Psychological Medicine (2013), **43**, 2361–2367. © Cambridge University Press 2013
doi:10.1017/S0033291713000032

ORIGINAL ARTICLE

Both low birthweight and high birthweight are associated with cognitive impairment in persons with schizophrenia and their first-degree relatives

M. Torniainen[1,2*], A. Wegelius[1,3], A. Tuulio-Henriksson[1,2,4], J. Lönnqvist[1,2,5] and J. Suvisaari[1,6]

[1] *Department of Mental Health and Substance Abuse Services, National Institute for Health and Welfare, Helsinki, Finland*
[2] *Institute of Behavioral Sciences, University of Helsinki, Finland*
[3] *Department of Psychiatry, Helsinki University Central Hospital, Finland*
[4] *Social Insurance Institution of Finland, Helsinki, Finland*
[5] *Department of Psychiatry, University of Helsinki, Finland*
[6] *Department of Social Psychiatry, Tampere School of Public Health, University of Tampere, Finland*

Background. Both low birthweight and high birthweight have been associated with an increased risk for schizophrenia and cognitive impairments in the general population. We assessed the association between birthweight and cognitive performance in persons with schizophrenia and their unaffected first-degree relatives.

Method. We investigated a population-based family sample comprising persons with schizophrenia ($n=142$) and their unaffected first-degree relatives ($n=277$). Both patients and relatives were interviewed with the Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV) and a comprehensive neuropsychological test battery was administered. Information on birthweight was obtained from obstetric records. We used generalized estimating equation (GEE) models to investigate the effect of birthweight, as a continuous variable, on cognitive functioning, adjusting for within-family correlation and relevant covariates.

Results. Both low birthweight and high birthweight were associated with lower performance in visuospatial reasoning, processing speed, set-shifting and verbal and visual working memory among persons with schizophrenia and their unaffected first-degree relatives compared to individuals with birthweight in the intermediate range. The group × birthweight interactions were non-significant.

Conclusions. Both low birthweight and high birthweight are associated with deficits in cognition later in life. Schizophrenia does not seem to modify the relationship between birthweight and cognition in families with schizophrenia.

Received 26 June 2012; Revised 17 December 2012; Accepted 19 December 2012; First published online 29 January 2013

Key words: Birthweight, cognition, neuropsychology, relatives, schizophrenia.

Introduction

Cognitive impairment in schizophrenia is prominent, persistent and a good predictor of functional outcome (Reichenberg & Harvey, 2007). Similar but milder cognitive impairments have been demonstrated in unaffected siblings of persons with schizophrenia (Sitskoorn *et al.* 2004). The pathogenesis of cognitive impairments in schizophrenia is complex, being partly inherited and partly resulting from environmental adversities (Morgan *et al.* 2012).

Low birthweight has been associated with various neurodevelopmental disabilities in the general population, and with poorer cognitive performance in the general population and in persons with schizophrenia (Rifkin *et al.* 1994; Aarnoudse-Moens *et al.* 2009; Tanskanen *et al.* 2011). The possible effect of high birthweight has received less attention, although high birthweight is associated with many adversities, such as an elevated risk for obstetric complications (Jolly *et al.* 2003; Henriksen, 2008), and associations between high birthweight and learning disabilities, depression and autism have been reported (Kirkegaard *et al.* 2006; Leonard *et al.* 2008; Van Lieshout & Boyle, 2011). Several studies in the general population depicted an association between high birthweight and increased cognitive impairment (Shenkin *et al.* 2004; Silva *et al.* 2006; Sorensen *et al.* 2006). Both low birthweight and high birthweight have been associated with increased susceptibility to schizophrenia (Gunnell *et al.* 2003; Abel *et al.* 2010; Wegelius *et al.* 2011).

* Address for correspondence: M. Torniainen, M.Psych., Department of Mental Health and Substance Abuse Services, National Institute for Health and Welfare, PO Box 30, 00271 Helsinki, Finland. (Email: minna.torniainen@thl.fi)

Some studies have suggested that people with a high genetic risk for schizophrenia are more susceptible to the effects of obstetric complications. Cannon *et al.* (2002) observed that obstetric complications indicating fetal hypoxia are associated with greater structural brain abnormalities in people with schizophrenia and their unaffected siblings than in controls at low genetic risk for schizophrenia. Furthermore, the effects of hypoxia on brain structure were more widespread in people with schizophrenia than their siblings, suggesting that there was an additional vulnerability in people with schizophrenia compared to their unaffected siblings (Cannon *et al.* 2002). In addition, a study with a small sample size found that low birthweight had a stronger effect on cognitive functions in persons with schizophrenia than in controls (Freedman *et al.* 2012).

In the present study, which represents the first study of its kind, we set out to investigate whether low or high birthweight is associated with increased cognitive impairment in patients with schizophrenia and their unaffected first-degree relatives and whether the effect of birthweight on cognition is different in these groups. Based on previous research in the general population, we hypothesized that both high and low birthweight would be associated with cognitive deficits and that the effect would be more pronounced in patients than in unaffected first-degree relatives.

Method

Participants

Persons with schizophrenia, schizo-affective disorder or schizophreniform disorder and born between 1940 and 1976 were identified from the Finnish Hospital Discharge Register, the Pension Register and the Medication Reimbursement Register, and their families from the Population Register Centre (Torniainen *et al.* 2011; Wegelius *et al.* 2011). From the identified families, we compiled two samples with assumed high genetic risk for schizophrenia. The all-Finland sample consisted of families with at least two siblings with schizophrenia, schizo-affective disorder or schizophreniform disorder (Hoti *et al.* 2004). The isolate sample consisted of families with at least one sibling with schizophrenia and one parent born within a genetically isolated region in northeastern Finland, in which the prevalence of schizophrenia is known to be high (Hovatta *et al.* 1997; Arajärvi *et al.* 2004). The isolate region is rural with one primary care hospital. The nearest hospital with specialized services is 200 km away (Videman & Heikkilä, 1978).

Written informed consent was obtained from each participant. The lifetime diagnoses of the participants were made by two independent psychiatrists on the basis of the Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV; First *et al.* 1996) and case records from hospitals and outpatient treatments.

A total of 280 patients with schizophrenia and 567 first-degree relatives without a lifetime diagnosis of psychotic disorder or bipolar disorder were interviewed and a neuropsychological test battery was administered. The exclusion criteria for the current study were: age >70 years, a severe neurological or general medical condition, mental retardation, current substance use disorder, untestable, for example due to severe disorganized symptoms and, in the relatives group, current psychiatric disorder. After applying the exclusion criteria, the schizophrenia group comprised 218 persons and the relatives group 438 persons. We had birthweight data for 142 (65%) persons in the schizophrenia group and 277 (63%) persons in the relatives group.

Assessment methods

Cognitive assessment

The cognitive variables used in the present study were: the Vocabulary subtest, the Similarities subtest, the Block Design subtest and the Digit Symbol subtest from the Wechsler Adult Intelligence Scale – Revised (WAIS-R; Wechsler, 1981); parts A and B of the Trail Making Test (Reitan & Wolfson, 1985); the interference score from the Stroop test (Golden, 1978; MacLeod, 1991); the Digit Span Forward and Backward tasks and the Visual Span Forward and Backward tasks from the Wechsler Memory Scale – Revised (WMS-R; Wechsler, 1987); and immediate recall (sum of trials 1–5), short delay recall and long delay recall in the California Verbal Learning Test (CVLT; Delis *et al.* 1987).

In a previous study we reported large, generalized cognitive impairments in the schizophrenia group and impaired processing speed and set-shifting in the relatives group (Torniainen *et al.* 2011). Persons in the relatives group outperformed persons with schizophrenia in all the variables used.

Birthweight

Birthweights were collected from obstetric and healthcare records. Of the sample, 69% were born in hospitals, 16% at home with professional help and 15% at home without professional help (Table 1).

Covariates

For covariates in the statistical analyses, we chose those characteristics that might have an impact on

https://doi.org/10.1017/S0033291713000032 Published online by Cambridge University Press

Table 1. *Demographic and clinical characteristics*

	Patients	Relatives
Sex, female/male	45/97	144/133
Age (years)		
Mean (S.D.)	44 (7)	46 (8)
Range	24–67	28–59
Education (years), mean (S.D.)	10 (2)	12 (3)
GAF score, mean (S.D.)	37 (10)	78 (12)
Birthweight (g), mean (S.D.)	3519 (609)	3410 (562)
Birthweight distribution, *n* (%)		
<2500 g	4 (3)	12 (4)
2500–2999 g	17 (12)	32 (12)
3000–4000 g	93 (65)	201 (73)
>4000 g	28 (20)	32 (12)
Type of delivery, *n* (%)		
Hospital	91 (75)	168 (66)
Home with professional help	17 (14)	43 (17)
Home without professional help	13 (11)	43 (17)
Age of onset (years)		
Mean (S.D.)	23 (5)	–
Range	11–41	–
Negative symptoms, mean (S.D.)	53 (21)	–
Positive symptoms, mean (S.D.)	44 (21)	–
Medication use		
Antipsychotics, *n* (%)	136 (96)	–
CPZE, mean (S.D.)	584 (566)	–

GAF, Global Assessment of Functioning; CPZE, chlorpromazine equivalents; S.D., standard deviation.

cognitive functioning. The type of delivery (hospital *versus* home with professional assistance *versus* home without professional assistance) was included as a covariate because possible complications, which are more probable in persons with low or high birthweight than in persons with intermediate birthweight, would be more difficult to treat at home than at hospital. The Global Assessment of Functioning (GAF; APA, 2000) reflects the level of functioning and symptom severity. The GAF score is related to cognitive functioning (Karilampi *et al.* 2011). Familial loading for the illness may have a small effect on cognitive functioning (Tuulio-Henriksson *et al.* 2003) and therefore the number of affected siblings in each family was included as a covariate. The place of birth (isolate *versus* the rest of Finland) was included in the analyses to ensure that the sampling method did not confound the results. Age and sex were also used as covariates.

Statistical analyses

Statistical analyses were performed with Intercooled Stata v. 9.2 for Windows (StataCorp, USA). Because the assessed variables are correlated within families (Hoti *et al.* 2004), the analyses were performed with the generalized estimating equation (GEE) approach. The method takes this correlation into account and estimates unbiased population-averaged regression coefficients (Zeger & Liang, 1986).

In the statistical models, birthweight (in kg) was entered as a continuous variable. A statistically significant squared birthweight indicates that the association between birthweight and cognitive functioning is not linear but instead follows a curvilinear trajectory. We analyzed whether the association between birthweight and cognitive performance was different in the schizophrenia and the relatives groups by group × birthweight and group × squared birthweight interactions. Non-significant interactions were removed from the analyses. The probability level $p < 0.05$ indicated statistical significance. The effect size of the mean differences between the schizophrenia and the relatives group was measured with Cohen's *d* (Cohen, 1988). Effect sizes of >0.20, >0.50 and >0.80 were considered as small, medium and large respectively.

Results

Demographic and clinical characteristics

In the schizophrenia group, men were over-represented (68%), whereas in the relatives group, the number of men (48%) and women (52%) was more equally balanced. In the schizophrenia group, 15% had a birthweight <3000 g and in the relatives group, 16%. Of the patients, 20% had a birthweight >4000 g and of the relatives, 12%. Demographic and clinical characteristics are presented in detail in Table 1.

Birthweight and cognitive functioning

When examining scatter plots with LOWESS (locally weighted scatter plot smoothing) curves (see online Supplementary Material), the association between birthweight and several cognitive variables, including Digit Span Forward (Fig. 1), was seen to be non-linear, with both low and high birthweight being associated with poorer performance than average birthweight. The association between birthweight and most of the cognitive variables was similar in the schizophrenia and relatives groups.

The association between birthweight and cognitive performance was statistically significant and followed a curvilinear trajectory in the Block Design subtest, the Digit Symbol subtest, the Trail Making Test parts A and B, and the Digit Span Backward and the Visual Span Backward tasks (Table 2), when controlling for the type of delivery (hospital *versus* home with

https://doi.org/10.1017/S0033291713000032 Published online by Cambridge University Press

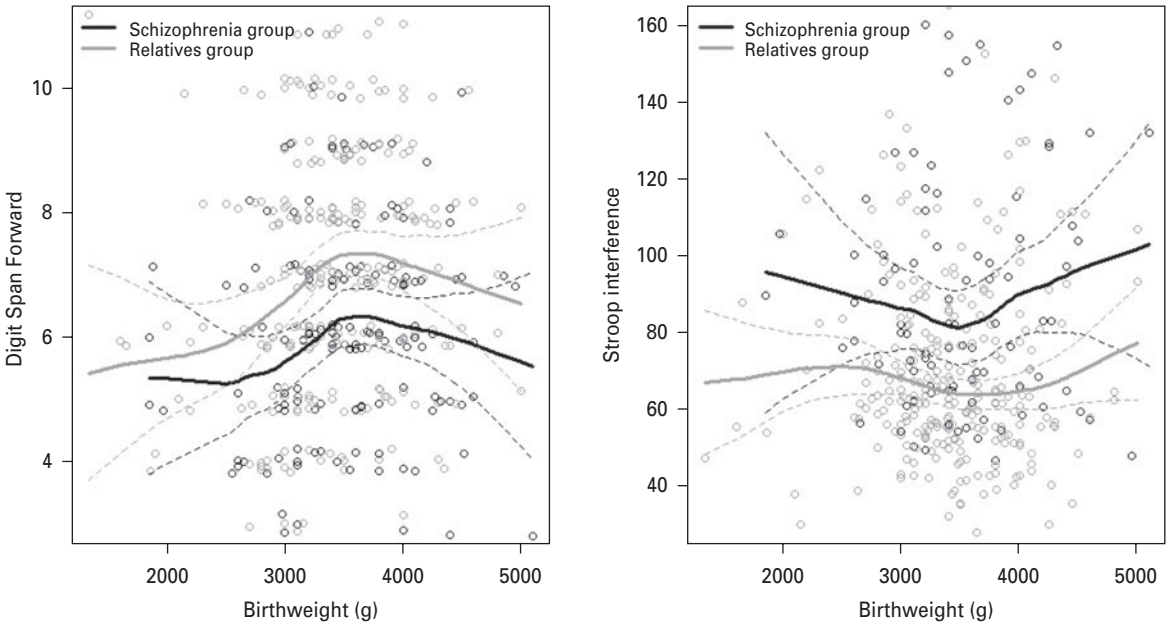

Fig. 1. Scatter plots with LOWESS curves and 95% confidence intervals of the association between birthweight and cognitive performance. High scores in the Digit Span Forward task and low scores in the Stroop interference reflect good performance.

professional assistance *versus* home without professional assistance), the GAF score, the number of affected siblings per family, place of birth (isolate *versus* the rest of Finland), age and sex. A curvilinear association of borderline statistical significance was observed between birthweight and performance in the Similarities subtest, the Stroop interference and immediate and long delay recall in the CVLT. In the tests where the association was non-linear, a birthweight of approximately 3500–4000 g was associated with the highest performance. The group × birthweight interactions were non-significant.

Discussion

The association between birthweight and cognitive functioning was similar in persons with schizophrenia and their unaffected first-degree relatives, even though the impairments were larger in the schizophrenia group than in the relatives group (Torniainen *et al.* 2011). Persons in the intermediate birthweight range had the highest cognitive performance and both low birthweight and high birthweight were associated with small impairments in visuospatial reasoning, processing speed, set-shifting, and verbal and visual working memory.

Our results on persons with schizophrenia and their first-degree relatives are in line with studies in the general population. In previous studies, cognitive performance was reported to be lower in persons with low birthweight than in persons with birthweight in the intermediate range in the general population and also in persons with schizophrenia (Rifkin *et al.* 1994; Tanskanen *et al.* 2011). To date, research has focused predominantly on the association between low birthweight and cognitive functioning whereas few studies have investigated high birthweight. However, some studies in the general population have suggested that high birthweight may increase the risk for cognitive impairments (Shenkin *et al.* 2004).

The association between low birthweight and cognitive impairments may stem from adverse effects during pregnancy, such as inadequate supply of nutrients and oxygen to the fetus altering brain growth and causing many adaptations in endocrine and metabolic processes (e.g. in glucocorticoids and insulin-like growth factors, IGFs), referred to as 'fetal programming' (Morgane *et al.* 1993; Barker, 1995; Fowden *et al.* 2006). In addition, low birthweight may result from pre-term birth, which has been shown to have negative effects on brain development and cognitive functioning (Volpe, 2009; Baron *et al.* 2012). Little is known about the mechanisms underlying the association between high birthweight and cognition. Similar mechanisms related to fetal adaptations to suboptimal intrauterine environment, caused for example by maternal diabetes, might be involved (Van Lieshout & Voruganti, 2008). High birthweight is also associated with elevated risk for complications, which may affect cognition (Henriksen, 2008). In particular, the risk of a prolonged second stage of labor is increased, and Caesarean section is more often required

https://doi.org/10.1017/S0033291713000032 Published online by Cambridge University Press

Table 2. *The association between birthweight and cognitive performance in GEE models and the birthweight where cognitive performance was the highest. The birthweight of the highest performance was reported if the association between a cognitive variable and birthweight was significant at least at trend level ($p < 0.10$). The effect size of the group difference between the schizophrenia group and the relatives group is also shown*

	Quadratic term		Linear term		Birthweight at peak performance (g)	Schizophrenia group *versus* relatives group Cohen's *d*
	β	p	β	p		
Verbal ability and visuospatial reasoning						
WAIS-R Vocabulary	−0.83	0.49	8.17	0.31		−1.12
WAIS-R Similarities	−0.86	0.07	6.81	0.05	4000	−1.03
WAIS-R Block Design	−2.40	0.006	16.8	0.004	3500	−0.89
Processing speed and executive functions						
WAIS-R Digit Symbol	−2.82	0.003	20.3	0.002	3600	−1.25
Trail Making Test part A	−0.002	0.002	0.01	0.001	3900	1.14[a]
Trail Making Test part B	−0.001	0.003	0.008	<0.001	4000	0.79[a]
Stroop Interference	5.10	0.06	−32.7	0.07	3200	0.82[a]
Attention and working memory						
WMS-R Digit Span Forward	−0.33	0.17	2.57	0.14		−0.51
WMS-R Digit Span Backward	−0.31	0.03	2.26	0.02	3700	−0.85
WMS-R Visual Span Forward	−0.31	0.13	2.24	0.09		−0.64
WMS-R Visual Span Backward	−0.37	0.04	2.65	0.02	3600	−0.61
Verbal learning						
CVLT Immediate recall	−1.98	0.08	15.0	0.04	3800	−1.46
CVLT Short delay recall	−0.14	0.60	1.40	0.45		−1.30
CVLT Long delay recall	−0.51	0.07	4.00	0.03	3900	−1.44

GEE, Generalized estimating equation; WAIS-R, Wechsler Adult Intelligence Scale – Revised; WMS-R, Wechsler Memory Scale – Revised; CVLT, California Verbal Learning Test.

[a] High scores represent low performance.

in deliveries of large babies compared to babies of average birthweight (Koskela, 1965). This might be a problem when the baby is born at home or in a local hospital where personnel lack the expertise for performing Caesarean sections. Both of these situations were relatively common in the rural areas of Finland at the time this study population was born.

The effects of a suboptimal intrauterine environment on brain development are diverse (Morgane *et al.* 1993). The results of the present study are in agreement with diverse impairments in cognitive functions in persons with low or high birthweight. The results suggest that the widespread influence of a suboptimal intrauterine environment may be one of the factors contributing to broad cognitive impairments in schizophrenia. The strongest effect of birthweight was detected in tasks demanding processing speed, which has also shown pronounced impairments compared to other cognitive functions in schizophrenia (Dickinson *et al.* 2007). Processing speed impairments have been detected before illness onset both in persons with subclinical psychotic experiences and in persons who later develop schizophrenia (Cannon *et al.* 2006; Kelleher *et al.* 2012). Processing speed is dependent on distributed brain networks and the integrity of white matter tracks, which, in earlier studies, were found to be impaired in persons with low birthweight or preterm birth (Skranes *et al.* 2007; Turken *et al.* 2008; Allin *et al.* 2011).

The limitations of our study include the lack of a control group or a patient group without familial loading for schizophrenia, and therefore we do not know if the effects of birthweight differ in magnitude in patients with or without familial loading for schizophrenia or among the general population. The results of the present study only show that the pattern is the same as that found in studies on general populations. In addition, we did not have data on gestational age and therefore were not able to discern the effects of gestational age at birth and of fetal growth on the association between birthweight and cognitive functioning.

The strengths of the study include obtaining birthweights from obstetric records rather than relying on maternal recall. In addition, the sample was large and identified from health-care registers, which improves

https://doi.org/10.1017/S0033291713000032 Published online by Cambridge University Press

the representativeness of the sample because persons with schizophrenia without a current treatment contact were also included in the sample.

To conclude, both low birthweight and high birthweight were found to be associated with impairments in several cognitive functions among persons with schizophrenia and their unaffected first-degree relatives. The association between birthweight and cognitive functions was similar in both groups. The cognitive impairments in persons with low and high birthweight resemble results from previous studies of the general population. This suggests that our findings may reflect a general effect of birthweight on cognition that is not modified by the illness.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291713000032.

Acknowledgments

This study was funded by grants from the Sigrid Juselius Foundation to J. Lönnqvist and J. Suvisaari (129434).

Declaration of Interest

J. Suvisaari has served as a consultant for Janssen Cilag in a study that is not related to this manuscript. A. Wegelius has received an unrestricted research grant from Lundbeck Oy.

References

Aarnoudse-Moens CS, Weisglas-Kuperus N, van Goudoever JB, Oosterlaa J (2009). Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. *Pediatrics* **124**, 717–728.

Abel KM, Wicks S, Susser ES, Dalman C, Pedersen MG, Mortensen PB, Webb RT (2010). Birth weight, schizophrenia, and adult mental disorder: is risk confined to the smallest babies? *Archives of General Psychiatry* **67**, 923–930.

Allin MP, Kontis D, Walshe M, Wyatt J, Barker GJ, Kanaan RA, McGuire P, Rifkin L, Murray RM, Nosarti C (2011). White matter and cognition in adults who were born preterm. *PLoS One* **6**, e24525.

APA (2000). *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn, text revision (DSM-IV-TR). American Psychiatric Association: Washington, DC.

Arajärvi R, Haukka J, Varilo T, Suokas J, Juvonen H, Suvisaari J, Muhonen M, Suominen K, Tuulio-Henriksson A, Schreck M, Hovatta I, Partonen T, Lönnqvist J (2004). Clinical phenotype of schizophrenia in a Finnish isolate. *Schizophrenia Research* **67**, 195–205.

Barker DJ (1995). Fetal origins of coronary heart disease. *British Medical Journal* **311**, 171–174.

Baron IS, Litman FR, Ahronovich MD, Baker R (2012). Late preterm birth: a review of medical and neuropsychological childhood outcomes. *Neuropsychology Review* **22**, 438–450.

Cannon M, Moffitt TE, Caspi A, Murray RM, Harrington H, Poulton R (2006). Neuropsychological performance at the age of 13 years and adult schizophreniform disorder: prospective birth cohort study. *British Journal of Psychiatry* **189**, 463–464.

Cannon TD, van Erp TG, Rosso IM, Huttunen M, Lönnqvist J, Pirkola T, Salonen O, Valanne L, Poutanen VP, Standertskjold-Nordenstam CG (2002). Fetal hypoxia and structural brain abnormalities in schizophrenic patients, their siblings, and controls. *Archives of General Psychiatry* **59**, 35–41.

Cohen J (1988). *Power Analysis for the Behavioral Sciences*, 2nd edn. Lawrence Erlbaum Associates: Hillsdale, NJ.

Delis DC, Kramer JH, Kaplan E, Ober BA (1987). *California Verbal Learning Test: Manual. Research Edition*. The Psychological Corporation/Harcourt Brace & Company: San Antonio, TX.

Dickinson D, Ramsey ME, Gold JM (2007). Overlooking the obvious: a meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. *Archives of General Psychiatry* **64**, 532–542.

First MB, Spitzer RL, Gibbon M, Williams JBW (1996). *Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version* (*SCID-CV*). American Psychiatric Press, Inc., Washington, DC.

Fowden AL, Giussani DA, Forhead AJ (2006). Intrauterine programming of physiological systems: causes and consequences. *Physiology* (*Bethesda*) **21**, 29–37.

Freedman D, Bao Y, Kremen WS, Vinogradov S, McKeague IW, Brown AS (2012). Birth weight and neurocognition in schizophrenia spectrum disorders. *Schizophrenia Bulletin*. Published online: 29 February 2012. doi: 10.1093/schbul/sbs008.

Golden C (1978). *Stroop Color and Word Test: Manual for Clinical and Experimental Uses*. Stoelting: Chicago, IL.

Gunnell D, Rasmussen F, Fouskakis D, Tynelius P, Harrison G (2003). Patterns of fetal and childhood growth and the development of psychosis in young males: a cohort study. *American Journal of Epidemiology* **158**, 291–300.

Henriksen T (2008). The macrosomic fetus: a challenge in current obstetrics. *Acta Obstetricia et Gynecologica Scandinavica* **87**, 134–145.

Hoti F, Tuulio-Henriksson A, Haukka J, Partonen T, Holmström L, Lönnqvist J (2004). Family-based clusters of cognitive test performance in familial schizophrenia. *BioMed Central Psychiatry* **4**, 20.

Hovatta I, Terwilliger JD, Lichtermann D, Mäkikyrö T, Suvisaari J, Peltonen L, Lönnqvist J (1997). Schizophrenia in the genetic isolate of Finland. *American Journal of Medical Genetics* **74**, 353–360.

Jolly MC, Sebire NJ, Harris JP, Regan L, Robinson S (2003). Risk factors for macrosomia and its clinical consequences: a study of 350,311 pregnancies. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* **111**, 9–14.

Karilampi U, Helldin L, Archer T (2011). Cognition and global assessment of functioning in male and female outpatients with schizophrenia spectrum disorders. *Journal of Nervous and Mental Disease* **199**, 445–448.

Kelleher I, Clarke MC, Rawdon C, Murphy J, Cannon M (2012). Neurocognition in the extended psychosis phenotype: performance of a community sample of adolescents with psychotic symptoms on the MATRICS neurocognitive battery. *Schizophrenia Bulletin*. Published online: 4 September 2012. doi: 10.1093/schbul/sbs086.

Kirkegaard I, Obel C, Hedegaard M, Henriksen TB (2006). Gestational age and birth weight in relation to school performance of 10-year-old children: a follow-up study of children born after 32 completed weeks. *Pediatrics* **118**, 1600–1606.

Koskela O (1965). Large fetus; a geographic modification. *Annales Chirurgiae et Gynaecologiae Fenniae* **54**, 461–471.

Leonard H, Nassar N, Bourke J, Blair E, Mulroy S, de Klerk N, Bower C (2008). Relation between intrauterine growth and subsequent intellectual disability in a ten-year population cohort of children in Western Australia. *American Journal of Epidemiology* **167**, 103–111.

MacLeod CM (1991). Half a century of research on the Stroop effect: an integrative review. *Psychological Bulletin* **109**, 163–203.

Morgan VA, Croft ML, Valuri GM, Zubrick SR, Bower C, McNeil TF, Jablensky AV (2012). Intellectual disability and other neuropsychiatric outcomes in high-risk children of mothers with schizophrenia, bipolar disorder and unipolar major depression. *British Journal of Psychiatry* **200**, 282–289.

Morgane PJ, Austin-LaFrance R, Bronzino J, Tonkiss J, Diaz-Cintra S, Cintra L, Kemper T, Galler JR (1993). Prenatal malnutrition and development of the brain. *Neuroscience and Biobehavioral Reviews* **17**, 91–128.

Reichenberg A, Harvey PD (2007). Neuropsychological impairments in schizophrenia: integration of performance-based and brain imaging findings. *Psychological Bulletin* **133**, 833–858.

Reitan RM, Wolfson D (1985). *The Halstead Reitan Neuropsychological Test Battery*. Neuropsychology Press: Tuscon, AZ.

Rifkin L, Lewis S, Jones P, Toone B, Murray R (1994). Low birth weight and schizophrenia. *British Journal of Psychiatry* **165**, 357–362.

Shenkin SD, Starr JM, Deary IJ (2004). Birth weight and cognitive ability in childhood: a systematic review. *Psychological Bulletin* **130**, 989–1013.

Silva A, Metha Z, O'Callaghan FJ (2006). The relative effect of size at birth, postnatal growth and social factors on cognitive function in late childhood. *Annals of Epidemiology* **16**, 469–476.

Sitskoorn MM, Aleman A, Ebisch SJ, Appels MC, Kahn RS (2004). Cognitive deficits in relatives of patients with schizophrenia: a meta-analysis. *Schizophrenia Research* **71**, 285–295.

Skranes J, Vangberg TR, Kulseng S, Indredavik MS, Evensen KA, Martinussen M, Dale AM, Haraldseth O, Brubakk AM (2007). Clinical findings and white matter abnormalities seen on diffusion tensor imaging in adolescents with very low birth weight. *Brain* **130**, 654–666.

Sorensen HJ, Mortensen EL, Reinisch JM, Mednick SA (2006). Height, weight and body mass index in early adulthood and risk of schizophrenia. *Acta Psychiatrica Scandinavica* **114**, 49–54.

Tanskanen P, Valkama M, Haapea M, Barnes A, Ridler K, Miettunen J, Murray GK, Veijola JM, Jones PB, Taanila AM, Isohanni MK (2011). Is prematurity associated with adult cognitive outcome and brain structure? *Pediatric Neurology* **44**, 12–20.

Torniainen M, Suvisaari J, Partonen T, Castaneda AE, Kuha A, Perälä J, Saarni S, Lönnqvist J, Tuulio-Henriksson A (2011). Sex differences in cognition among persons with schizophrenia and healthy first-degree relatives. *Psychiatry Research* **188**, 7–12.

Turken A, Whitfield-Gabrieli S, Bammer R, Baldo JV, Dronkers NF, Gabrieli JD (2008). Cognitive processing speed and the structure of white matter pathways: convergent evidence from normal variation and lesion studies. *NeuroImage* **42**, 1032–1044.

Tuulio-Henriksson A, Arajärvi R, Partonen T, Haukka J, Varilo T, Schreck M, Cannon T, Lönnqvist J (2003). Familial loading associates with impairment in visual span among healthy siblings of schizophrenia patients. *Biological Psychiatry* **54**, 623–628.

Van Lieshout RJ, Boyle MH (2011). Is bigger better? Macrosomia and psychopathology later in life. *Obesity Reviews* **12**, e405–e411.

Van Lieshout RJ, Voruganti LP (2008). Diabetes mellitus during pregnancy and increased risk of schizophrenia in offspring: a review of the evidence and putative mechanisms. *Journal of Psychiatry and Neuroscience* **33**, 395–404.

Videman T, Heikkilä J (1978). Frequent users of doctor services in a small rural community. *Scandinavian Journal of Social Medicine* **6**, 37–41.

Volpe JJ (2009). Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. *Lancet Neurology* **8**, 110–124.

Wechsler D (1981). *WAIS-R: Manual: Wechsler Adult Intelligence Scale – Revised*. The Psychological Corporation: Cleveland, OH.

Wechsler D (1987). *WMS-R: Wechsler Memory Scale – Revised, Manual*. The Psychological Corporation: San Antonio, TX.

Wegelius A, Tuulio-Henriksson A, Pankakoski M, Haukka J, Lehto U, Paunio T, Lönnqvist J, Suvisaari J (2011). An association between high birth weight and schizophrenia in a Finnish schizophrenia family study sample. *Psychiatry Research* **190**, 181–186.

Zeger SL, Liang KY (1986). Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* **42**, 121–130.