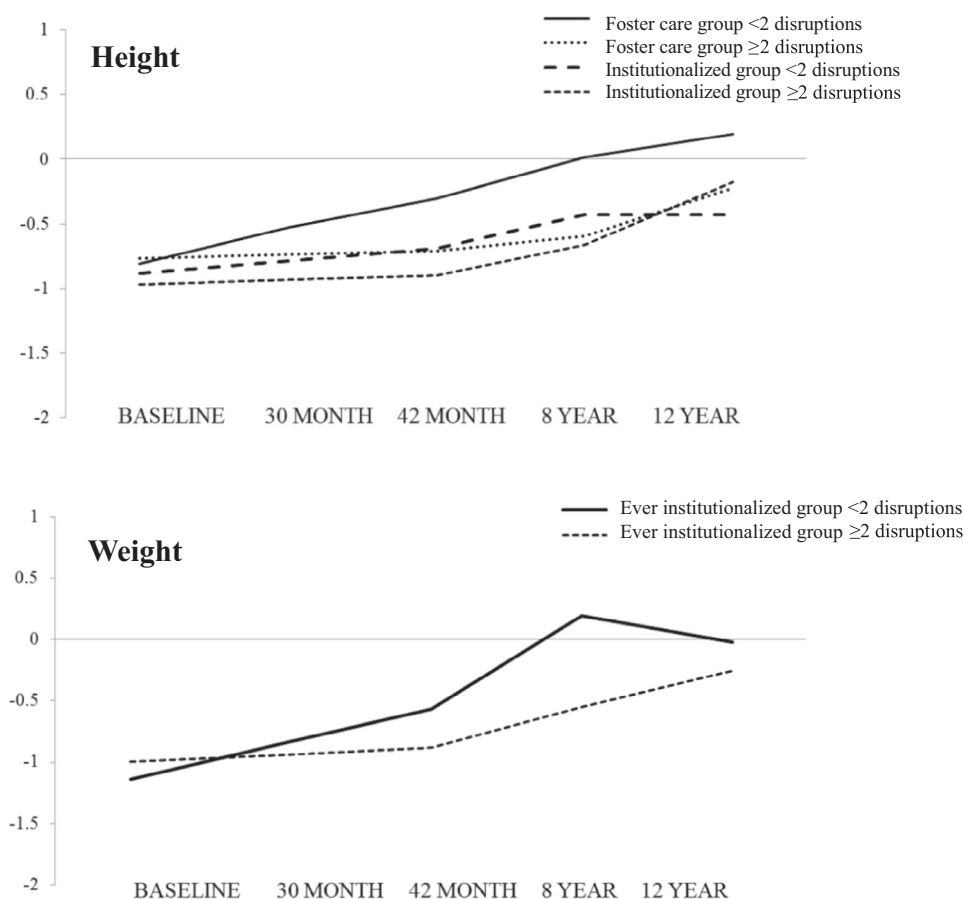


Figure 3. Fitted trajectories for height and weight z scores from baseline to age 12 years among institutionalized group, foster care group, and ever institutionalized group with 2 or more and less than 2 disruptions in stable caregiving.

0.48, 11.7), or the combined group of institutionalized group and foster care group (ever institutionalized) vs family care group (OR 1.56, CI 0.33, 7.44).

Disruption Effects on Pubertal Development among Ever-Institutionalized Adolescents

There was a group difference among the institutionalized group and foster care group boys with different numbers of disruptions in stable caregiving from 30 months to 12 years of age in Tanner scores at age 12 years, $F(3,35) = 4.07$, $P = .014$, $\eta^2 = .26$, but not at age 14 years, $F(3,37) = .42$, $P = .74$, $\eta^2 = .03$. Institutionalized group boys with ≥ 2 disruptions showed lower Tanner scores at age 12 years compared with institutionalized group (mean difference = $-.65$; CI $-1.33, -.02$) and foster care group (mean difference = -1.15 ; CI $-1.76, -.48$) boys with <2 disruptions (Figure 6 (available at www.jpeds.com)). For institutionalized group and foster care group girls with varying numbers of disruptions in stable caregiving from 30 months to 12 years of age, no group difference emerged in Tanner scores at age 12 years, $F(3,40) = .28$, $P = .85$, $\eta^2 = .02$, but there was a group difference in Tanner scores at age 14 years, $F(3,38) = 3.07$, $P = .04$, $\eta^2 = .22$. foster care group girls with ≥ 2 disruptions had higher Tanner scores at age 14 years

compared with foster care group girls with <2 disruptions (mean difference = 1.08 ; CI $.29, 2.01$) (Figure 6). There were no group differences in the age of menarche among foster care group and institutionalized group with different levels of disruption, $F(3,33) = .48$, $P = .69$, $\eta^2 = .04$. As noted above, mean caregiving disruptions between 30 months and 12 years were greater in institutionalized group vs foster care group but within each group, there were no differences by sex: institutionalized group; female subjects (2.00 [CI $1.37, 2.63$], range 0-6, $n = 26$), male subjects (2.19 [CI $1.58, 2.81$], range 0-6, $n = 26$): foster care group; female subjects (0.78 [CI $0.30, 1.27$], range 0-4, $n = 23$), male subjects (1.13 [CI $.61, 1.64$], range 0-4, $n = 23$).

Discussion

Our present findings indicate that foster care group experienced greater rates of growth in height, weight, and BMI, but not head circumference through age 12 years compared with institutionalized group. Increasing disruptions in the caregiving environment were related to decreasing rates of growth in height in foster care group and weight in institutionalized group and foster care group, but not BMI or head circumference.

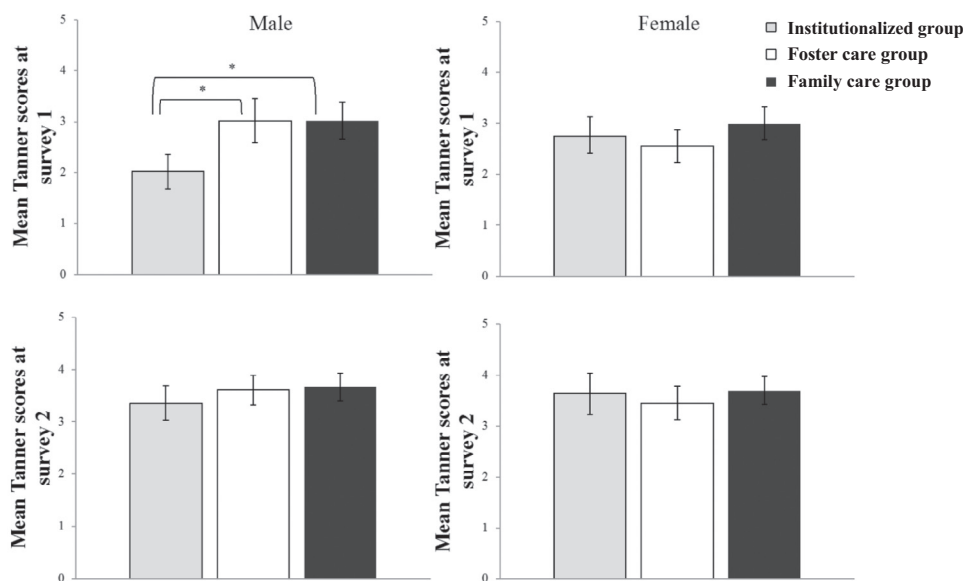


Figure 4. Sum of Tanner genital/ breast and pubic hair development for each sex and group at the time of the first and second surveys. Error bars are bootstrapped 95% CIs. * $P < .05$.

Furthermore, our findings suggest that altered patterns of pubertal development were linked to both number of caregiving disruptions and the child's sex.

Despite placement in a more stable, nurturing, and stimulating environment, head circumference, a surrogate for brain size, did not significantly improve in foster care group between baseline and 12 years. This result is consistent with a meta-analysis that identified head circumference as the growth parameter least likely to improve among postinternationally adopted children.¹¹ Under normal circumstances, postnatal brain and consequent head circumference growth velocity are greatest immediately after birth then rapidly decrease during the first year of life.⁴⁰ Because none of our institutionalized subjects evaluated at baseline were <5 months of age and only 17% were <12 months, a lack of head catch-up growth in foster care group as a group could be anticipated. Aside from group differences in growth, the compromised height and weight growth patterns linked to individual differences in caregiver disruptions in foster care group underscore the importance of a consistent caregiving environment for child well-being.

A previous survey of pubertal development in children experiencing severe deprivation within Romanian orphanages revealed that the onset of puberty was delayed by approximately 2.5 years in girls and 1.5 years in boys.¹⁶ In contrast, in children adopted out of adverse environments such as institutional or foster care, many, though not all studies,^{15,19} have documented a higher rate of early pubertal development particularly in girls.^{10,17} In a longitudinal study of 276 internationally adopted girls to Denmark, the normal probability curves for breast development and menarche were similar in shape to those of typically developing Danish girls but were displaced 1.3 years earlier for both breast development and menarche.⁴¹ Consequently, 16% entered puberty prior to 8 years

of age and approximately the same percentage experienced menarche prior to 11 years of age. In that Danish cohort, an early but otherwise normal rise in pituitary and ovarian hormones that predated external signs of sexual maturation suggested that this early pubertal development is centrally driven through early activation of the hypothalamic-pituitary axis.⁴¹ Earlier pubertal development has also been observed in Romanian children placed in adoptive families in the United Kingdom.¹⁴ In that study, a combined group of boys and girls who had spent >6 months within institutional care prior to adoption had greater summated Tanner scores at age 11 years than the comparison group consisting of within UK adoptees and Romanian adoptees spending <6 months within institutional care. Despite expectations of altered pubertal tempo, the only difference noted was that Tanner scores at age 12 years in institutionalized group boys were lower compared with both foster care group and family care group boys. Tanner development and age of menarche were comparable among girls in institutionalized group, foster care group, and family care group. A shift to earlier Tanner development or age of menarche seen in the Danish study⁴¹ was not observed in foster care group girls. Neither was puberty delayed in institutionalized group girls as previously described.¹⁶

Tanner development in boys and girls was differentially influenced by caregiving disruptions. This finding extends the number of sex-related differences in the response to adversity or the foster care intervention documented in BEIP.⁴²⁻⁴⁴ Boys in institutionalized group with ≥ 2 caregiving disruptions had lower mean Tanner scores at 12 years of age vs institutionalized group and foster care group boys with <2 disruptions. Girls in foster care group who experienced ≥ 2 caregiving disruptions had greater mean Tanner scores at 14 years of age than foster care group girls experiencing <2

caregiving disruptions. Thus, although we did not observe major changes in pubertal development among groups, caregiving disruptions deserves further investigation as a factor that could moderate changes in pubertal tempo in girls and boy. Whether growth failure in institutionalized group or more advance Tanner development in girls experiencing ≥ 2 disruptions at 14 years of age portend the development of adult disease is presently unclear but is the subject of ongoing investigations in BEIP.

Our study has several important limitations. First, despite the fact that data on growth and testosterone levels varied in the expected direction with Tanner scores at 12 years of age, a shortcoming is the use of a self-administered Tanner assessment tool. Though considered reliable^{45,46} and necessary in the current situation because of the vulnerable nature of our sample, self-assessment never quite attains the accuracy of direct examination by trained observers.^{47,48} Additional factors in this cohort such as IQ differences between groups at 12 years of age could further bias self-report measures.⁴⁹ Even if we assume that Tanner self-evaluation is reliable, there are limitations as to what can be determined from a cross-sectional survey at 2 time points, particularly when the onset and pace of pubertal development is different in boys and girls.⁵⁰ Second, implicit in the assumption that we might observe earlier or later pubertal development was that our subjects and previously reported adopted or institutionalized children experienced similar adverse environments. Past studies reporting earlier puberty in girls were conducted in intercountry adoptees placed in Western Europe and the US.^{10,17,18} Considering the social and financial requirements that parents must meet to qualify to adopt internationally, these children likely experienced permanent placement in economically stable families within high resource countries.⁵¹ Conversely, our children were placed in foster care during the difficult economic times preceding Romania's accession to the European Union in 2007 when nutrition or the level of overall family stress, may have been significantly different. Late pubertal development was described in children experiencing a lifetime of severe adversity in the worst Romanian orphanages during and immediately after the Ceausescu era. Although children in institutionalized group did not experience the same quality of family care as foster care group neither did they experience the unspeakable conditions endured by the previously reported cohort.^{16,52} Third, adversity in early life encompasses many domains and the present study was designed to examine only a limited number of variables that could potentially impact physical development. Taking into account the presence and magnitude of additional adverse experiences in the 3 groups is difficult if not impossible. The randomized controlled design of this study minimizes but can never exclude the influence of other factors on our results. Finally, because of decisions over time by Romanian child protection official, many children originally randomized to institutionalized group found placement within family care. Because all analyses we reported are based on the children's original group assignments, the movement of higher risk children to more nurturing environments may moderate or obscure differences in outcomes

between foster care group and institutionalized group. Because of these limitations, we recommend caution about generalizing our results to other groups of children experiencing adversity in early life.

In conclusion, this study highlights that stable placement within family care for children who experience adversity in early life is essential to ensure the best outcomes for physical development. Unfortunately, caregiving disruptions in the US foster care system are common. Between 2011 and 2015 slightly more than one-third of children in foster care experienced ≥ 2 placements.⁵³ The current opioid crisis in the US foretells worsening conditions as the number of children entering foster care increases and further strains the ability of child welfare systems to provide uninterrupted family-based care.⁵⁴ Children enter foster care with a sum of adverse childhood experiences.⁵⁵⁻⁵⁷ The current study demonstrates that a small number of caregiving disruptions within foster care, which adults may view as trivial and even routine, can have significant additional effects on child well-being. The stress of having to accommodate changing care environments alters normal developmental processes and changes outcome for the worse. ■

We thank our dedicated Bucharest-based laboratory members, Elizabeth Furtado, BA and Leanna Papp, BS for US-based administrative and database support, and the many families and children who participated in this project.

Submitted for publication Jan 23, 2018; last revision received Jul 5, 2018; accepted Jul 9, 2018

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Data Statement

Data will be made available on request.

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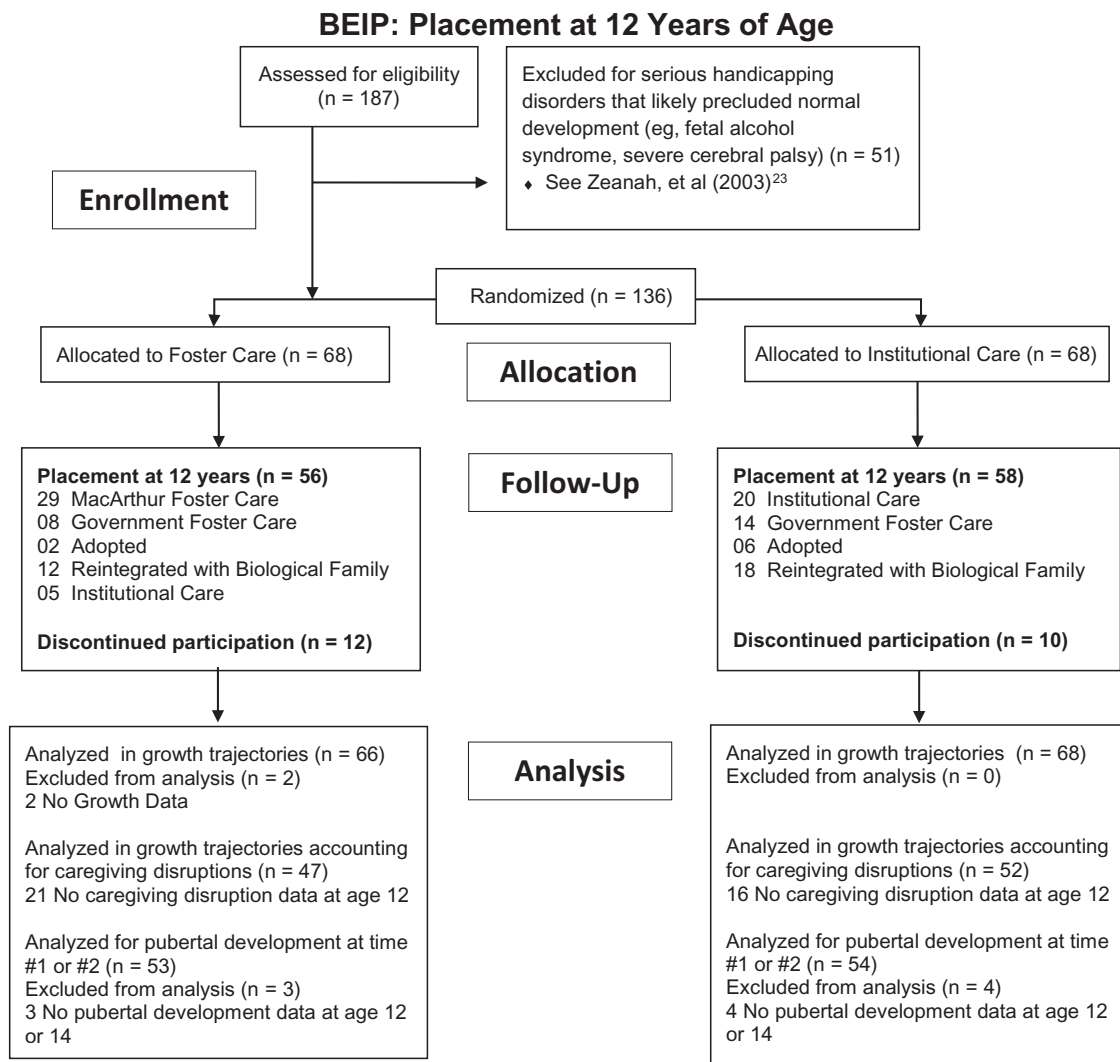


Figure 1. Cohort derivation (CONSORT diagram).

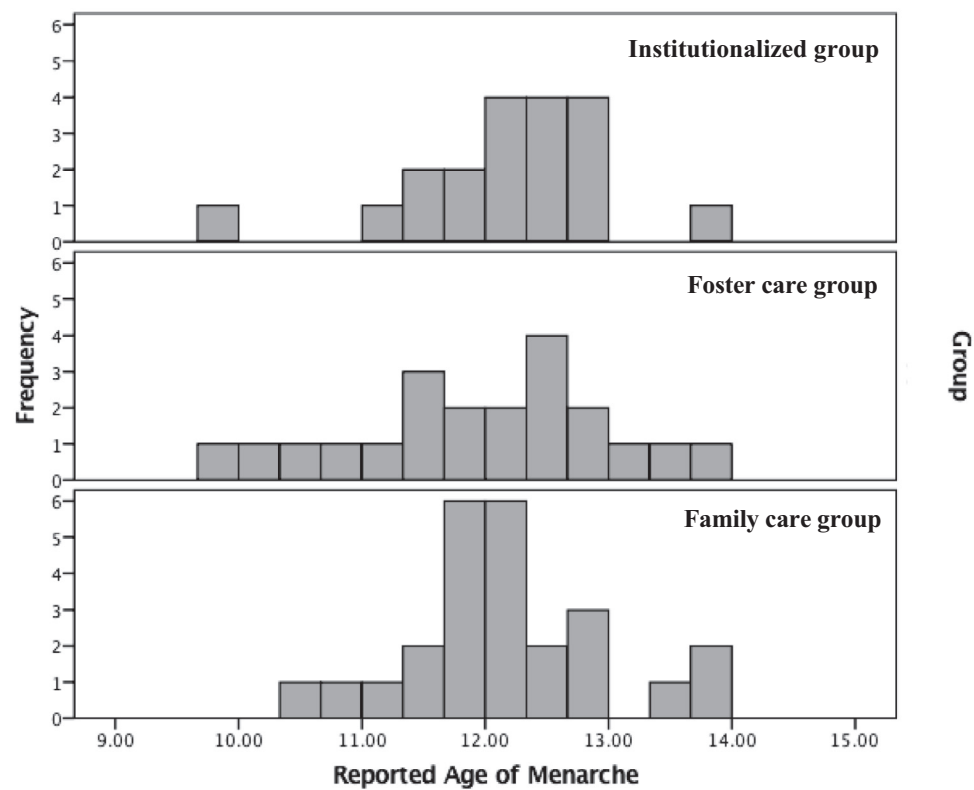


Figure 5. Reported age of menarche by group.

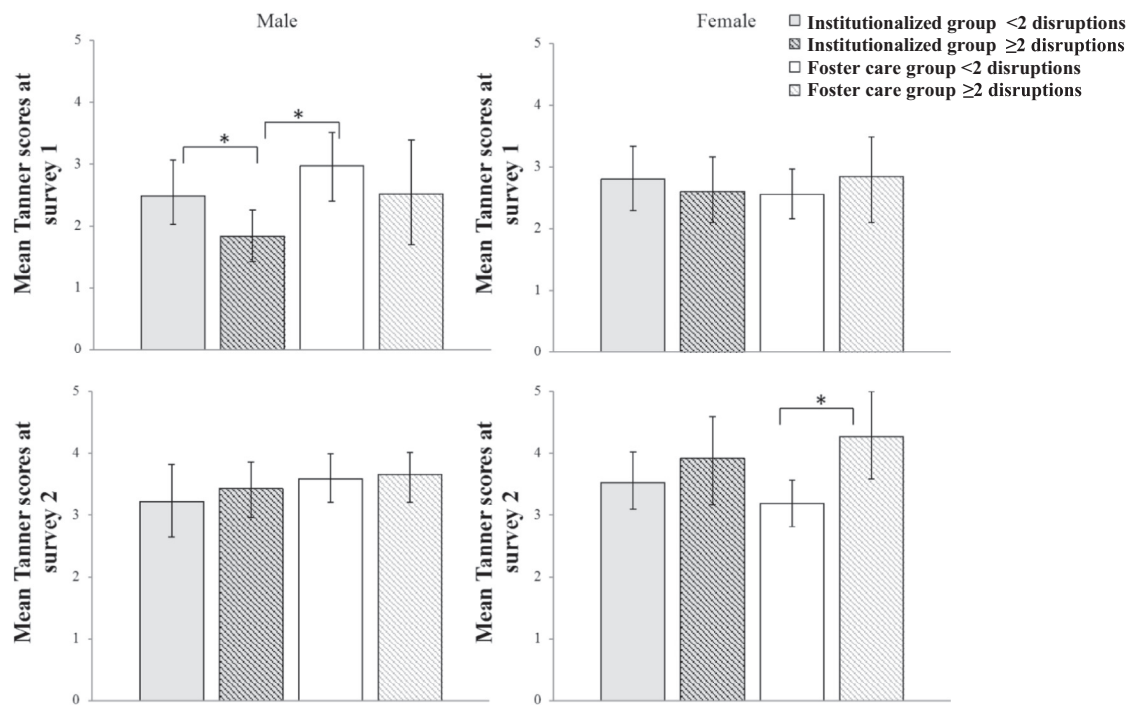


Figure 6. Sum of Tanner genital/breast and pubic hair development at the time of the first and second surveys by sex, group, and disruptions in stable caregiving between 30 months and 12 years of age (<2 and ≥2). Error bars are bootstrapped 95% CIs. * $P < .05$.

Table. Z scores of height, weight, head circumference, weight-for-length/BMI, and sex by group at baseline, 30 months, 42 months, 8 years, and 12 years of age

Measures	Group	Age at measurement									
		Baseline	n	30 mo	n	42 mo	n	8 y	n	12 y	n
Length or height	Institutionalized group	−0.89	58	−0.96	57	−0.68	55	−0.60	53	−0.27	53
	Foster care group	−0.83	62	−0.67	59	0.13	55	−0.03	57	0.27	54
Weight	Institutionalized group	−1.23	58	−1.12	57	−0.85	55	−0.54	53	−0.25	53
	Foster care group	−1.29	62	−0.63	59	−0.22	55	0.18	57	0.16	54
Head circumference	Institutionalized group	−1.13	58	−1.27	57	−1.39	55	−1.34	53	−0.55	53
	Foster care group	−1.07	62	−1.06	60	−1.13	55	−1.08	57	−0.24	54
Weight-for-length or BMI	Institutionalized group	−0.60	58	−0.72	57	−0.67	55	−0.34	53	−0.16	53
	Foster care group	−0.78	62	−0.30	59	−0.53	55	0.22	57	0.06	54

f, female.

Values were obtained through repeated measures analysis with unstructured covariance.