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Neurodevelopmental Outcomes of Twins Compared With Singleton Children: A Systematic Review

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More than 200 million children aged <5 years fail to reach their full cognitive potential, and children born as twins are particularly at risk. In this article, we review studies that examined differences in the neurodevelopmental outcomes of twins compared to singletons. We searched the Medline database for articles on twins, singletons, neuro, and cognitive development. We also inspected bibliographies of relevant publications to identify related articles from 2011 to 2017. Our search criteria yielded 162 studies, 8 of which met the inclusion criteria. Of the eight studies examined, four were prospective follow-up studies, three were cross-sectional studies, and one was a randomized controlled trial. Five of these studies were carried out in developed countries, and they found no statistically significant difference in neurodevelopmental outcomes among twins and singletons. However, two of the three studies carried out in developing countries found a difference with singletons having significantly higher academic ratings than twins. Studies in which neurodevelopmental outcomes were measured early in life (1–5 years) showed no significant twin–singleton differences, while those in which it was measured later in life showed mixed twin–singleton differences. Overall, these studies may have been underpowered and may not have been optimally designed and implemented. There is need for studies with adequate sample sizes, good design, and optimal measurement of all relevant covariates in order to resolve the conflicting reports in the literature.

■ **Keywords:** cognitive development, neurodevelopment, singleton, twins

More than 200 million children aged <5 years in low- and middle-income countries fail to reach their cognitive developmental milestones due to various biological and psychosocial factors (Walker et al., 2007). These children become adults with physical and mental health challenges that are associated with increased risk of problem behavior, poor academic performance, and problems with interpersonal relationships. Individuals with neurobehavioral difficulties may also be at increased risk of non-communicable diseases, physical, psychological, and sexual abuse (Grantham-McGregor et al., 2007).

The incidence of multiple births is rising because of increased use of assisted reproductive technologies (Asztalos et al., 2001; Hamilton et al., 2006). Multiple pregnancies have risen to account for about 3% of all births, yet they account for 15% of all perinatal mortality (Acosta-Rojas et al., 2007; Giuffre et al., 2012). Twins are pre-disposed to higher risk of mortality and morbidities (Bodeau-Livinec et al., 2010; Bodeau-Livinec et al., 2013; Pharoah, 2005; 2006).

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Children born as twins have a greater likelihood of poor neurodevelopmental outcomes compared to singletons when birth weight and gestational age are not controlled for (Lorenz, 2012). Previous studies have shown that there is a higher prevalence of delay in attainment of cognitive neurodevelopmental milestones among twins compared to singletons. This delay has been attributed to lower gestational age and birth weight of twins compared to singletons (Lorenz, 2012; Ronalds et al., 2005). There have been few studies of failure to achieve cognitive and neurodevelopmental milestones comparing twins and singleton children, and the results have been conflicting (Cooke, 2010; Eras et al., 2013).

In addition to lower gestational age and birth weight, other factors that have been shown to contribute to the differences in attainment of neurodevelopmental milestones when comparing twins and singleton children include gender, birth order of twins (Gnanendran et al., 2015; Smith et al., 2007; Wadhawan et al., 2009), congenital anomalies, socio-economic status of parents (Urquia et al., 2007), maternal age at delivery, presence of twin-to-twin transfusion syndrome, birth by assisted conception, and whether the twins are mono- or di-chorionic (Luu & Vohr, 2009; Papiernik et al., 2010; Petit et al., 2011; Ronalds et al., 2005; Shinwell et al., 2009; Zeitlin et al., 2010).

The objective of this article was to systematically review the literature on neurodevelopmental outcomes of twins compared to singletons published between January 2011 and December 2017.

Methodology

Epidemiological studies of cognitive and neurodevelopmental outcomes of twins compared to singleton children were selected from PubMed (U.S. National Library of Medicine, Bethesda, MD, USA) and Web of Science databases using the following search terms: twin and singleton and neurodevelopmental; twin and singleton and cognitive; twin and singleton and intelligence; twin and singleton and mental development; twin and singleton and motor development; twin and singleton and educational development; twin and singleton and test score; twin and singleton and academic performance. The search was restricted to studies in humans that were published between January 2011 and December 2017 because a similar review had been conducted up to 2010 (Lorenz, 2012).

We reviewed the abstracts of the identified documents and searched their references for additional articles. We created a protocol using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Moher et al., 2009; Shamseer et al., 2015). We retrieved information about each study's location, type of study, follow-up period (for interventional studies), sample size, neurodevelopmental outcomes, age of the children in the study, recruitment strategy, methods of statistical analyses, confounding variables, and magnitude of difference (Tables 1 and 2). The selected articles were independently assessed by two authors (B.O. and A.S.), and any disagreement and discrepancies were resolved by discussion among authors. Articles retrieved from the two databases were entered into EndNote (EndNote X7, Thomas Reuter) where we removed duplicates. We excluded literature reviews, commentaries, and papers about study design (Figure 1 and Appendix). All included studies were written in English language.

The top six studies utilized at least two different instruments to assess neurodevelopmental outcomes (Bodeau-Livinec et al., 2013; Eras et al., 2013; Gnanendran et al., 2015; Hjern et al., 2012; Manuck et al., 2014; Raz et al., 2016). Manuck et al. (2014) utilized the Bayley Scale of Infant Development (BSID) and Mental Development Index (MDI), and cerebral palsy was assessed by a pediatric neurologist (Manuck et al., 2014). Bodeau-Livinec et al. (2013) utilized the Kaufmann Assessment Battery for Children for cognitive assessment, and cerebral palsy was also assessed, while Gnanendran et al. (2015) utilized the BSID and Griffiths Mental Development Scales. Hjern et al. (2012) utilized test scores from the 'Enlistment Battery 80', used for military conscription at 18–19 years of age to create an indicator of IQ and grade point averages from the national school register, while Eras et al. (2013) utilized the BSID, MDI, and Psychomotor Developmental Index (PDI).

Results

Our search yielded 162 abstracts (Figure 1) and of these, 15 were excluded because they were duplicates and 87 were excluded because they did not fall between 2011 and 2017, leaving 60 abstracts. Of the remaining 60 abstracts, we excluded 49 because they were not singleton versus twin studies ($n = 22$), the main outcome was not neurodevelopmental outcomes ($n = 16$), or study participants were adults ($n = 7$) or review articles ($n = 4$). We reviewed the remaining 11 full-text articles and excluded three because one was not a singleton versus twin study, and the main exposures were placental pathology and assisted reproductive techniques in two each.

We examined the remaining eight studies and four of them were prospective follow-up studies (Bodeau-Livinec et al., 2013; de Zeeuw et al., 2012; Eras et al., 2013; Gnanendran et al., 2015), three were cross-sectional studies (Hjern et al., 2012; Hur & Lynn, 2013; Raz et al., 2016), while one was a randomized controlled trial (Manuck et al., 2014).

The eight studies were ranked based on four factors. The first factor was the sample size. The study with the lowest sample size was assigned a value of 1, while the study with highest sample size was assigned a value 8. The second factor that was used in the ranking was study design. Studies that were cross-sectional were scored 1, follow-up and prospective studies were scored 4, while an RCT was scored 8. Next, we scored the type of instrument used. If an educational instrument only was used, the study was scored 1;

TABLE 1

Characteristics of Epidemiological Studies Investigating Neurodevelopmental Outcomes of Twins Compared With Singleton Children

Author	Article title	Neurodevelopmental outcomes studied	Sample size	Country where study was conducted	Age group of children considered in the study	Ranking
Bodeau-Livinec et al. (2010)	Do very pre-term twins and singletons differ in their neurodevelopment at 5 years of age?	Cognitive assessment cerebral palsy	2,773	France	All children born between 22 and 32 weeks followed-up and measured at 5 years	2
De Zeeuw et al. (2012)	Twin-specific risk factors in primary school achievements	Educational achievement in primary school	1,375	Netherland	7-year-old twins from birth cohorts 1992–2003	7
Eras et al. (2013)	Neurodevelopmental outcome among multiples and singletons: A regional neonatal intensive care unit's experience in Turkey	Presence of moderate or severe cerebral palsy, severe bilateral hearing loss or bilateral blindness, mental developmental score or psychomotor developmental index	370	Turkey	All children born $\leq$32 weeks followed up till 12–18 months (corrected age)	5
Gnanendran et al. (2015)	Neurodevelopmental outcomes of pre-term singletons, twins and higher order gestations: A population-based cohort study	Moderate to severe functional disability using neurodevelopmental assessments tools was the main outcome	1,473	Australia	Infants born <29 weeks and followed-up till age of 2–3 years. The infants underwent follow-up assessment at 2– 3 years corrected age	3
Hjern et al. (2012)	Educational achievement and vocational career in twins — A Swedish national cohort study	Grade point averages at the time of leaving the compulsory primary school (usually at 15–16 years of age) and IQ test on a nine grade point scale.	83,7752 singleton, 13,368 twins, and 3,019 siblings of twins	Sweden	Ninth-grade children were considered at age 15–16 years for GPA and ages 18–19 years for IQ test	4
Manuck et al. (2014)	Correlation between initial neonatal and early childhood outcomes following pre-term birth	Cerebral palsy Cognitive assessments using the Bayley II Scales of Infant Development and Psychomotor Development Indices	1,771 302 babies were twins	USA	Infants born at 23.0–33.9 weeks were followed up and underwent follow-up assessment at 2 years	1
Hur and Lynn (2013)	Twin–singleton differences in cognitive abilities in a sample of Africans in Nigeria	Two cognitive ability tests: Standard Progressive Matrices-Plus Version (SPM+) Mill-Hill Vocabulary (MHV)	413 pairs of twins and 280 singletons	Nigeria	9–20 years 14.6 $\pm$ 2.2 years for twins 16.1 $\pm$ 1.8 years for singletons	8
Raz et al. (2016)	Neuropsychological functioning in pre-term-born twins and singletons at pre-school age	Neuropsychological functioning measured in memory skills, language skills, visual processing, and motor skills	77 twins and 144 singletons.	USA	3–6 years (pre-school age)	5

Note: [a]Ranking: Sample size = Lowest: 1, Highest: 8.
Study design = Cross-sectional: 1, Follow-up: 4, Randomized trial: 7.
Reliability and validity of instrument used: Educational only: 1, Standard only (e.g., Bayley): 4, Standard and Clinical (e.g., Bayley & CP Assessment): 7.
Number of variables adjusted for in the analysis: Lowest: 1, Highest 7.

if standard instruments (e.g., Bayley scale) were used, the study was scored 4; and if standard instruments were combined with clinical assessments, the study was scored 8. The fourth factor used was the number of confounding variables adjusted for in the study. Each study was assigned a score based on the number of confounding variables in the analyses. The scores were added together and the seven studies were ranked from 1 to 8. (Table 3).

Manuck et al. (2014) was ranked first. In this study, secondary analysis of a multicenter randomized controlled trial of antenatal magnesium sulfate versus placebo administered to women at imminent risk for pre-mature delivery was done. Singletons and twins delivered at 23.0 to 33.9 weeks who survived to 2 years of age were assessed by trained physicians using the BSID and PDI. The outcomes measured were childhood diagnosis of

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TABLE 2

Characteristics of Epidemiological Studies Investigating Neurodevelopmental Outcomes of Twins Compared With Singleton Children

	Risk of bias				Other factors		
Author	Recruitment strategy	Study design	Measure of neurodevelopmental outcomes	Information on validation, reproducibility, and sensitivity analysis	Method of analysis and statistical approach	Variables that were adjusted for	Measurement of magnitude of difference
Bodeau-Livinec et al.	EPIPAGE is a population-based cohort of very pre-term infants followed from birth in France.	Prospective cohort	Cognitive assessment: using the Kaufman Assessment Battery for Children. Cognitive deficiency was defined as a score less than 70. CP as proposed by the European Network.	Children lost to follow-up and those assessed at 5 years were compared according to maternal and infant characteristics at birth. Stratified analysis by level of severity of cognitive deficiency was done.	Bivariate analyses were utilized to assess association between type of pregnancy and all outcomes. Weighted logistic regression models were used to study the relationships between type of pregnancy and categorical outcomes while weighted linear regression was used to compare continuous variables.	GA, infant's gender, IUGR, pre-natal steroids, socio-demographic factors (maternal age at birth, maternal education, maternal birthplace, family social class)	Bivariate analysis showed no significant difference between singletons and twins in their cognitive assessment. There was no difference in CP after adjustment for GA, gender, IUGR, and pre-natal steroids. In children without severe deficiency, singletons had slightly higher mean MPC scores compared with twins at the limit of significance ($p = .5$).
De Zeeuw et al. (2012)	Twins in the Netherlands Twin Register were followed-up.	Prospective cohort	Educational achievement was assessed by the evaluation of several school subjects.	Nil	Independent sample *t* test, paired sample *t*-test, Chi-square test, and a linear structural equation model were utilized.	GA, birth weight	Singletons had significantly higher ratings in arithmetic, language, and reading. Twins with a younger sibling had the same or even higher, ratings, in contrast, twins with an older sibling had significantly lower ratings than the non-twin sibling.
Eras et al. (2013)	Pre-term infants born and hospitalized at Zekai Tahir Burak Maternity Teaching Hospital Neonatal Intensive Care Unit.	Prospective cohort study	Diagnosis of CP was based on the presence of hypertonicity, hyperreflexia, and dystonic and spastic movement in the involved extremities. Developmental assessment was performed using Bayley Scales of Infant Development II and the MDI and PDI.	Nil	Chi-square test for categorical variables and a *t* test was used for continuous variables.	Adjustments not made	There were no significant differences between singletons and twins in MDI and PDI scores. There was also no significant differences in the proportion of children with CP among singletons and twins.

TABLE 2
Continued

Author	Risk of bias: Recruitment strategy	Risk of bias: Study design	Risk of bias: Measure of neurodevelopmental outcomes	Risk of bias: Information on validation, reproducibility, and sensitivity analysis	Other factors: Method of analysis and statistical approach	Other factors: Variables that were adjusted for	Other factors: Measurement of magnitude of difference
Gnanendran et al. (2015)	Pre-mature infants in 10 Intensive care units (ICUs) between 1 January 1998 and 31 December 2004 were followed-up.	Longitudinal follow-up study	Bayley Scales of Infant Development II (15% of children) or the Griffiths Mental Developmental Scales (85% of children).	497 infants were lost to follow-up.	Multiple logistic regression analysis was performed.	Adjustments were made using significant confounding factors such as Apgar scores, antenatal corticosteroids, pregnancy-induced hypertension, outborn status, gender, gestational age, assisted conception, postnatal corticosteroids, and birth weight.	Moderate-to-severe functional disability of singletons and multiples at 2–3 years of corrected age did not differ significantly. Stratification by GA showed that disability rate was higher in the 2–26 weeks' GA group compared with the 27–28 weeks' GA group and it was higher among multiples compared to singletons.
Hjern et al. (2012)	The study was based on routinely collected data from Swedish National Registers held by Statistics Sweden, National Board of Health and Welfare.	Cross-sectional study	Data were collected from the National School Register on grade point averages at the time of leaving the compulsory primary school (usually at 15–16 years of age). Test scores from the 'Enlistment battery 80' from military conscription at 18–19 years was used to create indicator of IQ for men.	Nil	Outcome variables (GPA and IQ) were compared in gender stratified univariate analysis among twins and singletons. Twins were further compared with their singleton siblings using generalized estimated equation. Mean GPA were also analyzed in a multivariate linear regression model.	All analysis adjusted for birth order and gender. Gender differences were in effect estimated by introducing interaction terms in the analyses that included both genders. Adjustment for GA, single-parent household, having an older sibling and maternal age was also made when analyzing mean GPA in multivariate linear regression model.	Twins had slightly better mean GPAs in ninth grade and more often had completed a university education in young adulthood compared with singletons. Male twins had higher mean GPA but lower test scores compared with individuals born as singletons while twin females had slightly higher GPAs compared with female singletons.

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TABLE 2
Continued

	Risk of bias				Other factors		
Author	Recruitment strategy	Study design	Measure of neurodevelopmental outcomes	Information on validation, reproducibility, and sensitivity analysis	Method of analysis and statistical approach	Variables that were adjusted for	Measurement of magnitude of difference
Manuck et al. (2014)	This was a secondary analysis of a multi-center randomized controlled trial.	Randomized controlled trial	CP assessed by pediatricians and pediatric neurologists with further use of Gross Motor Function Classification System to assess CP severity when present Bayley II Scales of Infant Development MDI and PDI were used to assess Cognitive development. Childhood neurodevelopmental impairment was defined as moderate/severe CP and/or Bayley MDI and/or PDI scores >2 *SD* below the mean.	Nil	Univariate analysis was conducted using χ^2 and Student's *t* test. Multiple logistic regression models and area under receiver operating characteristic curves (AUC) were also utilized.	GA at delivery, maternal education, maternal race/ethnicity, maternal use of tobacco, alcohol, and/or drugs during pregnancy, treatment group assignment (e.g., magnesium sulfate vs. placebo), fetal sex, and chorioamnitis.	Rates of neurodevelopmental impairment at age 2 were similar among twins and singletons. The predictive value of the number of neonatal diagnoses in determining neurodevelopmental outcomes in twins was similar to the overall group analysis.
Hur and Lynn (2013)	Participants recruited in the capital city of Nigeria and neighboring states from secondary schools (equivalent of middle and high schools in the United States).	Cross-sectional study	SPM+ is a measure of general ability. This is a non-verbal measure useful for children aged 7 years and above. MHV is a verbal measure of general ability.	The internal consistency reliability of 60 items of the SPM+ was 0.90 and that for MHV was 0.76.	Structural-equation model-fitting analyses and Mx maximum likelihood analysis were performed.	School environment, neighboring characteristics, sex and age were adjusted for.	Mean scores for singletons were consistently higher than that of twins.
Raz et al. (2016)	Pre-term twins and singletons born at <34 weeks and followed-up until pre-school age.	Cross-sectional	Memory skills were assessed using Woodcock–Johnson (W–J) III Tests of Cognitive Abilities. Language skills assessed using Preschool Language Scale. Visual processing assessed using W–J III Picture Recognition sub-test. Motor skill assessed using the Peabody Developmental Motor Scales (PDMS-2; Folio and Fewell, 2000).	Construct reliability estimates of W–J III tests reveals that the values for most constructs reach the minimum threshold for acceptability.	Multivariable regression analyses were carried out with the predictor variable being multiplicity (twins versus singletons).	Birth weight, intrauterine growth score, *z* score, total complication score. GA and birth weight were highly correlated so birth weight was selected as a proxy for both birth weight and gestational age.	Twins had a lower global language performance compared to twins. Twins also had a lower visual processing skill compared to singletons.

Note: IUGR = intrauterine growth retardation, CP = cerebral palsy, GA = Gestational age, MDI = Mental Development Index, PDI = Psychomotor Development Index, AUC = area under receiver operating characteristic curve, SPM+ = Standard Progressive Matrices-plus, MHV = Mill-Hill vocabulary scale.

TABLE 3

Ranking of Papers Based on Sample Size, Study Design, Instrument, and Adjusted Variables

Author	Sample size	Study design	Instrument	Adjusted variables	Total	Ranking
Bodeau-Livinec et al. (2013)	7	4	8	5	24	2
De Zeeuw et al. (2012)	5	4	1	2	12	7
Eras et al. (2013)	2	4	8	0	14	5
Gnanendran et al. (2015)	4	4	4	9	21	3
Hjern et al. (2012)	8	1	1	6	16	4
Manuck et al. (2014)	6	8	8	8	30	1
Hur and Lynn (2013)	3	1	1	4	9	8
Raz et al. (2016)	1	1	8	3	13	6

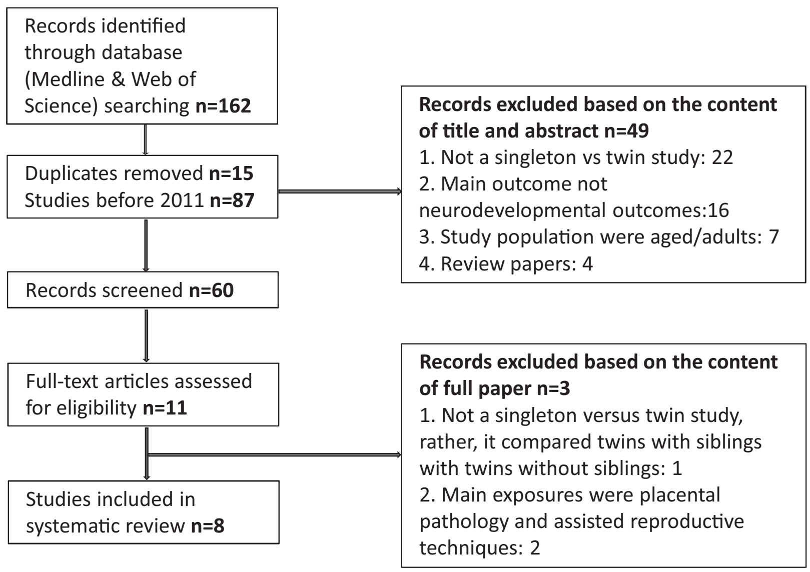

FIGURE 1

PRISMA flow diagram of search and manuscript review.

moderate/severe cerebral palsy and/or Bayley scores >2 standard deviations below the mean. This study showed that rates of neurodevelopmental impairment at 2 years of age were similar among twins and singletons. The study by Bodeau-Livinec et al. (2013) was ranked second. In this study, researchers examined the records of very pre-term live births occurring from 22 to 32 weeks of gestation in all maternity wards in nine French regions in 1997. They found that twins were more likely to have lower Mental Processing Composite scores (mean difference: −2.4 (95% CI [−4.8, 0.01]) at 5 years of age.

We ranked the Gnanendran et al. (2015) study third. The researchers conducted a population-based retrospective cohort study of the neurodevelopmental outcomes of multiple (twins, triplets, and quads) compared with singleton extremely pre-term infants who were younger than 29 weeks at gestation at a network of 10 neonatal intensive care units in Australia. They found that pre-mature infants from multiple gestation pregnancies had comparable neurodevelopmental outcomes to singletons. Hjern et al. (2012) ranked fourth in our study. In contrast to the three previous studies that were in pre-term children, this study was based on the national birth cohorts (1973–1981) in the Swedish Medical Birth Register; therefore, it contained children of all range of gestational ages. This study showed that Swedish male and female twins had slightly higher mean grade points in primary school compared with singletons, while male twins had slightly lower scores on IQ tests at military conscription at 18–19 years of age. The studies by Eras et al. (2013) and Raz et al. (2016) were ranked 5th and 6th, respectively. Eras et al. conducted a prospective study of pre-term infants ($\leq$32 weeks gestational age) and examined them for moderate or severe cerebral palsy, and severe bilateral hearing loss or bilateral blindness at 12 to 18 months of age They also used the MDI and PDI scores to determine neurodevelopment, but did not find significant differences between singletons and twins in MDI or PDI. In contrast, Raz et al., in a study of pre-term (<34 gestational weeks) twins and singletons who were evaluated at pre-school age, using standardized tests of memory, language, perceptual, and motor

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abilities, found that twins had a lower global language performance and lower visual processing skills compared with singletons.

Singletons had significantly higher academic ratings than twins in the other two studies (de Zeeuw et al., 2012; Hur & Lynn, 2013). de Zeeuw et al. (2012) studied twins and their non-twin siblings registered with the Netherlands Twin Register and rated their proficiency in arithmetic, language, reading, physical education, and a national educational achievement test score (CITO). They found that twins had significantly lower ratings on arithmetic, reading, and language compared to singletons, but most of these effects could largely be explained by birth order within families. Hur and Lynn (2013) studied cognitive abilities in twins and singletons aged between 9 and 20 years from over 45 public schools in Nigeria using Standard Progressive Matrices-Plus Version and the Mill-Hill Vocabulary Scale. They found that singletons did better than twins across all the tests. They speculated that these differences may be due to malnutrition, poor health, and the educational systems in Nigeria but did not clarify how these would have differential effects on twins.

Discussion

We identified eight articles published between 2011 and March 2017 that compared neurodevelopmental outcomes of twins and singletons. Of the eight articles, five showed that there was no significant difference in neurodevelopmental outcomes between twins and singletons (Bodeau-Livinec et al., 2013; Eras et al., 2013; Gnanendran et al., 2015; Hjern et al., 2012; Manuck et al., 2014), while two showed that singletons had better academic outcomes than twins (de Zeeuw et al., 2012; Hur & Lynn, 2013). We did not conduct a meta-analysis because eight articles were too few and the studies used different study populations and instruments to measure neurodevelopmental outcomes. We restricted our studies to 2011–2017 because Lorenz had previously reviewed publications up to 2010 (Lorenz, 2012).

Lorenz (2012) found that studies that did not adjust for gestational age and birth weight tended to report worse neurodevelopmental outcomes among twins compared to singletons. Two of the studies in this review adjusted for birth weight and gestational age (de Zeeuw et al., 2012; Gnanendran et al., 2015). In one study of pre-term infants, there was no difference between twins and singletons in functional disability measured at 3 years of age (Gnanendran et al., 2015). The other study, based on a twins' cohort, found that singletons had significantly higher ratings in arithmetic, language, and reading measured at the age of 7 years (de Zeeuw et al., 2012). Two studies of pre-term singletons and twins adjusted for gestational age but not birth weight and did not find any difference in neurodevelopmental outcomes (Bodeau-Livinec et al., 2010; Manuck et al., 2014). Three studies did not adjust for gestational age or birth weight (Eras et al., 2013; Hjern et al., 2012; Hur & Lynn, 2013) and one showed no difference (Eras et al., 2013), while two showed a better neurodevelopmental outcome among singletons (Hjern et al., 2012; Hur & Lynn, 2013). Comparison of these results is challenging because of differences in the study population, study designs, number of covariates measured, and how neurobehavioral outcomes were measured. Studies with adequate power, better measurements of exposure, covariates, and neurodevelopmental outcomes are required in order to resolve these conflicting results.

In four of the studies reviewed, we found that measurement of twin–singleton neurodevelopmental outcomes between 1 and 5 years of age tended to show no differences compared to measurements done between age 7 to teenage years (Bodeau-Livinec et al., 2013; de Zeeuw et al., 2012; Eras et al., 2013; Gnanendran et al., 2015; Hjern et al., 2012; Hur & Lynn, 2013; Manuck et al., 2014). This is contrary to expectation because previous studies suggest that the neurodevelopment of twins catches up with that of singletons over time and any differences found in early life tends to disappear as the children grow older (Bodeau-Livinec et al., 2013). This finding suggests that future studies of neurodevelopment of twins and singletons should extend for a longer period and use instruments appropriate for different ages.

Some of the studies in this review adjusted for important covariates, such as gestational age at delivery (Bodeau-Livinec et al., 2010; Gnanendran et al., 2015; Hjern et al., 2012), gender (Bodeau-Livinec et al., 2010; Gnanendran et al., 2015; Hjern et al., 2012; Manuck et al., 2014), intrauterine growth retardation (IUGR; Bodeau-Livinec et al., 2013), maternal socio-demographic factors (i.e., maternal age at birth, maternal education, maternal birthplace, and family social class; Bodeau-Livinec et al. (2013), Hjern et al. (2012), and Manuck et al. (2014)), Apgar score (Gnanendran et al., 2015), pregnancy-induced hypertension (Gnanendran et al., 2015), assisted conception (Gnanendran et al., 2015), birth weight (Gnanendran et al., 2015), having an older sibling (Hjern et al., 2012), maternal tobacco use and chorioamnionitis (Manuck et al., 2014), others did not. Future studies should measure all covariates that may be associated with neurodevelopment and adjust for them.

The two studies that ranked lowest in our scores utilized educational attainment of children as an outcome variable (de Zeeuw et al., 2012; Hur & Lynn, 2013). They found higher levels of neurodevelopmental outcome among singletons compared to twins. The study by Hur and Lynn (2013) was the only study conducted in a developing country, and it questioned whether findings of differences in neurodevelopment among singletons and twins seen in those countries today are a reflection of socio-economic development that is similar to that of developed countries many years ago. Twins in developed countries may be able to catch up in early childhood because of better medical services, a high-quality educational system, and good diet (Calvin et al., 2009; Christensen et al., 2006; Webbink et al., 2008). This is in line with the findings by Record et al. (1970) that differences in cognitive development between singletons and twins are more likely due to postnatal factors.

Our study highlighted the paucity of research on neurodevelopmental outcomes of twins and singletons from developing countries where the burden of neurodevelopmental disorders is highest and twinning incidence is very high (Akinboro et al., 2008; Grantham-McGregor et al., 2007; Igberase et al., 2008; Mosuro et al., 2001). It also showed the marked variations in study design, duration of follow-up, and covariate measurements that make interpretation of findings quite challenging (Bodeau-Livinec et al., 2013; de Zeeuw et al., 2012; Eras et al., 2013; Gnanendran et al., 2015). Future research in this area needs to adopt a more uniform way of assessing exposures, covariates, and neurodevelopmental outcomes among twins and singletons.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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