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Birth Weight and Neurocognition in Schizophrenia Spectrum Disorders

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Low birth weight is associated with both schizophrenia and neurocognitive impairment. Yet, to our knowledge, no previous study has examined the relationship between lower birth weight and neurocognitive deficits in schizophrenia spectrum disorders (SSD). In this preliminary study, we investigated the relationship using a broad neuropsychological battery in cases with SSD and matched control subjects. The sample consisted of all subjects in the Developmental Insult and Brain Anomaly in Schizophrenia study, a nested case-control investigation developed from a large birth cohort, which followed subjects longitudinally. Case ascertainment was based on computerized record linkages between the birth cohort members and the Kaiser Permanente Medical Care Plan, and all diagnoses were confirmed by consensus diagnosis following the Diagnostic Interview for Genetic Studies. Lower birth weight was associated with impairment in executive function, working memory, generalized intellectual function, and neuromotor function in cases with SSD but not in control subjects. No deficits were observed in verbal memory for either group. These results support the hypothesis that lower birth weight plays a role in neuropsychological disruptions in SSD and that the antecedents of lower birth weight may have a greater impact on these disruptions in SSD than in controls. These data may facilitate a better understanding of the etiopathogenesis of the cognitive underpinnings of SSD.

Key words: executive functioning/working memory/epidemiology/risk factors/obstetric complications

Introduction

Low birth weight (LBW) is a widely replicated risk factor for schizophrenia. In a meta-analysis of population-based prospective studies by Cannon et al,[1] birth weight below 2500 g, and 2000 g, was related to 1.7-fold and 4-fold increases, respectively, in the risk of schizophrenia. Jones et al,[2] in a follow-up of the Northern Finland birth cohort, found a greater than 2-fold increased risk of schizophrenia for subjects with birth weight below 2500 g. In the largest such study to date, in which Abel et al[3] combined Danish and Swedish national population–based cohorts, a dose-response relationship between birth weight and schizophrenia spectrum disorders (SSD) was reported. Other studies, however, have been less conclusive,[2,4,5] with some effects either becoming attenuated or disappearing following control for potential confounders.[6]

Neurocognitive deficits represent a core phenotype of SSD, with multiple areas of impairment observed in the prodrome, at first episode, and chronically.[7–11] These deficits generally do not improve with existing treatments and lead to substantial disability. In numerous studies of nonschizophrenia samples, associations between LBW and neurocognitive deficits have been consistently reported in children and adolescents.[12–15] Functional areas of impairment have included motor, visual-motor, language, academic, and executive performance.[14] LBW was also shown to be related to IQ in a dose-dependent fashion.[12]

Seidman et al,[16] in the New England cohorts of the National Collaborative Perinatal Project, specifically sought to address potential etiologic mechanisms by comparing birth weight, hypoxia-ischemic complications, and chronic hypoxia as risks for neurocognitive deficits in a population-based study. After controlling for sociodemographic confounders, the authors found that LBW was associated with lower cognitive performance (academic-achievement, verbal-conceptual, and perceptual-motor skill functions) at age 7; the LBW effect was stronger than hypoxia-ischemic complications or chronic hypoxia, with little co-occurrence, suggesting that neurocognitive impairment is relatively specific to LBW among these factors.[16]

In summary, LBW has been associated with both SSD and neurocognitive deficits. Yet, to our knowledge, no

previous study has examined the relationship between LBW and neurocognitive deficits in SSD. Such work may shed light on the mechanisms by which LBW is related to SSD and begins to elucidate the underpinnings of neurocognitive deficits in SSD. Hence, the aim of the present study was to examine the relationship between birth weight and neurocognition in SSD and in matched controls in a well-defined population-based birth cohort. We hypothesized that lower birth weight would be related to neurocognitive deficits in SSD cases and that this association would be attenuated in controls.

Methods

Subjects

The sample consisted of all subjects in the Developmental Insult and Brain Anomaly in Schizophrenia (DIBS) study, one of the aims of which was to examine the relationship between early developmental risk factors and neurocognition in SSD cases and controls using a comprehensive neuropsychological protocol.[17] The methods of the DIBS study, including a flow diagram of the ascertainment, recruitment, and selection of subjects, have been extensively described in a previous publication.[17–19] Subjects were derived from a follow-up study of SSD among offspring of mothers who were enrolled in the Child Health and Development Study (CHDS), a large birth cohort, from 1959–1966.[18,20] Nearly, every pregnant woman received obstetric care from the Kaiser Permanente Medical Care Plan (KPMCP) in Alameda County, California.

Ascertainment and Diagnosis of Cases

SSD was defined as schizophrenia, schizoaffective disorder, delusional disorder, psychotic disorder not otherwise specified, and schizotypal personality disorder, in accord with previous studies.[21] Case ascertainment was based on computerized record linkage between the CHDS and KPMCP identifiers from inpatient, outpatient, and pharmacy databases, and all diagnoses of SSD were confirmed by consensus diagnosis of 3 research psychiatrists following assessment with the Diagnostic Interview for Genetic Studies[22] by clinicians with a minimum of a master's degree in a mental health field who were trained to reliability. Diagnostic chart reviews were conducted for potential cases who were not interviewed, and all diagnoses were confirmed by a research psychiatrist (A.S.B.). These procedures resulted in 71 total SSD cases.

Ascertainment of the DIBS Study Sample

The DIBS study is a nested case-control study based on the larger schizophrenia follow-up of the CHDS cohort described above. All subjects who met eligibility criteria were targeted for neuropsychological assessments. Exclusion criteria have been detailed previously.[17]

Twenty-six SSD case subjects (13 with schizophrenia, 7 with schizoaffective disorder, and 6 with other SSD) and 25 control subjects matched to cases in a 1:1 ratio on Kaiser Permanente membership at the time of case ascertainment, date of birth (±28 days), and availability of maternal serum were enrolled and assessed using a comprehensive neuropsychological battery (see next section). Cases and controls in the DIBS were similar to subjects in the overall sample with regard to maternal age, race, education, and parity.[17]

All subjects provided written informed consent. The study protocol was approved by the Institutional Review Boards of the New York State Psychiatric Institute, the Kaiser Foundation Research Institute, the University of California, San Francisco, and the San Francisco Department of Veterans Affairs Medical Center.

Neuropsychological Assessment

The comprehensive neuropsychological assessment was designed to obtain global neurocognitive functioning data as well as functional domains thought to be most important in SSD.[17,23] The battery included a number of tests in each functional area: executive function (Wisconsin Card Sorting Test, Trail Making Test Part B, Ruff Figural Fluency Test, and Verbal Fluency); motor function (Grooved Peg Board and Finger Tapping); working memory (Digit Span Forward, Digit Span Backward, Letter-Number Sequencing [LNS], and Auditory N-Back Test); IQ (Wechsler Adult Intelligence Scale III [WAIS] subtests: Information, Digit Symbol, and Picture Completion); and verbal episodic memory (California Verbal Learning Test [CVLT]). The battery was administered over 2 days by graduate students (master's level or higher) in a mental health–related field and supervised by 2 senior research neuropsychologists.

We also constructed composite scores for executive functioning, working memory, and verbal memory (see "Statistical Analysis" section). We utilized composite scores for these 3 domains to provide overall indicators of functioning among the major domains and to minimize the potential for spurious findings from multiple comparisons.

At the time of neuropsychological testing, case subjects were an average of 39.4 years of age (SD = 1.8), and control subjects were 40.4 years (SD = 1.8).

Birth Weight

Birth weight was measured at the time of delivery by Kaiser medical staff, documented in the newborn's medical record, and extracted into the CHDS database.[24]

Statistical Analysis

We conducted stratified within group analyses of the relationship between birth weight, case status, and neurocognitive outcomes. Generalized linear models (GLM)

were utilized for all analyses because these are a flexible parametric class of models appropriate for small data sets in which the conditional distribution of the response given the predictor is determined, making use of the structure of the outcome variable. Each neuropsychological test has a specific outcome structure that helps suggest the particular GLM model; the canonical link function is used in each case, as described in a previous publication on neuropsychological outcomes in the DIBS.[17] Data from the Wisconsin Card Sorting Test, which consists of a series of trials with binary correct/incorrect responses, was analyzed using binomial regression, as were Digit Span and LNS. For the Trail Making Test (hereinafter Trails A and Trails B) and Grooved Peg Board, gamma distributions are a natural choice because the outcomes (time) are nonnegative. For the Verbal Fluency and the Ruff Figural Fluency tests, in which the outcome is the number of correct responses and which have no predetermined upper bound, Poisson models were applied. Gaussian models were applied to the CVLT, Auditory *N*-Back Test, and WAIS subtests. In order to obtain composite scores for each functional area, sums of standard scores for the tests of each domain were constructed and Gaussian modeling was used.

Birth weight was defined as a continuous variable. The use of a continuous measure of birth weight was predicated on 3 reasons. First, previous studies indicate that neurocognitive performance generally increases in a linear fashion across the continuum of increasing birth weights.[3,12] Second, the sample had very few newborns below the traditional 2500 g threshold for LBW ($n = 4$ subjects, 2 cases, and 2 controls). Mean birth weight for cases was 3420 g (SD = 602) and for controls was 3209 g (SD = 545). Third, use of a continuous variable maximizes statistical power. Therefore, we refer to the primary exposure as "lower birth weight."

Potential Confounders

Maternal age, maternal race, maternal education (a marker of socioeconomic status), maternal smoking, off-spring sex, and use of medication at the time of neuropsychological testing were considered as potential confounders. Variables were considered a priori as potential confounders based on associations with birth weight and with neurocognition at a statistical significance threshold of $P < .1$. We found no association between birth weight and any of these covariates, and they were therefore not included in the statistical models to avoid inducing bias.[25,26]

In order to better approximate small for gestational age status, gestational age was controlled for in all neuropsychological outcome analyses (table 1).

Results

Table 2 presents a comparison of mean scores on each neuropsychological test for all subjects. Case subjects performed significantly worse on every test administered except for the CVLT total learning slope and the 0-Back component of the N-Back; on these 2 measures, diminished performance did not reach statistical significance.

Birth Weight and Neurocognition in Case Subjects

Lower birth weight was positively associated with impairment on several neurocognitive outcomes among those with SSD (table 3). The findings were most clearly observed on executive function performance, with significant deficits on the composite measure of executive functioning, all 3 components of the Wisconsin Card Sorting Test (total errors, perseverative errors, and nonperseverative errors), Trails B, and the Ruff Figural Fluency Test.

With regard to working memory, lower birth weight was associated with significant impairment on the LNS test. Birth weight was not significantly related to the other working memory measures (composite score, Auditory 2-Back, or Digit Span Backward). For general intellectual function, lower birth weight was significantly associated with decreased full-scale IQ. Additionally, lower birth weight was related to diminished performance on the Finger Tapping Test (total taps). Verbal memory and verbal fluency were not associated with birth weight.

Birth Weight and Neurocognition in Control Subjects

Birth weight was not significantly associated with neurocognitive performance among the controls. Statistical trends were observed between lower birth weight and worse performance on the information ($P = .06$) and Digit Span Backward ($P = .10$) subtests of the WAIS, and the long delay free recall condition of the CVLT ($P = .08$) (table 4).

Discussion

Lower birth weight was consistently associated with impairment in executive function, working memory, general intellectual function, and neuromotor performance for case subjects but not for control subjects. To our knowledge, this is the first time that birth weight has been examined in relation to neurocognition in a sample of adult patients with SSD and controls. Given that most of the cases were well within the "normal" weight range, with few births below the traditional 2500 g threshold, our findings extend those of Abel et al,[3] who demonstrated that decreasing birth weight acts incrementally to increase SSD risk.

Performance on executive functioning was impaired on a number of tests in this domain. The findings suggest that lower birth weight is related to impairment in cognitive switching (set shifting) and abstract reasoning, as indicated by performance on the Trails B and the Wisconsin Card Sorting Test; and perseveration, as indicated

Table 1. Characteristics of Case and Control Subjects and Birth Weight in Ounces

	Case Subjects (N = 26)			Comparison Subjects (N = 25)		
		Birth Weight			Birth Weight	
	Number (%)	Mean (SD)	P value	Number (%)	Mean (SD)	P value
Maternal age			.131			.170
≤29	12 (46)	127.5 (19.5)		13 (52)	108.1 (16.2)	
>29	14 (54)	114.8 (21.6)		12 (48)	118.8 (21.4)	
Maternal race			.655			.456
White	14 (54)	123.2 (15.8)		14 (56)	117.4 (19.6)	
Black	10 (38)	115.8 (28.5)		8 (32)	106.6 (19.0)	
Other	2 (8)	127.0 (18.4)		3 (12)	111.0 (19.0)	
Maternal education			.948			.440
≤High school grad/trade school	16 (67)	119.9 (19.3)		14 (56)	110.5 (18.1)	
Some college/college grad/RN	8 (33)	119.4 (21.0)		11 (44)	116.6 (20.9)	
Maternal smoking			.853			.152
Exposed[a]	11	119.7 (20.0)		10	105.7 (16.4)	
Unexposed	10	121.4 (20.9)		14	117.2 (20.2)	
Offspring sex			.966			.206
Male	18 (69)	120.8 (23.5)		17 (68)	116.6 (18.4)	
Female	8 (31)	120.4 (16.6)		8 (32)	106.0 (20.2)	
Antipsychotic use among cases[b]			.29			
Used	8 (31)	127.4 (13.9)				
Never used	18 (69)	117.7 (23.5)				
Stimulant and anticholinergic use among cases[c]			.24			
Used	3 (12)	122.4 (19.8)				
Never used	23 (88)	107.0 (32.2)				

[a]Exposure to maternal smoking is defined as smoking at the time of pregnancy or until the pregnancy; no exposure to maternal smoking is defined as never smoking or not currently smoking.
[b]Antipsychotic medications case subjects reported using at the time of testing: Clozaril, Haldol, Navane, Risperdal, Seroquel, Stelazine, Thorazine, Trilafon, and Zyprexa.
[c]Stimulant and anticholinergic medications case subjects reported using at the time of testing: benztropine and methylphenidate.

by performance on the Ruff Figural Fluency Test and the Wisconsin Card Sorting Test. Nonverbal fluency also appeared to be associated with lower birth weight.

Interestingly, lower birth weight cases also evidenced a statistical trend for diminished performance on the WAIS picture completion subtest (P = .06). Together with the results on the Ruff Figural Fluency Test, these findings may indicate broad visuospatial deficits. Visuospatial impairment has been observed in offspring with very LBW in previous studies.[27–29] Moreover, no relationship was found between lower birth weight and verbal fluency in cases, supporting possible specificity to figural fluency. It is also possible that diminished performance on the Ruff Figural Fluency Test may be explained by the fact that self-generation of novel designs, which this instrument assesses, requires abstraction and greater strategic resources as compared with word generation, which is measured by verbal fluency tests. Consistent with this notion, picture completion also requires some level of abstract reasoning to properly sequence the pictures.

The working memory results varied by functional ability area as well. Within the case group, lower birth weight was significantly related to worse performance on LNS. While similar to Digit Span Backward, LNS assesses visuospatial working memory, which Digit Span does not.[30,31] The 2-Back component of the N-Back, which was also not associated with lower birth weight, is believed to be more specific to working memory updating. In light of the differences captured by these working memory tests and the observed pattern of findings, lower birth weight may therefore be related to impaired visuospatial working memory. Direct tests of visuospatial working memory would, of course, be needed to confirm this assertion.

Similarly, the relationship between lower birth weight and neuromotor performance differed between the 2 measures assessed, with a significant relationship for

Table 2. Comparison of Neuropsychological Performance Between Cases and Controls[a] ($N = 51$)

	Case ($n = 26$)		Control ($n = 25$)		
	Mean	SD	Mean	SD	*P* Value from GLM
Executive function					
Composite score	−3.00	5.07	2.96	2.75	**<.0001**
Wisconsin Card Sort Test					
Total errors	14.96	11.62	6.42	5.72	**<.0001**
Perseverative errors	5.62	6.78	1.67	2.46	**<.0001**
Nonperseverative errors	9.34	6.88	4.75	3.70	**<.0001**
Trail Making Test					
Trails A time	41.73	17.46	22.63	5.39	**<.0001**
Trails B time	104.39	50.79	52.92	12.36	**<.0001**
Trails B regressed on Trails A	1.10	29.62	−8.27	10.64	**.0401**
Verbal Fluency Test					
Letter fluency (total correct)	12.23	3.67	14.46	2.96	**.0431**
Category fluency (total correct)	18.20	5.23	22.42	5.50	**.0006**
Ruff Figural Fluency Test					
Ruff Figural Fluency (total correct)	61.88	24.09	89.25	28.65	**<.0001**
Working memory					
Composite score	−1.03	2.28	1.07	2.03	**.002**
WAIS Digit Span					
Forward last correct	5.08	1.38	5.92	1.02	**.0263**
Backward last correct	3.31	1.29	4.04	1.33	**.0322**
Letter-Number Sequencing (LNS)					
LNS scaled score	7.69	2.90	10.21	3.02	**.0003**
Auditory *N*-Back					
0-Back *d*-prime	0.92	0.13	0.94	0.05	.8667
2-Back *d*-prime	0.62	0.28	0.81	0.14	**.0145**
Neuromotor function					
Grooved Peg Board dominant hand time	98.27	44.63	70.04	9.48	**.0007**
Finger Tap total taps for trials 1–3	85.15	32.40	116.43	22.85	**<.0001**
WAIS					
Full-scale IQ Estimate	93.42	14.43	107.75	13.91	**<.0001**
WAIS info total scaled score	15.67	5.46	18.96	5.42	**.0258**
WAIS picture completion total scaled score	16.81	4.53	20.67	4.37	**.0026**
Verbal memory					
Composite score	−1.35	2.88	0.36	1.64	.0569
CVLT[b] trial 5	−1.21	1.31	−0.09	0.90	**.0039**
CVLT total learning slope trials 1–5	−0.13	1.66	0.44	0.92	.3690

Note: Bolded values are statistically significant at the $P = .05$ level; GLM, generalized linear models; CVLT, California Verbal Learning Test; WAIS III, Wechsler Adult Intelligence Scale III.
[a]All adjusted for gestational age.
[b]All CVLT scores are standard scores.

Finger Tapping but a nonsignificant relationship for the Grooved Peg Board Test. Slower Finger Tapping, a measure of self-directed manual motor speed captures a different functional ability than manual precision, as measured by the Grooved Peg Board Test.[32]

The finding of no association between birth weight and Verbal Fluency, combined with the results of the CVLT, suggest that birth weight may spare verbal ability. This may also help explain the nonsignificant result on the WAIS information subtest, which tends to draw on verbal skills.

Lower birth weight can result from a host of risks, including maternal infection, genetic factors, congenital anomalies, inadequate nutrition, environmental toxins, and placental factors.[33] Hence, each, or some combination, of these risk factors may account for the observed findings. While the present sample is not sufficiently powered to test for relationships between these antecedents and neurocognitive dysfunction, we believe that this can be accomplished in future research studies with larger sample sizes.

It is worth emphasizing that, with the exception of a few scattered statistical trends, there were no relationships

Table 3. Birth Weight and Neuropsychological Performance in Case Subjects[a]

Domain/Measure	Parameter Estimate	Parameter 95% CI	*P* Value from GLM
Executive function			
Composite score	0.096 [b]	0.016 to 0.177	**.019**
Wisconsin Card Sort Test			
Total errors	−0.022 [b]	−0.028 to −0.015	**<.001**
Perseverative errors	−0.016 [b]	−0.025 to −0.007	**<.001**
Nonperseverative errors	−0.027 [b]	−0.036 to −0.018	**<.001**
Trail Making Test			
Trails A time	0.0000	−0.0002 to 0.0002	.778
Trails B time	0.0001 [b]	0.0000 to 0.0002	**<.001**
Trails B regressed on Trails A	−0.628 [b]	−1.272 to 0.017	0.056
Verbal Fluency Test			
Letter fluency (total correct)	0.001	−0.004 to 0.007	.672
Category fluency (total correct)	0.0005	−0.004 to 0.005	.811
Ruff Figural Fluency Test			
Ruff Figural Fluency (total correct)	0.005 [b]	0.002 to 0.007	**<.001**
Working memory			
Composite score	0.030[b]	−0.012 to 0.072	.168
WAIS Digit Span			
Forward last correct	0.012[b]	−0.002 to 0.026	.091
Backward last correct	0.009	−0.006 to 0.023	.249
Letter-Number Sequencing (LNS)			
LNS scaled score	0.011[b]	0.002 to 0.020	**.012**
Auditory *N*-Back			
0-Back *d*-prime	−0.002	−0.004 to −0.000	**.037**
2-Back *d*-prime	−0.001	−0.007 to 0.004	.640
Neuromotor function			
Grooved Peg Board dominant hand time	0.00003	−0.00004 to 0.00009	.408
Finger Tap total taps for trials 1–3	0.003[b]	0.001 to 0.006	**<.001**
WAIS			
Full-scale IQ estimate	0.327[b]	0.093 to 0.560	**.006**
WAIS info total scaled score	0.083	−0.024 to 0.191	.128
WAIS picture completion total scaled score	0.083[b]	−0.003 to 0.169	.060
Verbal memory			
Composite score	−0.017	−0.067 to 0.034	.526
CVLT[c] trial 5	−0.008	−0.031 to 0.016	.511
CVLT total learning slope trials 1–5	−0.009	−0.038 to 0.021	.565

Note: Bolded values are statistically significant at the $P = .05$ level; GLM, generalized linear models; CVLT, California Verbal Learning Test; WAIS III, Wechsler Adult Intelligence Scale III.
[a]All adjusted for gestational age.
[b]Parameter indicates worse performance for lower birth weight.
[c]All CVLT scores are standard scores.

between lower birth weight and neurocognition among controls. This lack of association suggests that SSD cases may be more vulnerable than controls to the neurodevelopmental effects on neurocognitive functioning associated with lower birth weight or its antecedent exposures. We therefore postulate that the predisposition for neurocognitive deficits likely requires additional environmental risk factors or genetic mutations that are related to SSD vulnerability and which interact with the determinants of lower birth weight. Given the exploratory nature of the study, however, further research on these questions is warranted.

Longitudinal studies of LBW and neurocognition in nonpsychiatric populations suggest that as LBW children age, their neurocognitive performance often catches up to within a normal range of scores compared with their peers. This process is often referred to as "normalization." For example, the Port Pirie birth cohort utilized age appropriate IQ assessments at aged 2, 4, 7, and 11–13 years old, concluding that differences in cognition became progressively attenuated as the cohort aged until there were no differences at ages 11–13.[13] It is possible that the observed findings in those who develop SSD reflect a premorbid neurocognitive process that interferes with the neural plasticity that could explain normalization. Our subjects were tested at age 40, meaning that any normalization of performance, which might have

Table 4. Birth Weight and Neuropsychological Performance in Control Subjects[a]

Domain/Measure	Parameter Estimate	Parameter 95% CI	*P* Value from GLM
Executive function			
Composite score	0.007	−0.059 to 0.074	.828
Wisconsin Card Sort Test			
Total errors	−0.005	−0.016 to 0.005	.331
Perseverative errors	0.006	−0.014 to 0.026	.538
Nonperseverative errors	−0.010	−0.023 to 0.003	.132
Trail Making Test			
Trails A time	−0.0001	−0.0003 to 0.0001	.548
Trails B time	−0.00002	−0.00011 to 0.00007	.672
Trails B regressed on Trails A	0.003	−0.242 to 0.247	.983
Verbal Fluency Test			
Letter fluency (total correct)	−0.003	−0.009 to 0.003	.362
Category fluency (total correct)	0.004	−0.001 to 0.009	.106
Ruff Figural Fluency Test			
Ruff Figural Fluency (total correct)	−0.0003	−0.0027 to 0.0022	.832
Working memory			
Composite score	0.026	−0.026 to 0.078	.323
WAIS Digit Span			
Forward last correct	0.001	−0.018 to 0.020	.901
Backward last correct	0.016[b]	−0.003 to 0.034	.099
Letter-Number Sequencing (LNS)			
LNS scaled score	0.003	−0.007 to 0.013	.600
Auditory *N*-Back			
0-Back *d*-prime	−0.000	−0.001 to 0.001	.998
2-Back *d*-prime	0.000	−0.003 to 0.003	.831
Neuromotor function			
Grooved Peg Board dominant hand time	−0.00002	−0.00006 to 0.00002	.398
Finger Tap total taps for trials 1–3	0.0001	−0.0020 to 0.0022	.906
WAIS			
Full-scale IQ Estimate	0.228	−0.058 to 0.514	.119
WAIS info total scaled score	0.106[b]	−0.006 to 0.218	.063
WAIS picture completion total scaled score	0.017	−0.083 to 0.117	.738
Verbal memory			
Composite score	0.006	−0.032 to 0.045	.748
CVLT[c] trial 5	0.006	−0.015 to 0.027	.574
CVLT total learning slope trials 1–5	0.000	−0.021 to 0.022	.976

Note: Bolded values are statistically significant at the $P = .05$ level; GLM, generalized linear models; CVLT, California Verbal Learning Test; WAIS III, Wechsler Adult Intelligence Scale III.
[a]All adjusted for gestational age.
[b]Parameter indicates worse performance for lower birth weight.
[c]All CVLT scores are standard scores.

occurred, would have already been completed by the time of the testing. This would tend to "flatten" the relationship between performance and birth weight in our subjects, making it less likely that we would observe an effect of birth weight on neurocognitive functioning. Limited neural plasticity is thought to explain the lack of normalization in extremely LBW infants (below 750 g) who do not experience normalization over development but remain substantially impaired throughout the life course.[34] We speculate that a similar process occurs for those who later develop SSD. This process may interact with already impaired cognitive reserve found in schizophrenia to give rise to diminished normalization of cognitive impairment.

More broadly, these findings provide further support for the "fetal programming hypothesis," which is based on a body of literature indicating that the risk for several chronic adult-onset diseases, including depression, increases as birth weight decreases.[4,34–37] This phenomenon has been attributed to a number of risk factors and mechanisms including nutritional deprivation and hormonal alterations and a possible interaction with genetic vulnerabilities. It is plausible that similar mechanisms could account for the associations between

neurodevelopmental exposures and later onset of neurocognitive deficits in SSD.

Strengths and Limitations

The study had several notable strengths, including the fact that it is based on a well-defined birth cohort, utilized prospective, objective measures of birth weight, and included controls that were representative of the source population that gave rise to the cases. There were also some limitations. First, the sample size was modest. As a result, we are unable to definitively conclude that the nonsignificant findings are not the result of limited power. Second, the multiple comparisons may have led to inflated probability of Type I error. It is worth noting, though, that lower birth weight was significantly related to diminished performance on executive functioning in SSD cases as measured by the composite score, and this resulted from a convergence of individual test findings within this domain. Additionally, within domains, a limited number of tests were administered, and composite scores were analyzed at the domain level, reducing chance associations. We also observed consistency for specific functional abilities on some measures within a domain (eg, cognitive switching on Trails B and the Wisconsin Card Sorting Tests) but not on others that assess different abilities within a domain (eg, visuospatial ability on LNS but no association for Digit Span which does not assess that ability), diminishing the probability that these findings result from chance.[38,39]

Third, subjects were assessed in adulthood and intervening risks, which may have moderated the outcome, were not measured over the life course. This will need to await further studies that collect longitudinal data on neurocognition and moderating variables over the life course. Even so, this is a prospective nested case-control study drawn from a well-defined cohort and followed into adulthood, with birth record data.

Furthermore, lower birth weight was related to deficits in several additional domains of neurocognitive function, including working memory, neuromotor function, and general intellect, which are each adversely affected in SSD. The lack of associations between lower birth weight and these domains in controls, and the biological plausibility of this risk factor in neurocognitive deficits based on studies of SSD and of neuropsychological function, add further to the credence of these results.

Conclusions

In summary, this exploratory analysis of the relationship between birth weight and neurocognition in SSD, in a well-defined, representative birth cohort revealed that lower birth weight is associated with impairments in executive function and certain aspects of working memory, neuromotor function, and generalized intellectual function in patients with schizophrenia. These findings were not observed in controls, suggesting that neurocognitive development in patients with SSD may be more vulnerable to prenatal factors or genetic variants that give rise to lower birth weight. Given the modest sample size, these findings are suggestive, but not definitive, and require independent replications in larger samples. Moreover, since the cognitive measures were obtained at only one point in time, it would be enlightening to test relationships between birth weight and the trajectory of cognitive function in samples with longitudinal data as well as potential mediating or moderating factors over the life course. Finally, it would be of value to assess whether the observed associations are found in other psychiatric syndromes, such as bipolar disorder.

The focus on neurocognitive phenotypes in SSD may improve our ability to detect risk factors for these disorders that may not be readily apparent in studies in which the clinical phenotype is the sole outcome. This may lead to new preventive strategies and a better understanding of the etiopathogenic mechanisms that underlie the cognitive deficits in this disorder, a question of critical relevance given their marked impact on occupational and social functioning, and the lack of effective treatments for this dimension of SSD.

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