Cumulative Adversity in Childhood and Emergent Risk Factors for Long-Term Health

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Objective To examine whether and when effects of cumulative adversity in the first 7 years of life are evident in relation to 3 childhood markers of risk for poor adult physical health.

Study design The study data are from an English birth cohort. Parental reports of 8 social risk factors were obtained during the child's first 7 years, and scores were created to reflect cumulative adversity at 4 developmental periods. At age 7 and 11 years, weight, height, and blood pressure (BP) were measured by clinic staff, and caregivers reported behavior problems. Linear regression was used to estimate associations of cumulative adversity with each outcome (n = 4361) and changes in these outcomes between 7 and 11 years (n = 3348).

Results At age 7 years, mean adversity and chronic exposure to high adversity were associated with elevated body mass index (BMI) and internalizing and externalizing symptoms ($P < .05$), but not elevated BP. Adversity in all developmental periods was associated with elevated numbers of internalizing and externalizing symptoms ($P < .0001$), but associations were less robust for BMI. Adversity did not predict change in BMI or BP between age 7 and 11 years, however, it predicted increases in internalizing and externalizing symptoms ($P < .0001$).

Conclusion Cumulative adversity was associated with BMI and behavior problems at age 7 years, and our data indicate that timing and chronicity of exposure to adversity differentially influence diverse indicators of long-term health risk commonly measured in childhood. This research suggests the hypothesis that interventions to address adversity could reduce the development of multiple chronic disease risk factors and limit their effects on health. *(J Pediatr 2014;164:631-8)*.

Recent advances have increased our understanding of the enduring influence of childhood experiences for long-term physical health.[1] National policy statements suggest an urgent need to develop strategies to address social determinants of early risk factors for adult chronic diseases,[2,3] including higher body mass index (BMI),[4] high blood pressure (BP),[5] and behavior problems[6] in childhood. Evidence suggests that these conditions are associated with the accumulation of social stressors in youth,[7-9] and the impact of cumulative adversity in childhood on physical[10] or psychological[11,12] outcomes may vary depending on the developmental stage of exposure. Gaining greater insight into which childhood physical and behavior health conditions emerge early in the life course in response to social adversity is critical to enable earlier determination of who is at risk and to provide additional tools for evaluating interventions.

The goal of the present study was to examine the relationship of cumulative adversity occurring in the first 7 years of life with 3 childhood markers of risk for poor adult physical health. Our first aim was to examine the potential influence of cumulative exposure to adversity between birth and age 7 years on 3 early markers of risk for poor health in adulthood that can be relatively easily assessed by pediatricians—specifically, elevated BMI, BP, and behavior problems— with consideration of sensitive periods for the effects of exposure, mean level of risk exposure, and chronicity of high-risk exposure over time. Our second aim was to test whether cumulative adversity predicted greater increases in these risk factors 4 years later, at age 11 years. We considered risk indicators at age 11 years to examine the potentially sustained influence of cumulative adversity on physical health and behavior before entering the pubertal transition. We hypothesized that cumulative adversity occurring before age 7 years would be associated with elevated BMI, BP, and behavioral symptoms at age 7 years (baseline), as well as with continued increases in these risk factors between 7 and 11 years of age. We tested for interactions by sex, given that some related studies have reported sex differences in associations between adversity and child health outcomes.[13] We used additive cumulative risk measures throughout our analyses, because this approach is parsimonious, allows for inclusion of relatively uncommon exposures, and does not make assumptions about the relative strength of each risk factor.[14]

ALSPAC	Avon Longitudinal Study of Parents and Children
BMI	Body mass index
BP	Blood pressure
CCEI	Crown-Crisp Experiential Index
DBP	Diastolic blood pressure
SBP	Systolic blood pressure

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Methods

Study participants were members of the Avon Longitudinal Study of Parents and Children (ALSPAC), a prospective investigation of children born to mothers living in Avon County with estimated delivery dates between April 1991 and December 1992.[15] The ALSPAC was designed to study how biological, social, and environmental factors influence pregnancy outcomes and child development. Approximately 85% of eligible pregnant women agreed to participate (n = 14 541), and 13 988 children who were alive at age 12 months were enrolled. During the pregnancy and at regular intervals postpartum, researchers mailed questionnaires to parents and participants were invited to clinics for assessment, as described previously.[16] Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the local Research Ethics Committee.

This analysis uses data from children who attended clinics at age 7 and 11 years and who provided completed data on survey items that asked about social risk factors during the first 7 years of life. All surviving children with correct contact information and parental permission for ongoing study participation were invited to each clinic visit. Our analyses were restricted to individuals with complete data on the required variables. A total of 4361 children had complete survey data on social risk factors and valid outcomes for age 7 year study outcomes, and 3348 children had complete data on social risk factors and age 11 year study outcomes. As documented elsewhere,[16,17] children lost from the cohort were more likely to be from families with lower incomes and education, to have higher BMIs and behavior problems at age 7 years, and to experience more social adversity (**Table I**; available at www.jpeds.com).

Social Risk Factors

We examined 8 social risk factors (described below) that have been used to assess childhood adversity in the ALSPAC study[18-20] and other cohorts[21,22] and were assessed using mail surveys on at least 4 occasions before age 7 years. This facilitated the creation of 4 identical cumulative adversity scores in each of 4 developmental periods (0-1.5 years, >1.5-3 years, >3-5 years, and >5-7 years), a mean cumulative adversity score, and a measure to reflect chronicity of exposure to cumulative adversity. The developmental periods were informed by previous developmental timing research that examined exposures in 1- to 3-year intervals[12,13]; the specific age ranges were determined based on the availability of repeated survey items before age 7 years. Here we describe measurement of each risk factor and creation of the cumulative adversity scores.

Maternal Psychopathology. Maternal psychopathology was assessed at child age 8 months, 2 years, 3 years, 4 years, 5 years, and 6 years. Consistent with previous research in the ALSPAC study,[18] an indicator variable for maternal psychopathology was assigned if at least 1 of the following criteria was present: self-reported suicide attempt, Crown-Crisp Experiential Index (CCEI) depression score >9,[23] CCEI anxiety score >10, or Edinburgh Postnatal Depression Scale score >12.[24] Notably, a CCEI depression score was not available for the age 5-7 year period.

One Adult in the Household. At child age 8 months, 2 years, 3 years, 4 years, and 7 years, mothers were asked to report the number of adults (aged >18 years) living in the household. An indicator variable was created for children residing in households with only 1 adult.

Legal Problems. At child age 8 months, 2 years, 3 years, 4 years, 5 years, and 6 years, mothers and fathers were asked to the respond to the statement "You were in trouble with the law" (since the last interview) with a "yes/no" response. An indicator variable was assigned if either parent affirmed this statement.

Child Taken into Care. At child age 1.5, 2.5, 3.5, 5, 6, and 7 years, mothers completed a stressful event inventory that asked whether their child was ever taken into care since the last interview, referring to either institutional foster care or with relatives. An indicator variable was assigned if this item was endorsed.

Physical Injury. As part of the stressful events inventory (see above), mothers were asked whether their child had been physically hurt since the last interview. If this item was endorsed, an indicator variable was assigned.

Sexual Abuse. As part of the stressful events inventory (see above), mothers were asked whether their child had been sexually abused since the last interview. If mothers endorsed this item, an indicator variable was assigned.

Financial Strain. At child age 8 months, 2 years, 3 years, 5 years, and 7 years, mothers were asked about whether they had difficulty in affording food, clothing, heat, housing, and items for their child since the last interview. Items were rated on a scale of 0-3. Following previous research using this sample, financial strain was defined as the top 10% of scores.[18]

Neighborhood Disadvantage. Measures of neighborhood disadvantage were collected during pregnancy and at child age 2, 3, 5, and 7 years. The measure during pregnancy asked mothers to report on the extent to which their neighborhood was lively, friendly, noisy, clean, and polluted/dirty (rated on a scale of 1-3, with higher values reflecting greater disadvantage). Using the same rating system, the assessments at 2, 3, 5, and 7 years asked mothers to report on a similar set of neighborhood characteristics: noise from other homes, noise from the street, litter, dog dirt, vandalism, worry about burglary, worry about mugging, and disturbances from youth. Consistent with our coding of financial strain, an indicator variable was assigned to the top 10% of scores.

Cumulative Adversity Scores

We used cumulative adversity scores, based on evidence that risk factors tend to cluster together and that the effect of 1 risk factor alone may be small, but the effects of multiple risk factors together can be large.[25] First, to examine the role of timing of adversity, we created 4 identical cumulative adversity scores by summing the dichotomous variables for each of the 8 risk factors (possible range, 0-8) for each development period. If a risk factor was assessed more than once within a single developmental period, then a positive endorsement on either assessment was counted in the score. Second, we created a mean cumulative adversity score by calculating the average of the cumulative adversity scores across the 4 developmental periods. Third, to examine chronicity of exposure to high cumulative adversity, we dichotomized the cumulative adversity scores, whereby the presence of 2 or more risk factors was considered "high"[13] for each developmental period, and created a count variable to reflect of the number of developmental periods in which a child had high adversity.

Outcomes

BMI. At clinics held when participants were age 7 and 11 years, clinic staff measured height to 0.1 cm using a Harpenden stadiometer and measured unclothed weight to 0.1 kg. BMI was calculated as weight in kilograms divided by height in meters squared. BMI *z*-scores were defined based on UK 1990 BMI population reference data.[26] Obesity was defined as the 95th percentile or above (BMI *z*-score $\geq$1.64). This definition is widely used in studies of UK children,[27] has high diagnostic accuracy for identifying children with high fat mass, and performs well for boys and girls.[28]

BP. Clinic staff measured systolic BP (SBP) and diastolic BP (DBP) with a Dinamap 9301 Vital Signs Monitor (Critikon, Tampa, Florida). Reported BP values are based on the mean of 2 readings.

Behavior Problems. Behavior problems in the previous 6 months were assessed via mail questionnaire at age 7 and 11 years using the parent-rated Strengths and Difficulties Questionnaire,[29] a validated assessment of behavioral symptomatology in children. Mothers were asked to rate 25 items describing their child's behavior in the past 6 months as "not true," "somewhat true," or "certainly true," scored from 0 to 2. The Strengths and Difficulties Questionnaire measures 4 dimensions of problematic emotions and behaviors: conduct problems, hyperactivity, peer problems, and emotional symptoms. For research in population-based samples, evidence supports an "externalizing" subscale that combines the conduct and hyperactivity subscales, and an "internalizing" subscale that combines the emotional and peer subscales.[30] The internal consistency reliability scores for this sample were acceptable; for example, for the age 7 year measures, the Cronbach α was 0.70 for the 10 internalizing items and 0.76 for the 10 externalizing items. For regression analyses, we log-transformed the internalizing and externalizing scales owing to the skewed distributions.

Sociodemographic Characteristics

Our analysis included several measures of individual and family characteristics known to be associated with physical health and behavior problems or typically used as control variables. At birth, each mother reported her child's sex, ethnicity (white, nonwhite), and her own educational attainment (below O-level, O-level only, A-level only, university degree or more).

Statistical Analyses

Linear regression models were used to estimate relationships of cumulative adversity scores with BMI *z*-score, BP, and behavior symptoms. The first set of models examined outcomes at age 7 years. For each of the outcomes, we examined associations with the cumulative adversity scores for each of the 4 developmental periods, the mean cumulative adversity score, and the number of developmental periods in which a child had high adversity. All models included covariates for sociodemographic characteristics of the child (age, sex, ethnicity) and household (maternal education), and models of BP included an additional covariate for height at the time of BP assessmet.[31] The second set of linear regression models examined the association between cumulative adversity scores and change in each outcome between age 7 and 11 years. These models adjusted for baseline outcome values (ie, age 7 year outcomes).

We tested for interaction between childhood adversity and sex, and performed 2 sensitivity analyses to evaluate whether our conclusions were robust to changes to the models. First, we replicated the models to include all possible individuals in each analysis rather than limiting ourselves to a complete-case analysis (ie, listwise deletion). Second, we considered BMI as a dichotomous variable, to consider both the prevalence and incidence of obesity more specifically. We conducted this analysis using a modified Poisson regression approach, which produces a prevalence ratio (or incidence ratio) for the relationship between the adverse events score and obesity.[32-34] Models estimating incidence between age 7 and 11 years excluded identified cases at age 7 years.

Results

Characteristics of the study sample, including mean and proportional values of the outcomes, predictors, and covariates, are presented in Table II. The sample had a similar proportion of girls and boys and was almost entirely white (consistent with the regional population), and there was variation in maternal education. The number of children exposed to each risk factor ranged across the cumulative adversity scores at each developmental period: maternal psychopathology, 417-478; 1 adult in the household, 141-356; parental legal problems, 49-114; child taken into care, 0-3; child physically hurt, 99-237; child sexually abused, 0-15; financial strain, 317-539; and neighborhood disadvantage, 289-479.

A large majority of children in the sample did not have high cumulative adversity for any of the 4 developmental

Table II. Characteristics of participants included in analytic samples

Characteristics	Age 7 y (n = 4361)	Age 11 y (n = 3348)
Outcomes, mean (SD)		
BMI *z*-score	16.17 (1.99)	18.92 (3.26)
SBP, mmHg	98.49 (9.14)	104.98 (9.65)
DBP, mmHg	56.29 (6.62)	58.5 (6.37)
Internalizing symptoms, n	2.52 (2.50)	2.43 (2.63)
Externalizing symptoms, n	4.87 (3.26)	3.81 (3.09)
Number of adversities, mean (SD)		
Time 1: 0-1.5 y	0.32 (0.60)	0.3 (0.59)
Time 2: 1.5-3 y	0.53 (0.84)	0.49 (0.81)
Time 3: 3-5 y	0.44 (0.75)	0.41 (0.73)
Time 4: 5-7 y	0.47 (0.79)	0.44 (0.75)
Cumulative adversity score (0-7 y), mean (SD)	0.44 (0.59)	0.41 (0.56)
High cumulative adversity (≥2 risk factors), %		
Time 1: 0-1.5 y	5.64	5.14
Time 2: 1.5-3 y	11.88	10.60
Time 3: 3-5 y	9.47	8.87
Time 4: 5-7 y	10.25	8.93
High cumulative adversity scores, %		
None	78.81	80.5
1 time	11.03	10.6
2 times	5.69	5.02
3-4 times	4.47	3.88
Demographic data		
Female sex, %	48.68	49.76
White ethnicity, %	96.35	96.62
Maternal education at gestation, %		
Missing	0.71	0.51
Below O-level	17.91	16.4
O-level only	34.95	34.44
A-level	27.7	28.58
University degree+	18.73	20.07

periods before age 7 years (79%); 11% of the sample experienced high cumulative adversity in 1 developmental period, 6% did so in 2 developmental periods, and 5% did so in 3 or 4 developmental periods. The age 7 year and 11 year outcome measures were moderately to highly correlated over time (BMI *z*-score, $r = 0.84$; SBP, $r = 0.43$; DBP, $r = 0.37$; internalizing symptoms, $r = 0.51$; externalizing symptoms, $r = 0.65$; $P < .0001$ for all). There was no evidence of a significant interaction between sex and adverse events scores for any outcome; thus, we present findings for the combined sample.

Cumulative Adversity and Age 7 Year Outcomes

In models predicting BMI *z*-score at age 7 years (Table III), cumulative adversity at 0-1.5 years was associated with higher BMI *z*-score ($\beta = 0.05$, SE = 0.03), and cumulative adversity at 1.5-3 years and 5-7 years were marginally associated with higher BMI *z*-score, adjusted for sociodemographic factors. The mean cumulative adversity score (averaged across all developmental periods) was associated with elevated BMI *z*-score ($\beta = 0.06$, SE = 0.03), and models that examined the number of periods with high cumulative adversity (ie, ≥2 risk factors) showed a gradient pattern in which children who experienced high cumulative adversity in 3 or 4 of the developmental periods had higher BMI *z*-scores ($\beta = 0.17$, SE = 0.08) compared with those who did not experience high cumulative adversity at any time (reference) or those who experienced high cumulative adversity only during 1 developmental period ($\beta = 0.02$, SE = 0.05) or 2 developmental periods ($\beta = 0.12$, SE = 0.07).

Models that examined cumulative adversity in relation to SBP and DBP were almost entirely null. The model for examining the number of periods in which high cumulative adversity occurred showed 1 association, with high cumulative risk at 1 period associated with lower SBP relative to no periods of high cumulative adversity ($\beta = -1.04$, SE = 0.43).

The associations between cumulative adversity and (log) internalizing and externalizing symptoms exhibited similar patterns to one another. In models that considered age of exposure, cumulative adversity scores from all 4 developmental periods were associated with both outcomes ($P < .0001$), and the magnitude of the associations was slightly

Table III. β estimates for associations between cumulative social risk and BMI, SBP, DBP, and internalizing and externalizing symptoms at age 7 years (n = 4361)

Variable	BMI *z*-score β	(SE)		SBP, mm/Hg β	(SE)		DBP, mm/Hg β	(SE)		Log internalizing symptoms β	(SE)		Log externalizing symptoms β	(SE)	
Social risk score															
Time 1: 0-1.5 y	0.05	(0.03)	*	−0.13	(0.22)		−0.08	(0.17)		0.16	(0.02)	†	0.12	(0.02)	†
Time 2: 1.5-3 y	0.03	(0.02)	‡	−0.05	(0.16)		0.03	(0.12)		0.14	(0.01)	†	0.12	(0.01)	†
Time 3: 3-5 y	0.02	(0.02)		−0.07	(0.18)		0.10	(0.13)		0.17	(0.01)	†	0.14	(0.01)	†
Time 4: 5-7 y	0.04	(0.02)	‡	−0.01	(0.17)		0.12	(0.13)		0.19	(0.01)	†	0.14	(0.01)	†
Mean cumulative social risk score (0-7 y)	0.06	(0.03)	*	−0.10	(0.23)		0.09	(0.17)		0.28	(0.02)	†	0.22	(0.02)	†
High cumulative social risk scores (≥2 risk factors)															
None (reference)	—			—			—			—			—		
1 time	0.02	(0.05)		−1.04	(0.43)	*	−0.44	(0.32)		0.24	(0.03)	†	0.14	(0.03)	†
2 times	0.12	(0.07)	‡	0.00	(0.59)		0.50	(0.43)		0.36	(0.05)	†	0.26	(0.04)	†
3-4 times	0.17	(0.08)	*	0.81	(0.66)		0.59	(0.49)		0.44	(0.05)	†	0.37	(0.05)	†

Models adjusted for sex, ethnicity, maternal education at gestation, and age at measurement; in the case of BP, models were also adjusted for height at time of measurement. The associations between each outcome and time window were estimated in separate models.
*$P < .05$.
†$P < .0001$.
‡$P < .10$.

Table IV. β estimates for associations between cumulative social risk and change in BMI, SBP, DBP, and internalizing and externalizing symptoms between age 7 and 11 years (n = 3348)

	BMI *z*-score			SBP, mm/Hg			DBP, mm/Hg			Log internalizing symptoms			Log externalizing symptoms		
Variable	β	(SE)		β	(SE)		β	(SE)		β	(SE)		β	(SE)	
Social risk score															
Time 1: 0-1.5 y	0.01	(0.02)		−0.22	(0.25)		0.11	(0.17)		0.14	(0.02)	*	0.07	(0.02)	*
Time 2: 1.5-3 y	0.03	(0.01)	†	0.12	(0.18)		0.05	(0.13)		0.11	(0.01)	*	0.05	(0.01)	†
Time 3: 3-5 y	0.01	(0.02)		0.01	(0.20)		0.04	(0.14)		0.09	(0.02)	*	0.06	(0.01)	*
Time 4: 5-7 y	0.00	(0.01)		−0.05	(0.20)		0.04	(0.14)		0.11	(0.01)	*	0.06	(0.01)	*
Mean cumulative social risk score (0-7 y)	0.02	(0.02)		−0.01	(0.26)		0.09	(0.18)		0.19	(0.02)	*	0.10	(0.02)	*
High cumulative social risk scores (≥2 risk factors)															
None	–						–			–			–		
1 time	0.01	(0.04)		−0.84	(0.48)	§	−0.30	(0.33)		0.20	(0.04)	*	0.11	(0.03)	‡
2 times	0.02	(0.05)		0.03	(0.68)		−0.12	(0.47)		0.12	(0.05)	†	0.13	(0.04)	‡
3-4 times	0.04	(0.06)		−0.25	(0.77)		0.30	(0.53)		0.35	(0.06)	*	0.18	(0.05)	‡

Models adjusted for sex, ethnicity, maternal education at gestation, age at measurement, and outcome at 7 years of age; in the case of BP, models were also adjusted for height at time of measurement. The associations between each outcome and time window were estimated in separate models.
*$P < .0001$.
†$P < .05$.
‡$P < .01$.
§$P < .10$.

increased as the age of exposure became closer to the outcome. Associations between the mean cumulative adversity score and internalizing and externalizing symptoms ($P < .0001$) were of greater magnitude than the associations for cumulative adversity in any single developmental period. In models that examined chronicity of exposure to high cumulative adversity, children who experienced high cumulative adversity during 3 or 4 developmental periods had the most pronounced elevation of symptoms compared with those who did not experience high cumulative adversity at any time or those who experienced high adversity during 1 or 2 developmental periods (all $P < .0001$; **Table III**).

Cumulative Adversity and Change between Age 7 and 11 Years

Cumulative adversity between age 1.5 and 3 years was associated with an increase in BMI *z*-score ($\beta = 0.03$, SE = 0.01) between age 7 and 11 years; however, exposure to cumulative adversity during the other developmental periods, mean cumulative adversity from 0 to 7 years, and chronicity of exposure to cumulative adversity were not associated with an increase in BMI *z*-score between 7 and 11 years (**Table IV**). Similarly, none of the cumulative adversity scores were associated with increases in SBP or DBP. In contrast, all of the cumulative risk scores (ie, scores to reflect each developmental period, mean cumulative adversity score, and chronicity of exposure) were associated with increased internalizing and externalizing symptoms between 7 and 11 years ($P < .01$). The magnitudes of the association were relatively similar across developmental periods, and the mean cumulative adversity score was more strongly associated with internalizing and externalizing symptoms relative to measures for specific developmental periods (log internalizing symptoms, $\beta = 0.19$, SE = 0.02; log externalizing symptoms, $\beta = 0.10$, SE = 0.02; $P < .0001$).

Similar to models estimating outcomes at age 7 years, models examining chronicity of exposure to high adversity showed that children exposed to high adversity during 3 or 4 of the developmental periods had greater increases in internalizing and externalizing symptoms between age 7 and 11 years compared with children who did not experience high cumulative adversity at any time or those who experienced high cumulative adversity during 1 or 2 developmental periods (**Table IV**).

Sensitivity Analyses

We replicated all models to include all possible individuals in each analysis rather than limiting ourselves to complete-case analyses (ie, listwise deletion). Our findings were consistent with our data for a complete-case analysis, and our conclusions remained unchanged (**Tables V** and **VI**; available at www.jpeds.com). Second, in analyses that considered BMI as a dichotomous variable (ie, obesity as the outcome), we observed an identical pattern of statistical significance for models predicting obesity prevalence at age 7 years. No associations were observed between any of the social risk scores and incident obesity at age 11 years, which is largely consistent with the findings for the models of BMI *z*-score, with the exception that social risk at age 1.5-3 years was associated with increased BMI *z*-score between age 7 and 11 years (**Table VII**; available at www.jpeds.com).

Discussion

At age 7 years, mean cumulative adversity and chronic exposure to high adversity were associated with elevated BMI and internalizing and externalizing symptoms, but not with elevated BP. Adversity scores for all 4 developmental periods were associated with elevated internalizing and externalizing symptomatology, whereas these associations for BMI were less robust. Cumulative adversity at age 1.5-3 years was the

sole assessment associated with a change in BMI *z*-score between 7 and 11 years, and no cumulative adversity measures were associated with a change in BP during this period. In contrast, all of the cumulative adversity measures were associated with greater increases in internalizing and externalizing symptoms between age 7 and 11 years. We found no evidence of sex differences in the associations between childhood adversity and any outcome. Taken together, our results suggest that behavioral outcomes in childhood are more consistently affected by social adversity earlier in the life course relative to physical outcomes of BMI and BP. We view this finding as a major contribution of our study, given that few previous studies have explicitly addressed this question.

This study extends previous research by simultaneously considering a set of child physical and mental health outcomes previously linked to poor adult health to evaluate whether and when social adversity may influence each biobehavioral factor, and to further consider how variations in assessment of cumulative adversity (eg, age at exposure, chronicity) may influence potential associations. Our results agree with previous research showing that childhood adversity is strongly related to behavior problems in middle childhood,[8] and is not associated with resting BP in youth.[35,36] Our findings are partially consistent with previous research showing that adversity is associated with BMI among youth,[7,13,37] although our findings differ from other reports in some meaningful ways. For example, we observed no associations between mean cumulative adversity or chronic exposure to high adversity and a change in BMI between 7 and 11 years of age, which is inconsistent with a study showing an association between cumulative risk and a higher BMI trajectory between age 9 and 17 years.[37] Furthermore, we found no evidence for effect modification by sex, whereas a study of cumulative adversity and obesity among preschool-age children documented associations in girls, but not in boys.[13]

Our findings suggest that BMI and behavioral outcomes, but not BP, at age 7 years are sensitive to the effects of cumulative adversity. Several mechanisms potentially could explain these associations. It is possible that cumulative adversity has a direct influence on biological mechanisms that regulate metabolism and behavior,[38] or that cumulative adversity may have an indirect influence via health-related behaviors, including diet[39] and physical activity[40] (in the case of BMI), or compromised parenting in stressful settings (relevant to both BMI and behavior).[41] Visible effects of cumulative adversity on BP may have been less apparent, because BP may be less immediately vulnerable to dysregulation in younger individuals. In contrast, recent studies have documented that early stress is associated with other forms of biological dysregulation that may be more immediately apparent, including elevated levels of inflammation, stress hormones, and cardiovascular reactivity in children of similar age,[19,21,22] suggesting that other biological indicators may be used in conjunction with BMI and behavior problems to indicate which children are on a high-risk trajectory.

Our findings are subject to several limitations of this study. First, the prevalence of some of the risk factors in our cumulative adversity scores suggest that they were underreported (eg, sexual abuse, physical injury), which would bias findings toward the null.[42] Second, similar to many longitudinal studies, ALSPAC has incomplete participation over time; thus, associations are likely underestimated, given that disadvantaged children were lost to follow-up (**Table I**). Third, the assessment of cumulative adversity was not comprehensive, and important risk factors (eg, housing quality, witnessing of intimate partner violence) might have been omitted, which would bias our results toward the null. In addition, some of the adversity measures (eg, sexual abuse, physical injury) were based on single item questions rather than on complete standardized instruments; consequently, these measures may be less precise and could lead to underestimation of true associations. Fourth, the additive cumulative risk approach has some limitations; it does not incorporate variation in risk intensity across risk factors, enable identification of the most detrimental risks for a given outcome, or allow for the possibility of statistical interactions between individual risk factors.[14] Evans et al[14] provided a detailed discussion of the strengths and weaknesses of the cumulative risk approach and alternative multiple risk measurement models for child health research. Another limitation is the study's observational design. Although the findings are derived from a prospective analysis, we cannot exclude the possibility that some variable other than cumulative adversity is responsible for the findings.

Importantly, our study also has a number of strengths, including a large sample with diverse values of socioeconomic status, repeated measures of adversity, and objectively measured BMI and BP.

More research is needed to understand why adversity influences different risk factors uniquely—that is, whether there are shared or distinct mechanisms to explain associations between adversity with BMI and behavior problems. Moreover, it will be useful for studies to examine whether there are other physiological factors not examined in the present study that may be responsive to the social environment and also indicate early biological dysregulation and risk for later poor health. Studies are also needed to clarify how the behavioral and physiological alterations in response to cumulative adversity relate to one another at various developmental periods. In addition, it would be useful to examine whether the associations identified in this study endure into adolescence and adulthood, and how they relate to chronic disease risk in adulthood. It also may be valuable for future studies to examine the components of cumulative risk index separately, to delineate whether certain risk factors are particularly influential for a given type of outcome. Finally, future studies are needed to examine how trajectories of social risk factors (ie, movement from high risk to low risk over time, or vice versa) influence health outcomes in childhood and beyond.

From a practice perspective, it will be important to identify modifiable pathways that connect cumulative adversity to the risk of childhood behavioral problems and overweight and obesity, as well as interventions or life events that attenuate

these associations. Based on the present findings, childhood behavior problems appear to be more sensitive to cumulative adversity compared with BP or BMI. If replicated, these findings suggest that pediatricians might screen for behavioral problems to determine whether children exposed to adversity are on a trajectory that could lead to increased risk for later chronic diseases. In addition, this research supports the potential importance of interventions to address cumulative adversity in childhood as a way of influencing multiple risk factors for chronic diseases, rather than targeting primarily individual health risk factors, which are often resistant to change in adulthood. ■

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Hypoproteinemia and Edema in Infants with Cystic Fibrosis of the Pancreas

Fleisher DS, DiGeorge AM, Barnes LA, Cornfeld D. J. Pediatr 1964;64:341-8

When cystic fibrosis (CF) was first described in the 1500s, these children were thought to be bewitched. By the 1800s, the disease and its prognosis were depicted in a German children's song: "The child will soon die whose forehead tastes salty when kissed." Life expectancy was 1 year.

In the 1900s, malnutrition and diarrhea were the hallmarks of the disease described as a "celiac syndrome." In 1964, Fleisher et al reported their findings that breast milk or soy formula fed infants were significantly more malnourished with edema and hypoproteinemia and fared worse than those fed cow milk-based formula. Treatment for "cystic fibrosis of the pancreas" emphasized the importance of high fat diet and the use of pancreatic enzymes. Life expectancy was still limited, with 80% death rate by age 5 years.

In the following decades, significant strides were made in disease management without full understanding of its etiology, and life expectancy increased to almost 20 years by the 1980s. The landmark discovery of disease-causing mutations in the cystic fibrosis transmembrane regulator gene (*CFTR*) in 1989 provided a new focus in CF research.

State screens now help diagnose CF in infancy, resulting in earlier intervention and better outcomes. From 2000-2011, diagnoses through state screen increased from 10% to 60%. Life expectancy has risen significantly from 20 years to 37 years in just 2 decades. However, with improved survival, other complications of CF arise, including CF-related diabetes and liver disease with portal hypertension.

We are now entering a revolutionary era in CF with the development of breakthrough disease-modifying drugs targeting the CFTR protein defect. CFTR modulators are small molecules classified as potentiators, correctors, or premature stop codon suppressors. The first approved small molecule, Kalyedco (ivacaftor) is specific to less common *CFTR* mutations and increases CFTR channel opening. Other promising small molecules in clinical trials (http://www.cff.org/treatments/Pipeline) may be beneficial to those with classic delta F508 mutations.

Although previous advances in CF therapy mitigated the effects of CFTR dysfunction, the combination of early detection and initiation of personalized medicine targeting *CFTR* mutations may soon keep foreheads from tasting salty and truly alter the course of this devastating disease.

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Table I. Characteristics of participants

Characteristics	In sample n	In sample Mean/%	In sample SD	Not in sample* n	Not in sample* Mean/%	Not in sample* SD	*P* value
Outcomes, mean							
BMI z-score	4361	16.17	(1.99)	3849	16.37	(2.23)	<.0001
SBP, mmHg	4361	98.49	(9.14)	3728	99.57	(9.29)	<.0001
DBP, mmHg	4361	56.29	(6.62)	3726	56.73	(6.72)	.003
Internalizing symptoms, n	4361	2.52	(2.50)	2257	2.63	(2.59)	.11
Externalizing symptoms, n	4361	4.87	(3.26)	2242	5.04	(3.31)	.05
Number of adversities, mean							
Time 1: 0-1.5 y	4361	0.32	(0.60)	2140	0.40	(0.71)	<.0001
Time 2: 1.5-3 y	4361	0.53	(0.84)	2491	0.66	(0.92)	<.0001
Time 3: 3-5 y	4361	0.44	(0.75)	1734	0.53	(0.85)	<.0001
Time 4: 5-7 y	4361	0.47	(0.79)	1571	0.61	(0.90)	<.0001
Cumulative adversity score (0-7 y), mean	4361	0.44	(0.59)	272	0.48	(0.64)	.32
High cumulative adversity scores, %							
None	3437	78.81		204	75.00		.11
1 time	481	11.03		43	15.81		
2 times	248	5.69		13	4.78		
3-4 times	195	4.47		12	4.41		
Demographic data							
Female, %	2123	48.68		1962	49.94		.25
White, %	4202	96.35		3632	92.44		<.0001
Maternal education at gestation, %							
Missing	31	0.71		726	18.48		<.0001
Below O-level	781	17.91		866	22.04		
O-level only	1524	34.95		1145	29.14		
A-level	1208	27.7		799	20.34		
University degree+	817	18.73		393	10.00		

O-level, ordinary level; exams taken at age 15-16 y, the completion of legally required school attendance, equivalent to today's General Certificate of Secondary Education; *A-level*, advanced level.
*Comparisons for included/excluded respondents were based on all children who attended the clinic at 7 years of age (n = 8290).

Table V. β estimates for associations between cumulative social risk and BMI, SBP, DBP, and internalizing and externalizing symptoms at age 7 years (sensitivity analysis: listwise deletion)

Variable	BMI *z*-score β	BMI *z*-score (SE)		SBP, mm/Hg β	SBP, mm/Hg (SE)		DBP, mm/Hg β	DBP, mm/Hg (SE)		Log internalizing symptoms β	Log internalizing symptoms (SE)		Log externalizing symptoms β	Log externalizing symptoms (SE)	
Social risk score															
Time 1: 0-1.5 y	0.04	(0.02)	‡	−0.13	(0.18)		0.00	(0.13)		0.15	(0.02)	*	0.12	(0.01)	*
Time 2: 1.5-3 y	0.03	(0.01)	†	0.06	(0.13)		0.04	(0.09)		0.15	(0.01)	*	0.11	(0.01)	*
Time 3: 3-5 y	0.02	(0.02)		0.01	(0.15)		0.22	(0.11)	†	0.17	(0.01)	*	0.12	(0.01)	*
Time 4: 5-7 y	0.03	(0.01)	‡	0.11	(0.14)		0.17	(0.11)		0.20	(0.01)	*	0.13	(0.01)	*
Mean cumulative social risk score (0-7 y)	0.05	(0.03)	‡	−0.08	(0.23)		0.04	(0.17)		0.28	(0.02)	*	0.21	(0.02)	*
High cumulative social risk scores (≥2 risk factors)															
None (reference)	–			—			—			—			—		
1 time	0.03	(0.05)		−1.07	(0.43)	†	−0.47	(0.32)		0.23	(0.03)	*	0.14	(0.03)	*
2 times	0.9	(0.07)	‡	−0.03	(0.58)		0.44	(0.43)		0.37	(0.05)	*	0.27	(0.04)	*
3-4 times	0.14	(0.07)	‡	0.90	(0.65)		0.55	(0.48)		0.45	(0.05)	*	0.37	(0.05)	*

Models adjusted for sex, ethnicity, maternal education at gestation, and age at measurement; in the case of BP, models were also adjusted for height at time of measurement. The associations between each outcome and time window were estimated in separate models.
*$P < .0001$.
†$P < .05$.
‡$P < .10$.

Table VI. β estimates for associations between cumulative social risk and changes in BMI, SBP, DBP, and internalizing and externalizing symptoms between age 7 and 11 years (sensitivity analysis: listwise deletion)

	BMI z-score		SBP, mm/Hg		DBP, mm/Hg		Log internalizing symptoms		Log externalizing symptoms	
Variable	β	(SE)	β	(SE)	β	(SE)	β	(SE)	β	(SE)
Social risk score										
Time 1: 0-1.5 y	0.01	(0.02)	−0.02	(0.20)	0.01	(0.14)	0.13	(0.02) *	0.07	(0.01) *
Time 2: 1.5-3 y	0.03	(0.01) †	0.06	(0.14)	0.03	(0.10)	0.10	(0.01) *	0.04	(0.01) *
Time 3: 3-5 y	0.01	(0.01)	−0.02	(0.17)	−0.01	(0.12)	0.10	(0.01) *	0.07	(0.01) *
Time 4: 5-7 y	0.00	(0.01)	−0.10	(0.16)	−0.03	(0.11)	0.10	(0.01) *	0.06	(0.01) *
Mean cumulative social risk score (0-7 y)	0.02	(0.02)	−0.13	(0.24)	0.05	(0.17)	0.19	(0.02) *	0.11	(0.02) *
High cumulative social risk scores (≥2 risk factors)										
None	–				–		–		–	
1 time	0.00	(0.03)	−0.81	(0.46) §	−0.20	(0.32)	0.19	(0.03) *	0.10	(0.03) †
2 times	0.03	(0.05)	0.28	(0.62)	−0.08	(0.43)	0.13	(0.05) ‡	0.14	(0.04) ‡
3-4 times	0.05	(0.05)	−0.60	(0.71)	0.28	(0.49)	0.34	(0.05) *	0.19	(0.05) †

Models adjusted for sex, ethnicity, maternal education at gestation, age at measurement, and the outcome at 7 years of age. In the case of BP, models were also adjusted for height at time of measurement. The associations between each outcome and time window were estimated in separate models.
*$P < .0001$.
†$P < .05$.
‡$P < .01$.
§$P < .10$.

Table VII. β estimates for associations between cumulative social risk and obesity at age 7 years, and incidence of obesity between age 7 and 11 years

	Obesity at 7 y (n = 3 44/4361; 7.89%)		Incident obesity between 7 and 11 y (n = 256/3095; 8.27%)	
Association	OR	(95% CI)	OR	(95% CI)
Social risk score				
Time 1: 0-1.5 y	1.28	(1.08-1.48)*	1.09	(0.91-1.30)
Time 2: 1.5-3 y	1.10	(0.98-1.24)	1.07	(0.93-1.23)
Time 3: 3-5 y	1.10	(0.96-1.26)	1.06	(0.91-1.24)
Time 4: 5-7 y	1.12	(1.01-1.25)†	0.96	(0.82-1.12)
Mean cumulative social risk score (0-7 y)	1.22	(1.04-1.43)†	1.07	(0.88-1.30)
High cumulative social risk scores (≥2 risk factors)				
None (reference)	1.00		1.00	
1 time	1.29	(0.96-1.74)	0.97	(0.65-1.43)
2 times	1.39	(0.93-2.07)	0.99	(0.58-1.69)
3-4 times	1.73	(1.18-2.54)*	1.12	(0.64-1.97)

Models adjusted for sex, ethnicity, maternal education at gestation, and age at measurement. The associations between each outcome and time window were estimated in separate models.
*$P < .01$.
†$P < .05$.