Intellectual and Academic Functioning of School-Age Children With Single-Suture Craniosynostosis

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abstract

OBJECTIVE: We compared the developmental status of school-age children with single-suture craniosynostosis (case group) and unaffected children (control group). Within the case group we compared the performance of children distinguished by location of suture fusion (sagittal, metopic, unicoronal, lambdoid).

METHODS: We administered standardized tests of intelligence, reading, spelling, and math to 182 case participants and 183 control participants. This sample represented 70% of those tested during infancy before case participants had corrective surgery.

RESULTS: After adjustment for demographics, case participants' average scores were lower than those of control participants on all measures. The largest observed differences were in Full-Scale IQ and math computation, where case participants' adjusted mean scores were 2.5 to 4 points lower than those of control participants (*P*s ranged from .002 to .09). Adjusted mean case–control differences on other measures of achievement were modest, although case deficits became more pronounced after adjustment for participation in developmental interventions. Among case participants, 58% had no discernible learning problem (score <25th percentile on a standardized achievement test). Children with metopic, unicoronal, and lambdoid synostosis tended to score lower on most measures than did children with sagittal fusions (*P*s ranged from <.001 to .82).

CONCLUSIONS: The developmental delays observed among infants with single-suture craniosynostosis are partially evident at school age, as manifested by lower average scores than those of control participants on measures of IQ and math. However, case participants' average scores were only slightly lower than those of control participants on reading and spelling measures, and the frequency of specific learning problems was comparable. Among case participants, those with unicoronal and lambdoid fusions appear to be the most neurodevelopmentally vulnerable.

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WHAT'S KNOWN ON THIS SUBJECT: It is unclear whether developmental delays observed among infants with single-suture craniosynostosis (SSC) persist at school age. Few neurodevelopmental studies have examined children with SSC beyond age 3, with most having methodological limitations.

WHAT THIS STUDY ADDS: This study is the first to follow and test infants with SSC and a control group at school age. Infancy delays among children with SSC persisted at school age in some areas (IQ, math) but not others (reading, spelling).

Single-suture craniosynostosis (SSC) is defined as the premature fusion of any of the cranial sutures (eg, sagittal, metopic, coronal, or lambdoid) and occurs in ~1 in 1700 to 2500 live births.[1,2] Corrective surgery to restore the suture is preferentially performed in the first year of life. Neurodevelopmental impairment has long been suspected among children with SSC, because the prematurely fused suture is believed to constrain[3] or alter[4,5] brain structures and elevate intracranial pressure.[6,7] Early neurodevelopmental investigations were beset with methodological problems and inconclusive findings,[8,9] but in more recent and better-designed studies, infants and preschoolers with SSC have consistently scored lower, on average, than same-aged children with patent sutures.[10–13] In a large multisite study of children in the United States from infancy to 36 months, we observed children with SSC to score on average about 0.25 to 0.50 SD lower on standardized tests than a demographically matched control group.[11] Compared with unaffected children, case participants had nearly twice the odds of scoring in the delayed range. Similar findings have been reported in a well-designed study of Australian infants who were followed with similar developmental measures.[14]

A key question is whether these delays persist into the school-age years and manifest as learning disabilities or other problems in need of intervention.[15] Few neurodevelopmental studies have focused on children with SSC beyond age 3,[16–20] and most of these studies have lacked control groups[17,19,20] or used methods other than testing to estimate developmental progress.[19,20] In the current study we addressed these problems by following to early elementary school age a large sample of infants with SSC who were recruited and assessed before corrective surgery. A demographically matched control group was also followed, with approximately 70% of case and control infants retained for neuropsychological testing at school age. We hypothesized that children with SSC would score lower than children without craniosynostosis on standardized measures of IQ and academic achievement.

METHODS

Study Design

We used cross-sectional data from a school-age assessment of children with SSC (case group) and unaffected children (control group) who have been followed since infancy in a longitudinal study.[12] In the original study, we enrolled all eligible case participants between January 2002 and September 2006 from Seattle Children's Hospital, the Cleft Lip and Palate Institute and Northwestern University in Chicago, Children's Healthcare of Atlanta, St Louis Children's Hospital, and Children's Hospital of Philadelphia (starting in January 2006). Unaffected control participants were recruited by each center and frequency matched to case participants at the time of recruitment. Participants were assessed at a baseline visit that occurred, for case participants, before surgery (mean age = 7.4 months) and at 3 subsequent visits at which the average ages were 18 months, 36 months, and 7 years; the last age point is the focus of this report. The study was approved by institutional review boards at each participating institution and informed consent obtained from all parents.

Case Infants

Infants with SSC were referred at the time of diagnosis by a treating surgeon or pediatrician. Infants were eligible if they had SSC (isolated sagittal, metopic, unilateral coronal, or unilateral lambdoid synostosis) confirmed by CT scans, had not yet had cranial vault surgery, and were ≤30 months of age at recruitment. Exclusion criteria included prematurity (<34 weeks' gestation), major medical or neurologic conditions (eg, cardiac defects, seizure disorders, significant health conditions necessitating surgical correction), presence of ≥3 extracranial minor malformations,[16] or presence of other major malformations. For a subsample of 178 cases whose parents gave consent, we collected biospecimens and analyzed genetic data by array comparative genomic hybridization and candidate and gene resequencing (for details see Cunningham et al 2011[21]). Children with SSC who had a genetic variant (including a known or probable causal mutation for craniosynostosis) were eligible if they had no phenotypic features of a known syndrome and otherwise met all inclusion criteria.

We enrolled 270 case participants (84% of those eligible), 4 of whom were later found to be ineligible (for details about ascertainment, see Starr et al 2012[12]). The case sample included 76 children with sagittal synostosis, 48 with metopic, 46 with unicoronal, and 12 with lamboid synostosis. Among the 266 case infants seen at baseline, 182 children (68%) had a school-age assessment.

Control Infants

Infants were eligible as control participants if they had no known craniofacial anomaly and met none of the exclusionary criteria for case participants. Control group participants were recruited through pediatric practices, birthing centers, and announcements in publications of interest to parents of newborns. Control participants were frequency-matched to case participants on factors related to neurodevelopmental performance that may also be potential confounders: age at enrollment (within 3 weeks), gender, family socioeconomic status (SES) within the

same Hollingshead category,[22] and race or ethnicity.

We enrolled 76% of all eligible control participants (see Starr et al 2012[12] for details). Among the 259 control participants seen at baseline, 183 (71%) had a school-age assessment.

Measures

Intelligence was measured by the Full-Scale IQ score from the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV).[23] The Wide Range Achievement Test, Fourth Edition (WRAT-4) measured reading, spelling, and math with a composite or subscale score representing each of these areas.[24] The Test of Word Reading Efficiency (TOWRE) measured reading efficiency, that is, the child's ability to quickly and accurately decode increasingly difficult words and nonsense words.[25] We used the Comprehensive Test of Phonological Processing (CTOPP) to assess skills that support reading decoding, speed, and fluency.[26–29] Two CTOPP composite scores were used: phonological awareness (ie, sound blending, elision) and rapid naming (ie, verbal retrieval of symbols). All of these tests have demonstrated good to excellent reliability and validity.[23–29] Age-based standardized scores with a mean of 100 and SD of 15 were used for all measures.

All testing sessions were video recorded and all test administrations scored by a second psychometrist. Scoring errors were recorded and disagreements between psychometrists resolved by one of the psychologist investigators (K.K.S., B.R.C., or M.L.S.). Resolved scores were used for all analyses. Among all administrations of the 4 tests, 94% of WISC-IV test administrations were error-free, as were 97%, 94%, and 99% of WRAT-4, TOWRE, and CTOPP administrations, respectively.

Procedures

After psychometrists completed testing, parents were interviewed to update the family's demographic information and medical history and to provide information on any interventions received since the last assessment at age 3 (eg, speech or language therapy). Parents who so desired were mailed a summary of their child's test results, which they were encouraged to share with their child's pediatrician or teacher.

Data Analysis

We examined the distribution of demographic characteristics and IQ and achievement scores separately for case and control participants. Visual inspection of boxplots and histograms confirmed that the distributions of each outcome score were approximately normal in case and control participants. We also explored factors associated with attrition by comparing the distributions of baseline demographic and neurodevelopmental characteristics of participants seen at school age with those of participants who were lost to follow-up.

Unless otherwise specified, all of the following analyses were adjusted for 4 potential confounders: child age at assessment (in months, continuous), child gender, family SES (Hollingshead composite score, continuous), and maternal IQ (continuous, measured at baseline by the Wonderlic Cognitive Ability Test).[30]

Linear regression with robust SEs was used to estimate differences between case and control participants with corresponding 95% confidence intervals (CIs). Because limited sample size precluded direct adjustment of all potential confounders in the same model, we recalculated in secondary analyses the regression estimates of case–control differences after propensity score matching.[31,32] We used a logit model that predicted case status and matched on the 4 confounders from the primary analysis, plus race or ethnicity and study site. We repeated the primary linear regression analyses after excluding 19 children with SSC in whom known or probable causal mutations for craniosynostosis were detected through array comparative genomic hybridization and candidate and gene resequencing.[21]

To explore potential attrition bias over time, we repeated the analyses of case–control differences by using inverse probability weighting (IPW).[33] The predicted probability of school age participation was estimated with baseline characteristics that were known for all participants and included date of birth, gender, race or ethnicity, prematurity (<38 weeks' gestation, coded yes/no), case status, suture diagnosis, parents' marital status, maternal IQ, study site, and scores from the Bayley Scales of Infant Development 2 (Psychomotor Development Index) and the Preschool Language Scale 3 (auditory comprehension) completed at baseline (see Starr et al 2012[12]). Observations from participants assessed at school age are understood to represent participants who had similar baseline characteristics, but who were lost to follow-up and assigned weights to represent the full population.

Intervention services (eg, speech or language therapy, occupational or physical therapy, special education services) presumably improved some children's outcome scores. To account for these presumed positive effects and examine their influence on case–control differences, we repeated analyses by using censored normal regression.[34] This method assumes that the scores of children who received intervention are "left censored"; that is, although it is unknown what their scores would have been in the absence of the intervention they received, it is

assumed that the unknown scores are at least as low as their observed scores with intervention.

Logistic regression with robust SEs was used to compare the proportion of case and control participants with learning problems. We used an empirically derived definition of learning disability: scores below the 25th percentile on ≥1 of the achievement tests given.[35,36] We also examined the distribution of learning problems by case status and test and calculated the number of tests with scores <25th percentile for each participant.

Finally, in secondary analyses involving only case participants, we used linear and logistic regression to determine whether test scores or the odds of having a learning problem differed by the site of the affected suture (sagittal, metopic, unicoronal, and lambdoid). Indicators of suture site were included in each model, with sagittal cases considered the referent, and evidence for overall group differences evaluated on Wald tests.

We performed all analyses by using Stata version 12 (StataCorp, College Station, TX).

TABLE 1 Demographic Characteristics of Children With and Without SSC at Age 7

Characteristic	Control Group, *N* = 183		Case Group, *N* = 182	
	N	%	*N*	%
Age, y				
<7.5	144	78.7	124	68.1
>7.5	39	21.3	58	31.9
Gender				
Female	69	37.7	68	37.4
Male	114	62.3	114	62.6
Grade level[a]				
<1	2	1.1	3	1.7
1	130	71.0	110	60.4
2	37	20.2	56	30.8
≥3	9	4.9	9	4.9
Race or ethnicity[b]				
Nonwhite or Hispanic	47	25.7	37	20.3
White, non-Hispanic	136	74.3	145	79.7
SES				
I (highest)	53	29.0	43	23.6
II	102	55.7	81	44.5
III	15	8.2	36	19.8
IV	11	6.0	20	11.0
V (lowest)	2	1.1	2	1.1
Site				
Seattle	71	38.8	74	40.7
Chicago[c]	76	41.5	66	36.3
St Louis	9	4.9	18	9.9
Atlanta	27	14.8	24	13.2

[a] Grade level missing for 5 control and 4 case participants.
[b] Includes Hispanic or Latino ethnicity, Asian or Pacific Islander, black or African American, and mixed races or ethnicities.
[c] Includes children from Philadelphia, who were assessed by staff from the Chicago site.

RESULTS

Mean age at the time of the assessment was 7.5 years for case participants (range 6.9–9.5 years) and 7.4 years for control participants (range 7.0–11.1 years). Sixty-three percent of participants were male, 77% identified as white or non-Hispanic ethnicity, and 76% were of middle to upper SES (Hollingshead categories I–II) (Table 1). Mean maternal IQ was 109.7 (SD 12.7) in the control group and 106.2 (SD 13.7) in the case group. The proportion of single-parent families in the control and case groups was comparable (13% and 16%, respectively).

Parents of 31 case participants reported a history of craniosynostosis in immediate family members. Similar proportions of case and control participants were lost to follow-up (31% of case and 29% of control participants). Compared with participants seen at school age, participants lost to follow-up were more likely to be of lower SES (44% Hollingshead categories III–V vs 24% in participants), with slightly lower maternal IQ scores. Children lost to attrition also had lower Bayley Psychomotor Development Index scores at study baseline.

Case–Control Group Differences

Case participants' adjusted mean scores were lower than those of control participants on all measures (Table 2). The estimated average difference in standard scores comparing the case and control groups ranged from 0.3 to −4.2 (*P*s ranged from 0.002 to 0.80). The largest observed deficits were in WISC-IV Full-Scale IQ, WRAT-4 math computation, and CTOPP phonological awareness, where case participants' adjusted mean scores were 2.5 to 4 points lower than those of control participants (*P*s ranged from .002 to .09). Case–control differences on other measures of achievement were modest. The lower average IQ scores of the case group are also reflected in the distributions of scores relative to established clinical classifications (Table 3).

Differences between case and control participants were modestly shifted upward or downward after adjustment with propensity score matching, with a concomitant increase in the SEs of the estimates compared with direct adjustment. Case deficits increased by 0.6 to 1.8 points for WISC-IV Full-Scale IQ, WRAT-4 reading composite, TOWRE, and CTOPP phonological awareness (range in case–control differences −2.7 to −4.6 points). Case–control differences were unchanged or

TABLE 2 Comparison of Mean IQ and Achievement Scores for Children With and Without SSC

Neurodevelopmental Test	Control Group		Case Group		Case Versus Control Group			
					Unadjusted		Adjusted[a]	
	N	Mean (SD)	*N*	Mean (SD)	Difference (95% CI)	*P*	Difference (95% CI)	*P*
Full-Scale IQ	183	110.2 (15.3)	182	103.2 (16.0)	−7.0 (−10.2 to −3.8)	<.001	−3.9 (−6.7 to −1.2)	.006
Math computation	182	104.1 (14.6)	180	98.7 (13.4)	−5.5 (−8.4 to −2.6)	<.001	−4.2 (−6.8 to, −1.5)	.002
Reading composite	183	109.3 (17.2)	180	105.4 (16.5)	−4.0 (−7.4, −0.5)	.03	−2.0 (−5.2 to, 1.2)	.21
Spelling	182	107.2 (14.3)	180	105.2 (16.1)	−2.2 (−5.3 to 1.0)	.18	−0.9 (−3.8 to 2.0)	.54
Total word reading efficiency	179	106.6 (14.4)	180	104.0 (16.1)	−2.5 (−5.7 to 0.6)	.12	−0.9 (−3.9 to 2.1)	.57
Phonological awareness	179	111.1 (14.5)	179	107.1 (15.5)	−4.0 (−7.1 to −0.9)	.01	−2.5 (−5.4 to 0.4)	.09
Rapid naming	172	101.0 (10.9)	167	100.3 (12.2)	−0.8 (−3.3 to 1.7)	.53	0.3 (−2.1 to 2.7)	.80

[a] Adjusted for age (continuous), gender, SES (continuous), maternal IQ (continuous).

TABLE 3 Distribution of Full-Scale IQ Scores for Children With and Without SSC

Classification	Control Group		Case Group	
	N	%	*N*	%
Very superior (130+)	19	10.4	8	4.4
Superior (120–129)	33	18.2	14	7.7
High average (110–119)	46	25.3	44	24.2
Average (90–109)	66	36.3	81	44.5
Low average (80–89)	13	7.1	26	14.3
Borderline (70–79)	4	2.2	3	1.7
Extremely low (<69)	1	0.6	6	3.3
Total	182	100	182	100

decreased by ≤0.5 for the other tests (range in case–control differences 0.3 to −3.6 points). Case deficits after we excluded 19 children with known or probable causal mutations for craniosynostosis were attenuated by 0.1 to 0.8 points for all measures with 1 exception: CTOPP rapid naming, where the estimate shifted upward by 0.3 points (range in case–control differences −3.4 to 0.3 points). Estimates using IPW to gauge attrition bias were of similar magnitude to those from the adjusted analyses (data not shown).

Among those for whom we had intervention data, 82 case participants (46%) received ≥1 of the defined intervention services, as did 58 (35%) of control participants. In censored normal regression analyses, the differences between case and control participants became more pronounced for all measures (Table 4). Case deficits increased by 2.0 to 3.0 points for each test (*P*s ranged from <.001 to .24).

Seventy-three case participants (40%) and 54 (30%) control participants were classified as having learning problems. After adjustment for baseline demographics, there was little evidence that case participants were at higher odds of having learning problems than control participants (adjusted odds ratio [OR] = 1.4; 95% CI, 0.9 to 2.2). However, within each achievement test case participants were consistently more likely than control participants to meet the threshold for having a learning problem (Table 5). Case participants also met the criterion for having a learning problem on a greater number of tests than did control participants.

TABLE 4 Differences Between Children With and Without SSC Adjusted for Intervention Participation

Neurodevelopmental Test	Adjusted, With Censored Normal Regression[a,b]	
	Difference (95% CI)	*P*
Full-Scale IQ	−6.5 (−10.3 to −2.8)	<.001
Math computation	−6.8 (−10.4 to −3.1)	<.001
Reading composite	−5.0 (−9.3 to −0.6)	.03
Spelling	−2.5 (−6.4 to 1.5)	.23
Total word reading efficiency	−3.6 (−7.6 to 0.4)	.08
Phonological awareness	−5.2 (−9.1 to −1.3)	.010
Rapid naming	−1.9 (−5.0 to 1.3)	.24

[a] Adjusted for age (continuous), gender, SES (continuous), and maternal IQ (continuous).

[b] Among families reporting intervention data, 82/177 case participants (46%) and 58/167 control participants (35%) received ≥1 interventions.

Secondary Analyses by Diagnostic Subgroup

Within the case sample, children with metopic, unicoronal, or lambdoid synostosis scored lower on nearly all measures of achievement and IQ than did children with sagittal synostosis (Table 6). Adjusted mean differences in scores (Table 7) ranged from 1.0 to −3.2 points for children with metopic synostosis, from −1.6 to −11.7 for children with unicoronal synostosis, and from 1.4 to −14.8 for children with lambdoid synostosis (*P*s for overall group differences ranged from <.001 to .82). Children with metopic, unicoronal, and lambdoid synostosis were also more likely to have a learning problem than children with sagittal synostosis, although CIs were wide for OR estimates (metopic vs sagittal adjusted OR = 1.7; 95% CI, 0.7 to 3.8; unicoronal vs sagittal adjusted OR = 3.2; 95% CI,

TABLE 5 Distribution of Learning Problems for Children With and Without SSC by Test

Test[a]	Control Group		Case Group	
	Learning Problem	No Learning Problem	Learning Problem	No Learning Problem
	N (%)	*N* (%)	*N* (%)	*N* (%)
Math computation	28 (15.2)	156 (84.8)	36 (19.5)	149 (80.5)
Reading composite	27 (14.7)	157 (85.3)	41 (22.2)	144 (77.8)
Spelling	19 (10.3)	165 (89.7)	29 (15.7)	156 (84.3)
Total word reading efficiency	24 (13.0)	160 (87.0)	36 (19.5)	149 (80.5)
Phonological awareness	5 (2.7)	179 (97.3)	20 (10.8)	165 (89.2)
Rapid naming	9 (4.9)	175 (95.1)	29 (15.7)	156 (84.3)
Number of tests <25%[b]				
1	25 (46.3)	—[c]	28 (38.3)	—[c]
2	14 (25.9)	—	14 (19.2)	—
3	6 (11.1)	—	7 (9.6)	—
4	5 (9.3)	—	11 (15.1)	—
5	3 (5.6)	—	8 (11.0)	—
6	1 (1.8)	—	5 (6.8)	—
Total[a]	54 (30.9)	121 (69.1)	73 (42.2)	100 (57.8)

[a] Percentages by row.
[b] Percentages by column.
[c] Participants with no learning problem scored ≥25% on all tests.

1.2 to 8.1; lambdoid vs sagittal adjusted OR = 3.4; 95% CI, 0.7 to 17.2; *P* for overall group differences = .09).

DISCUSSION

This is the first large cohort study to track the development of children with SSC and unaffected control participants from infancy to school entry. Only case participants with isolated suture fusions, without the phenotypic features of known craniosynostosis syndromes, were included in this study. The focus on this population increases the utility of our study because it is based on phenotype rather than genotype, which may not be available or indicated in cases of nonsyndromic craniosynostosis.

As we observed previously at earlier age points,[11–13] school-age children with SSC on average scored lower on all measures than demographically similar children without SSC. The magnitude of adjusted group differences was modest for tests of spelling and reading achievement (<0.25 SD). However, case participants exhibited larger and educationally meaningful differences on measures of Full-Scale IQ and math achievement (~0.33 SD). Moreover, the effects of developmental interventions may have led to the underestimation of case deficits. Case participants had a higher frequency of intervention than control participants, and censored normal regression analyses suggested that in the absence of intervention, group differences favoring control participants might have been 2 to 3 points greater for each test given (eg, ~0.5 SD group difference in IQ and math).

TABLE 6 Distribution of Mean IQ and Achievement Scores for Children With SSC by Suture

Neurodevelopmental Test	Sagittal		Metopic		Unicoronal		Lambdoid	
	N	Mean (SD)	*N*	Mean (SD)	*N*	Mean (SD)	*N*	Mean (SD)
Full-Scale IQ	76	105.8 (14.7)	48	102.2 (17.8)	46	100.4 (16.3)	12	101.7 (14.3)
Math computation	75	101.1 (12.8)	48	98.7 (14.4)	45	95.7 (13.4)	12	94.5 (10.8)
Reading composite	75	109.4 (14.7)	48	105.8 (18.4)	45	100.1 (16.0)	12	98.3 (15.4)
Spelling	75	108.4 (13.4)	48	105.0 (17.7)	45	101.5 (17.9)	12	100.0 (15.5)
Total word reading efficiency	76	107.3 (13.8)	48	104.0 (17.3)	44	99.8 (17.0)	12	99.6 (19.2)
Phonological awareness	75	109.3 (14.0)	48	107.0 (17.8)	44	105.4 (14.7)	12	100.3 (15.9)
Rapid naming	71	100.2 (11.5)	45	101.1 (13.3)	41	99.5 (11.6)	10	100.0 (15.2)

The mean IQ scores for both case and control participants were in the average range relative to test norms. A higher-than-expected proportion of children scored above average, probably reflecting that both groups had high SES, a low rate of single-parent families (approximately half the US base rate[37]), and slightly above-average mean maternal IQs. However, even in this low social risk sample, the IQ frequency distributions exhibited important differences between case and control participants, with more than twice as many control participants as case participants scoring in the 2 highest categories of WISC-IV Full-Scale IQ. Conversely, twice as many case as control participants scored in the low average range, and there were 6 case participants (compared with a single control participant) scoring in the extremely low or intellectually disabled category. Although these differences are based on small numbers in some categories, previous studies of younger children with SSC have also indicated low rates of accelerated cognitive development[15,38] and higher-than-expected rates of intellectual disability.[39]

In the few previously published studies of older children with SSC, participants exhibited elevated rates of variably defined problems in academic and related skills (~30% to 50%),[16–20] leading several investigators to conclude that a large proportion of children with SSC have learning disabilities.[9,40,41] Consistent with these previous estimates, 42% of case participants in the current study scored below the 25th percentile on ≥1 academic achievement tests, a commonly used criterion in screening for learning problems.[35,36] However, nearly one-third of the control group also met this criterion, and after adjustment for demographic

TABLE 7 Comparison of Mean IQ and Achievement Scores for Children With SSC by Suture

Neurodevelopmental Test	Comparison and Mean Difference						
	Metopic Versus Sagittal		Unicoronal Versus Sagittal		Lambdoid Versus Sagittal		*P* for Differences Across All Groups
	Difference (95% CI)[a]	*P*	Difference (95% CI)[a]	*P*	Difference (95% CI)[a]	*P*	
Full-Scale IQ	−3.2 (−7.9 to 1.6)	.19	−7.3 (−12.7 to −1.9)	.009	−4.7 (−14.4 to 5.0)	.34	.05
Math computation	−1.8 (−6.3 to 2.7)	.44	−6.9 (−11.7 to −2.1)	.006	−6.6 (−15.1 to 1.9)	.13	.04
Reading composite	−3.0 (−8.4 to 2.4)	.27	−11.7 (−16.8 to, −6.7)	<.001	−14.8 (−25.8 to −3.7)	.009	<.001
Spelling	−2.9 (−7.9 to 2.2)	.26	−10.1 (−15.4 to −4.8)	<.001	−10.8 (−22.2 to 0.6)	.06	.002
Total word reading efficiency	−2.7 (−7.9 to 2.4)	.30	−10.0 (−15.2 to −4.7)	<.001	−10.5 (−23.1 to 2.0)	.10	.002
Phonological awareness	−1.5 (−7.0 to 4.0)	.59	−4.7 (−9.9 to 0.6)	.08	−11.6 (−21.2 to −1.9)	.02	.07
Rapid naming	1.0 (−3.5 to 5.5)	.65	−1.5 (−6.2 to 3.1)	.51	1.4 (−10.2 to 12.9)	.82	.82

[a] Adjusted for age (continuous), gender, SES (continuous), and maternal IQ (continuous).

characteristics, case participants were only slightly more likely to exhibit learning problems than control participants. The earlier studies cited, most without control groups, may have overestimated the risk of learning disabilities in the SSC population in relation to unaffected children.

Another long-standing question is whether neurocognitive outcomes in children with SSC are specific to the affected suture. In secondary analyses we observed that children with metopic, unicoronal, or lambdoid synostosis scored lower on nearly all measures of achievement and IQ than did children with the most common form of SSC, sagittal synostosis. Group differences were small between sagittal and metopic case participants (<0.25 SD for all measures). However, case participants with unicoronal and lambdoid synostosis exhibited much larger deficits (eg, 0.5 SD difference in IQ between participants with sagittal and unicoronal synostosis; 0.67 SD difference in academic achievement scores between participants with sagittal and lambdoid synostosis). Differences of this magnitude are clinically significant, suggesting that children with unicoronal and lambdoid synostosis are more likely than other children with SSC to need educational intervention. Although conclusions here are limited by small subgroups and wide CIs, the patterns have persisted at every postsurgery age at which we assessed this cohort and are similar across outcome measures.[12]

Limitations in this research include a sample of case and control participants with higher than average SES, repeated child testing with parent feedback that may have elevated referrals for intervention beyond expected levels in the community, and sample attrition approaching 30%. However, the demographic variables for which we controlled in all regression analyses at least partially mitigated the effect of SES on group comparisons of outcome measures. Moreover, IPW analyses, in which we used baseline data available for case and control participants to evaluate attrition bias, did not greatly alter regression estimates or their interpretation.

It is important to note that the design of this study does not allow analysis of the proposed mechanisms by which SSC or factors associated with SSC (eg, surgery and anesthesia exposure[42]) might lead to the group differences we observed. Possible causal pathways continue to be poorly understood and await additional study.[9,41,43]

CONCLUSIONS

The developmental delays observed among infants and young children with SSC are still partially evident at school age, as manifested by lower average scores than those of control participants on measures of IQ and math and a downward shift in IQ score distribution.[15] However, average scores of the case group were only slightly lower than those of the control group on reading and spelling measures, and the frequency of specific learning problems was comparable. Most children with SSC did well academically, and 58% had no discernible learning problem; however, we would anticipate lower levels of achievement in higher social risk samples. Among case participants, those with unicoronal and lambdoid synostosis appear to be the most neurodevelopmentally vulnerable.

Multidisciplinary care guidelines have called for neurodevelopmental screening in the preschool years for all children with craniosynostosis.[44] Our findings suggest that for patients with single-suture fusions, primary attention should be given to those with unicoronal and lambdoid synostosis, with more selective screening of children with isolated metopic and sagittal fusions.

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REFERENCES

1. French LR, Jackson IT, Melton LJ III. A population-based study of craniosynostosis. *J Clin Epidemiol*. 1990; 43(1):69–73
2. Shuper A, Merlob P, Grunebaum M, Reisner SH. The incidence of isolated craniosynostosis in the newborn infant. *Am J Dis Child*. 1985;139(1):85–86
3. Aldridge K, Marsh JL, Govier D, Richtsmeier JT. Central nervous system phenotypes in craniosynostosis. *J Anat*. 2002;201(1):31–39
4. Aldridge K, Kane AA, Marsh JL, et al. Brain morphology in nonsyndromic unicoronal craniosynostosis. *Anat Rec A Discov Mol Cell Evol Biol*. 2005;285(2): 690–698
5. Aldridge K, Kane AA, Marsh JL, Yan P, Govier D, Richtsmeier JT. Relationship of brain and skull in pre- and postoperative sagittal synostosis. *J Anat*. 2005;206(4): 373–385
6. Fok H, Jones BM, Gault DG, Andar U, Hayward R. Relationship between intracranial pressure and intracranial volume in craniosynostosis. *Br J Plast Surg*. 1992;45(5):394–397
7. Renier D, Sainte-Rose C, Marchac D, Hirsch JF. Intracranial pressure in craniostenosis. *J Neurosurg*. 1982;57(3): 370–377
8. Lekovic GP, Bristol RE, Rekate HL. Cognitive impact of craniosynostosis. *Semin Pediatr Neurol*. 2004;11(4): 305–310
9. Kapp-Simon KA, Speltz ML, Cunningham ML, Patel PK, Tomita T. Neurodevelopment of children with single suture craniosynostosis: a review. *Childs Nerv Syst*. 2007;23(3):269–281
10. Cohen SR, Cho DC, Nichols SL, Simms C, Cross KP, Burstein FD. American Society of Maxillofacial Surgeons outcome study: preoperative and postoperative neurodevelopmental findings in single-suture craniosynostosis. *Plast Reconstr Surg*. 2004;114(4):841–847, discussion 848–849
11. Starr JR, Kapp-Simon KA, Cloonan YK, et al Presurgical and postsurgical assessment of the neurodevelopment of infants with single-suture craniosynostosis: comparison with controls. *J Neurosurg*. 2007;107(suppl 2): 103–110
12. Starr JR, Collett BR, Gaither R, et al. Multicenter study of neurodevelopment in 3-year-old children with and without single-suture craniosynostosis. *Arch Pediatr Adolesc Med*. 2012;166(6): 536–542
13. Speltz ML, Kapp-Simon K, Collett B, et al. Neurodevelopment of infants with single-suture craniosynostosis: presurgery comparisons with case-matched controls. *Plast Reconstr Surg*. 2007; 119(6):1874–1881
14. Da Costa AC, Anderson VA, Savarirayan R, et al. Neurodevelopmental functioning of infants with untreated single-suture craniosynostosis during early infancy. *Childs Nerv Syst*. 2012;28(6):869–877
15. Knight SJ, Anderson VA, Spencer-Smith MM, Da Costa AC. Neurodevelopmental outcomes in infants and children with single-suture craniosynostosis: a systematic review. *Dev Neuropsychol*. 2014;39(3):159–186
16. Chieffo D, Tamburrini G, Massimi L, et al. Long-term neuropsychological development in single-suture craniosynostosis treated early. *J Neurosurg Pediatr*. 2010;5(3):232–237
17. Magge SN, Westerveld M, Pruzinsky T, Persing JA. Long-term neuropsychological effects of sagittal craniosynostosis on child development. *J Craniofac Surg*. 2002;13(1):99–104
18. Virtanen R, Korhonen T, Fagerholm J, Viljanto J. Neurocognitive sequelae of scaphocephaly. *Pediatrics*. 1999;103(4): 791–795
19. Kelleher MO, Murray DJ, McGillivary A, Kamel MH, Allcutt D, Earley MJ. Behavioral, developmental, and educational problems in children with nonsyndromic trigonocephaly. *J Neurosurg*. 2006;105(5 suppl):382–384
20. Becker DB, Petersen JD, Kane AA, Cradock MM, Pilgram TK, Marsh JL. Speech, cognitive, and behavioral outcomes in nonsyndromic craniosynostosis. *Plast Reconstr Surg*. 2005;116(2):400–407
21. Cunningham ML, Horst JA, Rieder MJ, et al. IGF1R variants associated with isolated single suture craniosynostosis. *Am J Med Genet A*. 2011;155A(1):91–97
22. Hollingshead AB. *Four Factor Index of Social Status*. New Haven, CT: Yale University; 1975
23. Sattler J, Dumont R. *Assessment of Children: WISC-IV and WPPSI-III Supplement*. San Diego, CA: Jerome M. Sattler; 2004
24. Wilkinson G. *Wide Range Achievement Test*. 4th ed. Odessa, FL: Psychological Assessment Resources, Inc; 1999
25. Torgenson JK, Wagner RK, Rashotte C. *Test of Word Reading Efficiency*. Austin, TX: Pro-Ed; 1999
26. Wagner RK, Torgesen JK, Rashotte CA. *Comprehensive Test of Phonological Processing (CTOPP)*. Austin, TX: PRO-ED; 1999
27. Wagner RK, Torgesen JK. The nature of phonological processing and its causal role in the acquisition of reading skills. *Psychol Bull*. 1987;101(2):192–212
28. Katzir T, Kim YS, Wolf M, Morris R, Lovett MW. The varieties of pathways to dysfluent reading: comparing subtypes of children with dyslexia at letter, word, and connected text levels of

reading. *J Learn Disabil*. 2008;41(1):47–66

29. Cronin VS. RAN and double-deficit theory. *J Learn Disabil*. 2013;46(2):182–190
30. Matthews TD, Lassiter KS. What does the Wonderlic Personnel Test measure? *Psychol Rep*. 2007;100(3 pt 1):707–712
31. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70(1):41–55
32. Abadie A, Drukker D, Herr JL, Imbens GW. Implementing matching estimators for average treatment effects in Stata. *Stata J*. 2004;4(3):290–311
33. Robins JM, Rotnitzky A, Zhao LP. Estimation of regression coefficients when some regressors are not always observed. *J Am Stat Assoc*. 1994;89(427):846–866
34. Tobin MD, Sheehan NA, Scurrah KJ, Burton PR. Adjusting for treatment effects in studies of quantitative traits: antihypertensive therapy and systolic blood pressure. *Stat Med*. 2005;24(19):2911–2935
35. Fletcher JM, Francis DJ, Morris RD, Lyon GR. Evidence-based assessment of learning disabilities in children and adolescents. *J Clin Child Adolesc Psychol*. 2005;34(3):506–522
36. Lyon GR, Fletcher JM, Barnes MC. Learning disabilities. In: Mash EJ, Barkely RA, eds. *Child Psychopathology*. 2nd ed. New York, NY: Guilford Press; 2003:520–586
37. US Department of Health and Human Services, Administration for Children and Families, Office of Planning, Research, and Evaluation. Temporary Assistance for Needy Families. Sixth annual report to Congress. Chapter VII. Formation and maintenance of married two-parent families. 2004. Available at: http://archive.acf.hhs.gov/programs/ofa/data-reports/annualreport6/chapter07/chap07.htm. Accessed November 3, 2009
38. Da Costa AC, Anderson VA, Holmes AD, et al. Longitudinal study of the neurodevelopmental characteristics of treated and untreated nonsyndromic craniosynostosis in infancy. *Childs Nerv Syst*. 2013;29(6):985–995
39. Kapp-Simon KA. Mental development and learning disorders in children with single suture craniosynostosis. *Cleft Palate Craniofac J*. 1998;35(3):197–203
40. van der Meulen J, van der Vlugt J, Okkerse J, Hofman B. Early beaten-copper pattern: its long-term effect on intelligence quotients in 95 children with craniosynostosis. *J Neurosurg Pediatr*. 2008;1(1):25–30
41. Speltz ML, Kapp-Simon KA, Cunningham M, Marsh J, Dawson G. Single-suture craniosynostosis: a review of neurobehavioral research and theory. *J Pediatr Psychol*. 2004;29(8):651–668
42. Naumann HL, Haberkern CM, Pietila KE, et al. Duration of exposure to cranial vault surgery: associations with neurodevelopment among children with single-suture craniosynostosis. *Paediatr Anaesth*. 2012;22:1053–1061
43. Speltz ML, Birgfeld CB, Starr JR, Collett BR, Kapp-Simon KA. Comments about Hashim et al. (2014) "The effects of whole vault cranioplasty versus strip craniectomy on long-term neuropsychological outcomes in sagittal craniosynostosis." *Plast Reconstr Surg*. (in press)
44. McCarthy JG, Warren SM, Bernstein J, et al Parameters of care for craniosynostosis. *Cleft Palate Craniofac J*. 2012;49(suppl):1s–24s

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