Neurocognitive function of 10 year-old multiples born less than 28 weeks gestational age

J. Wells Logan[a], **Elizabeth N. Allred**[b,c], **Michael E. Msall**[d], **Robert M. Joseph**[e], **T. Michael O'Shea**[f], **Timothy Heeren**[g], **Alan Leviton**[b,c], **Karl C. K. Kuban**[h], and **ELGAN Study Investigators**

[a]Department of Pediatrics, Nationwide Children's Hospital, The Ohio State University College of Medicine, Columbus, OH

[b]Harvard Medical School, Boston, MA

[c]Boston Children's Hospital, Boston, MA

[d]Developmental and Behavioral Pediatrics, University of Chicago Comer Children's Hospital; JP Kennedy Research Center on Intellectual and Developmental Disabilities, Chicago, Illinois.

[e]Department of Anatomy and Neurobiology, Boston University School of Medicine, Boston, MA

[f]Department of Pediatrics and Neonatology, University of North Carolina, Chapel Hill, NC

[g]Department of Biostatistics, Boston University School of Public Health, Boston, MA.

Corresponding author: J. Wells Logan, MD, Department of Pediatrics and Neonatology, Nationwide Children's Hospital, The Ohio State University College of Medicine, Columbus, OH 43205, JWells.Logan@NationwideChildrens.org, Phone: 614-722-4559, Fax: 614-722-4541.

Boston Children's Hospital, Boston MA
Janice Ware, Taryn Coster, Brandi Henson, Rachel Wilson, Kirsten McGhee, Patricia Lee, Aimee Asgarian, Anjali Sadhwani
Tufts Medical Center, Boston MA
Ellen Perrin, Emily Neger, Kathryn Mattern, Jenifer Walkowiak, Susan Barron
University of Massachusetts Medical School, Worcester MA
Jean Frazier, Lauren Venuti, Beth Powers, Ann Foley, Brian Dessureau, Molly Wood, Jill Damon-Minow
Yale University School of Medicine, New Haven, CT
Richard Ehrenkranz, Jennifer Benjamin, Elaine Romano, Kathy Tsatsanis, Katarzyna Chawarska, Sophy Kim, Susan Dieterich, Karen Bearrs
Wake Forest University Baptist Medical Center, Winston-Salem NC
T. Michael O'Shea, Nancy Peters, Patricia Brown, Emily Ansusinha, Ellen Waldrep, Jackie Friedman, Gail Hounshell, Debbie Allred
University Health Systems of Eastern Carolina, Greenville, NC
Stephen C. Engelke, Nancy Darden-Saad, Gary Stainback
North Carolina Children's Hospital, Chapel Hill, NC
Diane Warner, Janice Wereszczak, Janice Bernhardt, Joni McKeeman, Echo Meyer
Helen DeVos Children's Hospital, Grand Rapids, MI
Steve Pastyrnak, Wendy Burdo-Hartman, Julie Rathbun, Sarah Nota, Teri Crumb,
Sparrow Hospital, Lansing, MI
Madeleine Lenski, Deborah Weiland, Megan Lloyd
University of Chicago Medical Center, Chicago, IL
Scott Hunter, Michael Msall, Rugile Ramoskaite, Suzanne Wiggins, Krissy Washington, Ryan Martin, Barbara Prendergast, Megan Scott
William Beaumont Hospital, Royal Oak, MI
Judith Klarr, Beth Kring, Jennifer DeRidder, Kelly Vogt

hDepartment of Pediatrics, Division of Pediatric Neurology, Boston University School of Medicine, Boston, MA

Abstract

INTRODUCTION: Few studies have examined the relationship between birth plurality and neurocognitive function among children born extremely preterm.

STUDY DESIGN: We compared rates of Z-scores −2 on 18 tests of neurocognitive function and academic achievement at age 10 years in 245 children arising from twin pregnancies, 55 from triplet pregnancies, and 6 from a septuplet pregnancy to that of 568 singletons, all of whom were born before the 28th week of gestation.

RESULTS: 874 children were evaluated at age 10-years. After adjusting for confounders, children of multifetal pregnancies performed significantly better on one of 6 subtests of executive function than their singleton peers. Performance was similar on all other assessments of intelligence, language, academic achievement, processing speed, visual perception, and fine motor skills.

CONCLUSION: We found no evidence that children born of multifetal pregnancies had worse scores than their singleton peers on assessments of neurocognitive and academic function.

Keywords

Introduction

For decades, full-term twins were thought to have lower IQs than singletons.(1–4) More recent assessments, however, document only very small differences between twins and singletons,(5–7) suggesting that the "cognitive cost" of being a twin has diminished.(8) One explanation for this is that improvements in obstetric and neonatal care have mitigated the adverse consequences of being born to a multiple gestation pregnancy. Another interpretation is that over time, twinning has increasingly been the result of assisted reproductive technologies, which are more often utilized by women from higher socioeconomic categories, which, in turn, is associated with neurocognitve advantages.(9)

Large population-based cohorts have included preterm and low birthweight infants,(10, 11) but most studies exploring the association of birth plurality and neurocognitive function in children born very preterm have been confined to infants less than 4 years of age.(12–15) Roughly one-third of extremely preterm infants are products of a multiple gestation pregnancy;(16) yet to our knowledge there are no published studies exploring the risk of multiple gestation pregnancy and neurocognitive outcomes at school age. To see if what has been described among children of multi-fetal pregnancies born at or near term applies to children born extremely preterm, we used data from children born at less than 28 weeks and enrolled in the ELGAN Study who survived to 10 years of age. We compared measures of general cognitive ability, language, academic achievement, executive function, processing

speed, visual perception and fine motor function from children born of multifetal pregnancies to that of their singleton peers at 10 years of age.

METHODS

Participants

The ELGAN study is a multi-center prospective, observational study of the risk of structural and functional neurologic disorders in extremely preterm infants.(17) A total of 1506 infants born before the 28th week of gestation were enrolled during the years 2002-2004.[Table 1] Study participants were enrolled at 14 hospitals in the United States; neonates born alive at one of these hospitals were eligible for enrollment unless they had anencephaly. The sample size for this phase of the ELGAN study was chosen to ensure adequate power to detect associations between neonatal inflammation and cognitive impairment at 10 years of age. At age 10 years, 874 of these returned for an age-appropriate assessment of cognition, executive function, behaviors, and academic achievement. Enrollment and consent procedures for this follow up study were approved by the institutional review boards of all participating institutions.

Demographic and pregnancy variables

After delivery, a trained research nurse interviewed each mother in her native language using a structured data collection form and following procedures defined in a manual. Mothers reported their own pregnancy and prenatal characteristics and exposures. All mothers were asked, "Did you have any kind of infertility therapy to get pregnant this time (0=no, 1=yes)?" Those who answered "yes" were also asked the kind of assistance they received, including intrauterine insemination, ovulation-stimulant drugs (e.g., Clomiphene and Perganol), in vitro fertilization (IVF), assisted hatching, gamete intra fallopian transfer (GIFT), zygote intra fallopian transfer (ZIFT), and intra cytoplasmic sperm injection (ICSI).

Newborn variables

Gestational age estimates were based on a hierarchy of the quality of available information. Most desirable were estimates based on the dates of embryo retrieval, intrauterine insemination or fetal ultrasound before the 14th week (62%). When these were not available, reliance was placed sequentially on a fetal ultrasound at 14 or more weeks' gestation (29%), LMP without fetal ultrasound (7%), and gestational age recorded in the log of the neonatal intensive care unit (1%).

The birth weight Z-score is the number of standard deviations the infant's birth weight is above or below the median weight of infants at the same gestational age in referent samples not delivered for preeclampsia or fetal indications.(18, 19)

Follow-up procedures

We attempted to contact all families whose child/children were known to have survived to the 2 year follow-up by mail, and then by phone. Families that responded were invited to participate in the 10-year follow up. Lost-to-follow-up families were searched for on state

vaccination registries and other openly-available websites. Facebook was also used where approved by the local institution's Institutional Review Board (IRB).

Families willing to participate were scheduled for one visit during which all of the measures reported here were administered in 3 to 4 hours, including breaks. The assessments were selected to provide the most comprehensive information about neurocognitive and academic function in one testing session. Examiners were not aware of children's medical or educational history. While the child was tested, the parent or caregiver completed questionnaires regarding the child's medical and neurological status and behavior.

Neurocognitive measures at age 10 years

Neurocognitive function is rather complex outcome to measure, and there is no single test or composite outcome that is able to fully capture "neurocognitive function" in school-age children. Our analyses included seven measures of neurocognitive function in the hope of conveying a meaningful indicator of overall cognitive function: general cognitive ability, language, academic achievement, executive function, processing speed, visual perception, and fine motor function.

General cognitive ability.

General cognitive ability (or IQ) was assessed with the school-age differential ability scales-II (DAS-II) Verbal and Nonverbal Reasoning scales.(20) The DAS-II has several advantages for characterizing the wide range of IQ in a preterm sample, including more sensitive basal items than the Wechsler and other IQ scales, and extended standard scores (down to 25) for lower-ability individuals. In addition, the DAS nonverbal reasoning subtests require minimal visual-spatial processing and fine motor dexterity allowing measurement of nonverbal IQ in preterm children who have motor limitations.

Language ability.

Expressive and receptive language skills were evaluated with the Oral and Written Language Scales (OWLS), which assesses semantic, morphological, syntactic, and pragmatic production and comprehension of elaborated sentences.(21)

Academic Achievement

Academic achievement was assessed with the Wechsler Individual Achievement Test-III (WIAT-III). The WAIT-III is designed to assess a broad range of academic skills, but can be limited to specific areas in children aged 4 through adolescence. We assessed Word reading, Pseudoword decoding, Spelling, and Numeric operations.(22)

Executive function.

Attention and executive function were assessed with both the DAS-II and the NEPSY-II (A Developmental NEuroPSYchological Assessment-II).(23) The DAS-II Recall of Digits Backward and Recall of Sequential Order measures verbal working memory, while the NEPSY-II Auditory Attention and Response Set measures auditory attention, set switching and inhibition, and the NEPSY-II Inhibition subtests measure both simple inhibition

(Inhibition-Inhibition) and inhibition in the context of set switching (Inhibition-Switching). The NEPSY-II Animal Sorting subtest measures visual concept formation and set shifting.

Processing speed.

Speed of processing was assessed with NEPSY-II Inhibition-Naming, which provides a baseline measure of processing speed and has no inhibitory component.

Visual perception.

Visual perception was assessed using the Arrows and Geometric Puzzles components of NEPSY-II, which assesses mental rotation, visuospatial analysis, and attention to detail.

Fine motor function.

Visual motor function was assessed with the Visuomotor Precision and Fingertip Tapping components of NEPSY-II which assesses sensorimotor function and processing.

Data Analyses

Among children born less than 28 weeks gestation and survived to age 10 years, we evaluated the null hypothesis that those born of a multi-fetal pregnancy do not differ from their singleton peers on assessments of general cognitive ability, language, academic achievement, executive function, processing speed, visual perception and fine motor function.

We began by assessing correlates of multi-fetal gestation, including maternal demographic characteristics and newborn characteristics at birth. We then evaluated the overall distribution of IQ, language and academic achievement scores at age 10 years among children of a multi-fetal pregnancy and among singletons. Because we did not evaluate a full-term comparison group, we relied on comparisons to historical normative samples that are described by the authors of the assessments we used.(20, 21, 23) We used Z-scores to allow for differences in age at the time of the assessment. In our sample of extremely preterm infants, scores on most assessments of function had a larger number of children at the lower end of the distribution, prompting us to focus on those who had scores two or more standard deviations below the expected mean.

We focused analyses on scores that were 2 or more standard deviations below the normative mean for each assessment. While less prevalent than milder degrees of abnormality (e.g., scores 1 or more standard deviation below the normative mean), the outcome on which we focused has a considerably greater impact on the child's academic achievement and probability of gainful employment. We created logistic regression models of the risk of a score 2 or more standard deviations below the normative mean for each assessment comparing children of multi-fetal pregnancies to singletons. These models, which included variables for maternal education category (12, 13-15, 16+ years), gestational age category (23-24, 25-26, 27 weeks), sex, birth weight Z-score <−2, and clustering among multiples with a variance-covariance estimator that uses the number of pregnancies (568 singleton and 172 multifetal pregnancies) rather than the number of children (874), allowed us to calculate

odds ratios (and 95% confidence intervals). Odds ratios are significantly different from 1.0 (the null) at p < 0.05 when the 95% confidence intervals does not include 1.0.

Results

Sample of children of multi-fetal pregnancies evaluated at age 10-years (Figure 1)

874 children - 568 singletons, 245 twins from 149 pregnancies, 55 triplets from 22 pregnancies, and six children from one sextuplet pregnancy - were evaluated at a 10-year follow-up visit.

Characteristics of the mothers and their offspring (Table 1 and Figure 1)

Women who were white, older, married, better educated, and consumers of conception assistance services were more likely than others to have had two or more fetuses, and these differences were statistically significant for the mothers of offspring who did and did not undergo neurocognitive testing at age 10 years. Of the 740 pregnancies in the testing sample, 124 (17%) had some conception assistance and 109 (87%) received ovulation stimulation. While 12 of 22 (55%) mothers of triplets received an assisted technology procedure (*in vitro* fertilization or intracytoplasmic sperm injection), only 38 of 149 (26%) mothers of twins did (data not shown). Among children of a multi-fetal pregnancy receiving some conception assistance (N=153), more children underwent DAS-II testing (N=124) than not (N=29). And while pregnancies with an intra-uterine fetal demise (IUFD) or fetal death in the delivery room were uncommon, among those with surviving multiples at age 10 years, more pregnancies (N=13) had children that underwent a DAS-II assessment than those that did not (N=6).

There were essentially no differences in the characteristics of multifetal and singleton newborns except that infants born to a multifetal pregnancy were slightly less likely than singletons in the sample to be of lower gestational age. Nineteen percent of children in our sample had a birthweight Z-score < −2, 9% from multi-fetal pregnancies. Of the 1506 infants born less than 28 weeks gestational age and enrolled in the original ELGAN Study, 1198 survived to age 10 years and were eligible for follow-up. Of the 1198 eligible for follow-up, 874 (73%) infants from 740 pregnancies underwent DAS-II testing, 306/393 (78%) from multi-fetal pregnancies, and 568/802 (71%) from singleton pregnancies. In all, 245 twins, 55 triplets, and 6 sextuplets, for a total 306 infants from 172 pregnancies underwent DAS-II testing at age 10 years. Of the 1198 infants eligible for follow-up at age 10 years, 324/1198 (27%) did not undergo testing, 87 (7%) from multi-fetal pregnancies, and 237 (20%) from singleton pregnancies. There was no appreciable difference in either the maternal or neonatal characteristics of those who did and did not undergo neurocognitive testing.

Distribution of neurocognitive test scores among multiples at age 10 years (Table 2)

With one exception, children of multi-fetal pregnancies were slightly *less likely* than singletons to have intelligence, language and academic achievement scores one or more standard deviations below the expected mean (Z-score −1). For all but 1 subtest for academic achievement (WIAT-III Pseudoword decoding), differences in intelligence,

language, and academic achievement between children of multi-fetal and singleton pregnancies were not significant ($p > 0.05$).

Executive function assessments at age 10 (Table 3)

Low scores on assessments of executive function were generally not more common among children of multi-fetal pregnancies than among singletons. Scores two or more standard deviations below the expected mean (Z-score   −2) were more common on NEPSY-II Inhibition-Inhibition, Animal Sorting, and Inhibition-Naming among singletons than among children of multi-fetal gestations.

Box-and-whisker(24) plots showing the distribution of measures of neurocognitive and executive function at age 10 (Figure 2)

The distributions of scores on every assessment were lower than would be expected based on the distributions in the normative sample which are marked by the horizontal lines at Z-score values of 1, 0 and −1).

The top horizontal line of each box in Figure 1 represents the 75th centile, while the lowest horizontal line represents the 25th centile, and the middle line the 50th centile. The distributions of scores on every assessment were lower than would be expected based on the distributions in the normative sample.

Singletons and multiples had similar distributions of scores on NEPSY-II Geometric Puzzles, Inhibition-Switching, and Visuomotor Precision. On all other assessments, children of multi-fetal pregnancies tended to have modestly higher distributions (asterisk indicates significance with $p < 0.05$) than singletons in the sample.

Odds ratios and 95% confidence intervals of neurocognitive assessments (Table 4)

In the unadjusted analyses (first data column), the children born of multifetal pregnancies were at significantly reduced risk ($p < 0.05$) of Z-scores   −2 on the NEPSY-II Inhibition-Inhibition (OR 0.7; 95% CI 0.5, 0.98), Animal Sorting (OR 0.6; 95% CI 0.4, 0.8) and Inhibition-Switching (OR 0.6; 95% CI 0.4, 0.96) subtests compared to singleton children. When we adjusted for socioeconomic status variables--maternal education, non-white race, and single marital status (second data column) and for the SES variables plus male sex, gestational age, and birth weight Z-score < -2 (third data column), the multifetal children were no longer at significantly reduced risk of Z-scores   −2.

Discussion

In this sample of extremely preterm infants who survived to follow-up at age 10 years, we found no evidence that twins or triplets (who comprised 35% of this cohort) had worse neurocognitive outcomes than singletons born at the same gestational age. Our findings are consistent with the majority of follow-up studies that assessed children in the pre-school age period,(14, 15, 25, 26) but are in contrast to several prior population-based studies.(2–4, 10) Our findings suggest that the so called "cognitive cost" of being born a twin has diminished or that children born extremely preterm differ from those born at or near term. On the other

hand, our findings might reflect residual confounding associated with the social class differences between multi-fetal and singleton pregnancies.

Neurocognitive outcomes of multiples and singletons born at or near term

Overall, the literature is mixed with regard to differences in neurocognitive function between singletons and multiples born *at or near term*. Large population-based studies, dating back to the 1950's, demonstrated a disadvantage of as much as 4 to 5 IQ points among twins, when compared to singletons.(2–4, 10, 13, 27) Relatively recent population-based studies from the Netherlands,(11, 28) and Turkey,(25) however, suggests that twins born at or near term perform as well academically as singletons in adolescence.

Neurocognitive outcomes among twins born preterm

We found very few follow-up studies of multifetal gestation children born preterm,(12–15, 25, 26, 29) and we are not aware of any published studies comparing school-age neurocognitive function among multiples and singletons born extremely preterm. Twins might have a slight advantage over triplets.(26, 29) However, it is quite possible that social factors, such as maternal-infant interaction, which may be more challenging for parents of triplets, might contribute to these subtle differences.(26) Nonetheless, only one study has demonstrated an increased risk of neurodevelopmental impairments among twins at pre-school age follow-up.(12) One study demonstrated a small decrease in mental processing scores among twins compared to singletons,(13) but the majority of published studies that followed preterm twins have found no association between multifetal gestation and neurocognitive dysfunction at preschool age follow-up.(14, 15, 25, 26)

Possible explanations for our findings

The most likely explanation for our finding, and that of the majority of published studies, is that having a twin really does not place an ELGAN at greater risk of neurocognitive dysfunction than that of a singleton born at the same gestational age. Higher socioeconomic status was associated with multi-fetal pregnancy in our cohort, which might explain why infants of multifetal pregnancy had a slight, but non-significant, advantage over singletons.

The association between family socioeconomic status and cognitive development, especially among children born preterm, is well-documented.(30–32) Improvements in neurocognitive abilities among extremely preterm survivors over time are potentially related to a shift in the demographic characteristics of twins and higher-order multiples, and perhaps to advances in care (neonatal resuscitation, respiratory management, nutrition, and prevention of infection). In recent years, the increase in multi-fetal, dizygotic gestations among older women and women of higher socio-economic status suggests that twins and triplets are now born to older, better educated, and more financially secure women than ever before.(33–35) Consequently, twins and triplets born in recent years are not comparable to twins and triplets born decades ago.

Caring for multiples can be exhausting, regardless of socioeconomic status, but this may be especially so for families with limited socioeconomic and family support systems.(36, 37) Families from higher socioeconomic strata are less vulnerable to these challenges, as they

are better able to obtain the needed support, and generally live in less chaotic home environments. We adjusted for three levels of maternal education (12, 13-15, and 16 years), our main indicator of socioeconomic status, in the hope that this would minimize confounding.

The overall lower neurocognitive scores of children born extremely preterm highlights the need for appropriate educational resources to achieve optimal outcome is important. However, our findings should provide some reassurance, to parents and obstetricians alike, that multi-fetal pregnancy, even among infants born extremely preterm, is not associated with neurocognitive dysfunction at long-term follow-up.

Strengths of our study

One of the most important strengths of our study is that we evaluated a large, multicenter cohort of singletons, twins, and higher-order multiples born extremely preterm. The relatively large number of children provides power, while the inborn status removes the potential contribution of adversities encountered at small, low-volume centers, or centers less than optimally equipped to care for extremely preterm newborns (regardless of gestation).(38) In addition, we included potentially important confounders in logistic regressions, including gestational age, an indicator of fetal growth restriction, and maternal education. Finally, ascertainment bias was eliminated by blinding each infants medical history from those conducting evaluations of functional neurologic status.

Limitations of our study

The chief limitation of our study, like that of all observational studies, is that we are unable to make inferences about causation. Because of the close association between social class and receipt of conception assistance resulting in a multifetal gestation, our adjusting for three levels of education might not have eliminated all confounding. A third limitation is that we did not collect information about zygosity or chorionicity. Since no association was found between twinning and prematurity, regardless of chorionicity or the use of assistive reproductive technology, we suspect that this limitation has little bearing on our conclusions. Overall, the published literature is mixed as to whether multiples born after assistive reproductive technology are at increased risk of neurocognitive deficits at follow-up.(39–41) We are not aware of such a study in ELGANs, nor are we aware of any follow-up study of ELGANs born to women who took an ovulatory stimulant only.

Conclusion

In this large, multicenter cohort of singletons, twins, and higher-order multiples born extremely preterm, in which 80% of the mothers received an ovulation stimulant before pregnancy, we found no evidence that twins or triplets had any diminution of neurocognitive function at age 10 years. After adjusting for confounders, children born less than 28 weeks gestational age to a multi-fetal pregnancy, who survived to age 10 years (35% of the cohort), were similar to those of singletons on assessments of neurodevelopment in 7 neurocognitive domains.

Acknowledgements

References:

1. Deary IJ, Pattie A, Wilson V, Whalley LJ. The cognitive cost of being a twin: two whole-population surveys. Twin research and human genetics : the official journal of the International Society for Twin Studies 2005;8(4):376–83. [PubMed: 16176723]

2. Ronalds GA, De Stavola BL, Leon DA. The cognitive cost of being a twin: evidence from comparisons within families in the Aberdeen children of the 1950s cohort study. BMJ 2005;331(7528):1306. [PubMed: 16299014]

3. Silventoinen K, Myrskyla M, Tynelius P, Yokoyama Y, Rasmussen F. Social Modifications of the Multiple Birth Effect on IQ and Body Size: a Population-Based Study of Young Adult Males. Paediatr Perinat Ep 2013;27(4):380–7.

4. Voracek M, Haubner T. Twin-singleton differences in intelligence: a meta-analysis. Psychological reports 2008;102(3):951–62. [PubMed: 18763469]

5. Calvin C, Fernandes C, Smith P, Visscher PM, Deary IJ. Is there still a cognitive cost of being a twin in the UK? Intelligence 2009;37(3):243–8.

6. Eriksen W, Sundet JM, Tambs K. Twin-Singleton Differences in Intelligence: A Register-Based Birth Cohort Study of Norwegian Males. Twin Research and Human Genetics 2012;15(5):649–55. [PubMed: 22877999]

7. Webbink D, Posthuma D, Boomsma DI, de Geus EJC, Visscher PM. Do twins have lower cognitive ability than singletons? Intelligence 2008;36(6):539–47.

8. Deary IJ. Intelligence. Annu Rev Psychol 2012;63:453–82. [PubMed: 21943169]

9. Chambers GM, Hoang VP, Illingworth PJ. Socioeconomic disparities in access to ART treatment and the differential impact of a policy that increased consumer costs. Hum Reprod 2013;28(11): 3111–7. [PubMed: 23906901]

10. Record RG, McKeown T, Edwards JH. An investigation of the difference in measured intelligence between twins and single births. Annals of human genetics 1970;34(1):11–20. [PubMed: 5529232]

11. Christensen K, Petersen I, Skytthe A, Herskind AM, McGue M, Bingley P. Comparison of academic performance of twins and singletons in adolescence: follow-up study. BMJ 2006;333(7578):1095. [PubMed: 17012267]

12. Wadhawan R, Oh W, Perritt RL, McDonald SA, Das A, Poole WK, et al. Twin gestation and neurodevelopmental outcome in extremely low birth weight infants. Pediatrics 2009;123(2):e220–7. [PubMed: 19139085]

13. Bodeau-Livinec F, Zeitlin J, Blondel B, Arnaud C, Fresson J, Burguet A, et al. Do very preterm twins and singletons differ in their neurodevelopment at 5 years of age? Arch Dis Child-Fetal 2013;98(6):F480–F7.

14. Gnanendran L, Bajuk B, Oei J, Lui K, Abdel-Latif ME. Neurodevelopmental outcomes of preterm singletons, twins and higher-order gestations: a population-based cohort study. Archives of disease in childhood. Fetal and neonatal edition 2015;100(2):F106–14. [PubMed: 25359876]

15. Yee WH, Hicks M, Chen S, Christianson H, Sauve R. Triplet infants with birthweight < or = 1250 grams: how well do they compare with twin and singleton infants at 36 to 48 months of age? American journal of perinatology 2008;25(6):373–80. [PubMed: 18521776]

16. McElrath TF, Hecht JL, Dammann O, Boggess K, Onderdonk A, Markenson G, et al. Pregnancy disorders that lead to delivery before the 28th week of gestation: an epidemiologic approach to classification. American journal of epidemiology 2008;168(9):980–9. [PubMed: 18756014]

17. O'Shea TM, Allred EN, Dammann O, Hirtz D, Kuban KC, Paneth N, et al. The ELGAN study of the brain and related disorders in extremely low gestational age newborns. Early human development 2009;85(11):719–25. [PubMed: 19765918]

18. Yudkin PL, Aboualfa M, Eyre JA, Redman CW, Wilkinson AR. New birthweight and head circumference centiles for gestational ages 24 to 42 weeks. Early human development 1987;15(1): 45–52. [PubMed: 3816638]

19. Leviton A, Paneth N, Reuss ML, Susser M, Allred EN, Dammann O, et al. Maternal infection, fetal inflammatory response, and brain damage in very low birth weight infants. Developmental Epidemiology Network Investigators. Pediatric research 1999;46(5):566–75. [PubMed: 10541320]

20. Elliott CD. Differential Ability Scales. 2nd ed San Antonio, TX: Pearson; 2007.

21. Carrow-Woolfolk E Oral and Written Language Scales: Written Expression Scale Manual. Circle Pines, MN: American Guidance Service; 1996.

22. Wechsler D Wechsler Individual Achievement Test-III. United Kingdom: Pearson Assessment; 2009.

23. Korkman M, Kemp S. NEPSY: A Developmental Neuropsychological Assessment New York, New York: The Psychological Corporation; 1998.

24. Tukey JW. Exploratory Data Analysis. 6th ed Reading, MA: Addison-Wesley Co; 1977.

25. Eras Z, Ozyurt BM, Kanmaz G, Erdeve O, Sakrucu ED, Oguz SS, et al. Neurodevelopmental outcome among multiples and singletons: a regional neonatal intensive care unit's experience in Turkey. Twin research and human genetics : the official journal of the International Society for Twin Studies 2013;16(2):614–8. [PubMed: 23331543]

26. Feldman R, Eidelman AI. Does a triplet birth pose a special risk for infant development? Assessing cognitive development in relation to intrauterine growth and mother-infant interaction across the first 2 years. Pediatrics 2005;115(2):443–52. [PubMed: 15687454]

27. Lorenz JM. Neurodevelopmental outcomes of twins. Seminars in perinatology 2012;36(3):201–12. [PubMed: 22713502]

28. Posthuma D, De Geus EJ, Bleichrodt N, Boomsma DI. Twin-singleton differences in intelligence? Twin research : the official journal of the International Society for Twin Studies 2000;3(2):83–7. [PubMed: 10918620]

29. Wadhawan R, Oh W, Vohr BR, Wrage L, Das A, Bell EF, et al. Neurodevelopmental outcomes of triplets or higher-order extremely low birth weight infants. Pediatrics 2011;127(3):e654–60. [PubMed: 21357334]

30. Ford RM, Neulinger K, O'Callaghan M, Mohay H, Gray P, Shum D. Executive function in 7–9-year-old children born extremely preterm or with extremely low birth weight: effects of biomedical history, age at assessment, and socioeconomic status. Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists 2011;26(7):632–44. [PubMed: 21816952]

31. Wong HS, Edwards P. Nature or nurture: a systematic review of the effect of socio-economic status on the developmental and cognitive outcomes of children born preterm. Maternal and child health journal 2013;17(9):1689–700. [PubMed: 23135625]

32. Feldman R, Eidelman AI, Rotenberg N. Parenting stress, infant emotion regulation, maternal sensitivity, and the cognitive development of triplets: a model for parent and child influences in a unique ecology. Child development 2004;75(6):1774–91. [PubMed: 15566379]

33. Bortolus R, Parazzini F, Chatenoud L, Benzi G, Bianchi MM, Marini A. The epidemiology of multiple births. Human reproduction update 1999;5(2):179–87. [PubMed: 10336022]

34. Ooki S Effect of maternal age and fertility treatment on the increase in multiple births in Japan: vital statistics, 1974–2009. Journal of epidemiology 2011;21(6):507–11. [PubMed: 22001542]

35. Dawson AL, Tinker SC, Jamieson DJ, Hobbs CA, Rasmussen SA, Reefhuis J. Epidemiology of twinning in the National Birth Defects Prevention Study, 1997 to 2007. Birth defects research. Part A, Clinical and molecular teratology 2015;103(2):85–99. [PubMed: 25359509]

36. Feldman R, Eidelman AI. Parent-infant synchrony and the social-emotional development of triplets. Developmental psychology 2004;40(6):1133–47. [PubMed: 15535762]

37. Manley BJ, Roberts RS, Doyle LW, Schmidt B, Anderson PJ, Barrington KJ, et al. Social variables predict gains in cognitive scores across the preschool years in children with birth weights 500 to 1250 grams. The Journal of pediatrics 2015;166(4):870–6 e1–2. [PubMed: 25641237]

38. Phibbs CS, Baker LC, Caughey AB, Danielsen B, Schmitt SK, Phibbs RH. Level and volume of neonatal intensive care and mortality in very-low-birth-weight infants. The New England journal of medicine 2007;356(21):2165–75. [PubMed: 17522400]

39. Ludwig AK, Sutcliffe AG, Diedrich K, Ludwig M. Post-neonatal health and development of children born after assisted reproduction: a systematic review of controlled studies. European journal of obstetrics, gynecology, and reproductive biology 2006;127(1):3–25.

40. D'Haeseleer E, Vanden Meerschaut F, Bettens K, Luyten A, Gysels H, Thienpont Y, et al. Language development of children born following intracytoplasmic sperm injection (ICSI) combined with assisted oocyte activation (AOA). International journal of language & communication disorders / Royal College of Speech & Language Therapists 2014;49(6):702–9.

41. Pinborg A, Loft A, Schmidt L, Greisen G, Rasmussen S, Andersen AN. Neurological sequelae in twins born after assisted conception: controlled national cohort study. Brit Med J 2004;329(7461): 311–4B. [PubMed: 15256418]
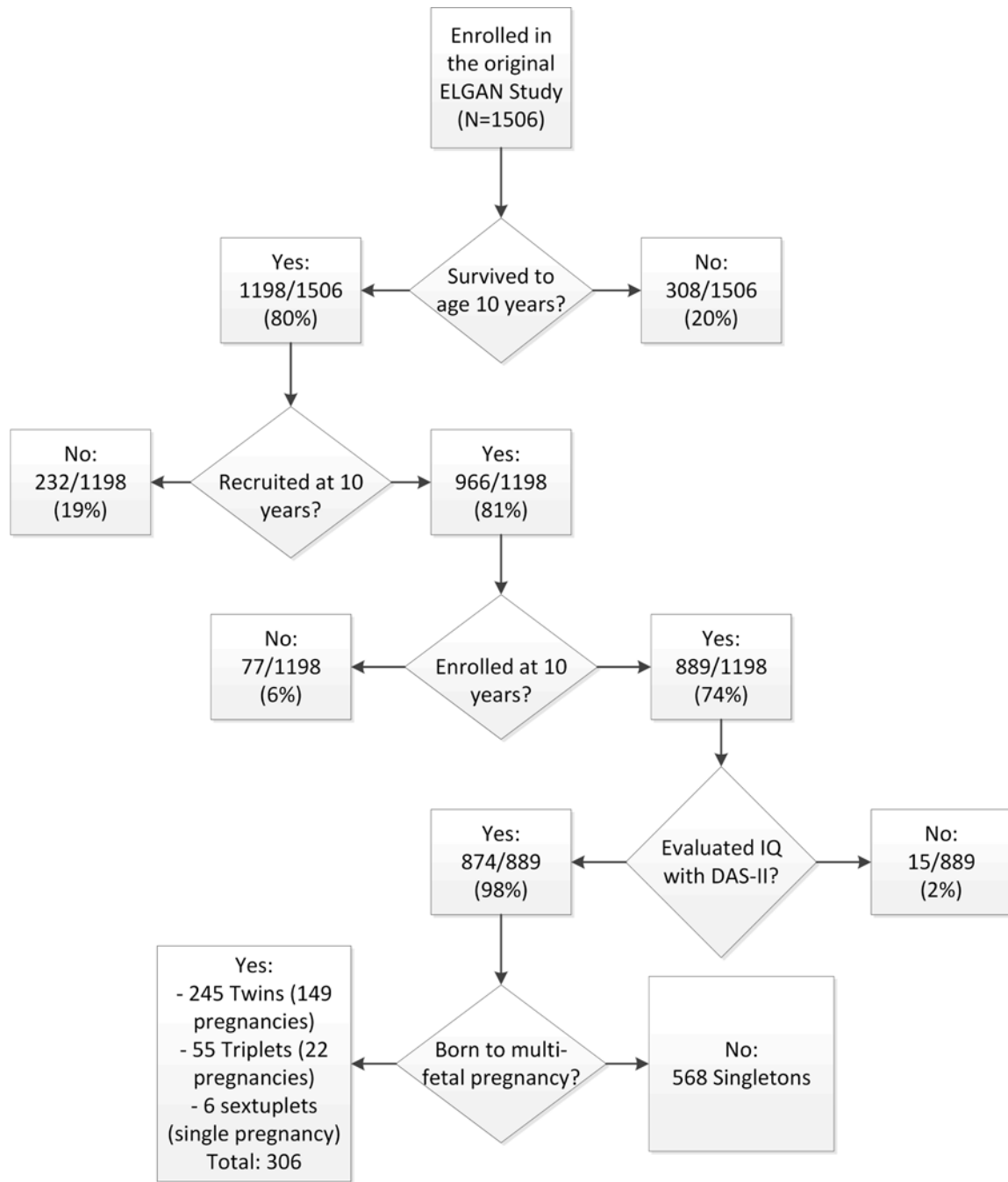
Figure 1.
Sample description. Children from multifetal and singleton pregnancies.
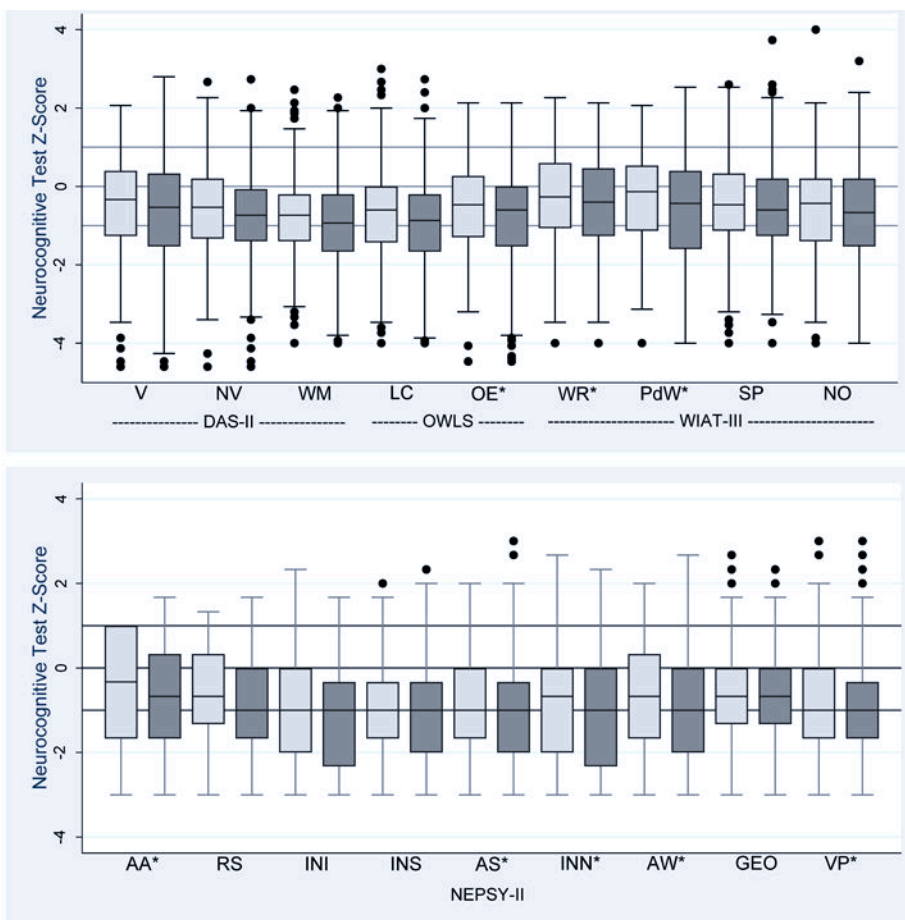
1   Lighter gray indicates multi-fetal pregnancy; darker gray indicates a singleton pregnancy. The horizontal line at the top of each box in Figure 2 represents the 75th centile, while the horizontal line at the bottom represents the 25th centile, and the line in the middle represents the 50th centile.

*   Median of stubtest for multiples and singletons are significantly different, p < 0.05 (Kruskal-Wallis test)

V	Verbal component of the Differential Ability Scales-II testing instrument (DAS-II)
NV	Non-Verbal component of the Differential Ability Scales-II testing instrument (DAS-II)
WM	Working Memory component of the Differential Ability Scales-II testing instrument (DAS-II)
LC	Listening Comprehension component of the Oral and Written Language Scales (OWLS)
WR	Word Reading component of the Wechsler Individual Achievement Test-III (WIAT-III)
PdW	Pseudoword component of the Wechsler Individual Achievement Test-III (WIAT-II
SP	Spelling component of the Wechsler Individual Achievement Test-III (WIAT-III)
NO	Numerical Operations component of the Wechsler Individual Achievement Test-III (WIAT-III)
AA	Auditory Attention components of NEPSY-II: A Developmental Neuropsycholigal Assessment-II
RS	Auditory Response of NEPSY-II: A Developmental Neuropsycholigal Assessment-II
INI	Inhibition-Inhibition of NEPSY-II: A Developmental Neuropsycholigal Assessment-II
INS	Inhibition-Switching of NEPSY-II: A Developmental Neuropsycholigal Assessment-II
AS	Animal Sorting of NEPSY-II: A Developmental Neuropsycholigal Assessment-II
INI	Inhibition-Naming of NEPSY-II: A Developmental Neuropsycholigal Assessment-II
AW	Arrows of NEPSY-II: A Developmental Neuropsycholigal Assessment-II
GEO	Geometric Puzzles of NEPSY-II: A Developmental Neuropsycholigal Assessment-II
VP	Visuomotor Perception of NEPSY-II: A Developmental Neuropsycholigal Assessment-II

Figure 2.

Box-and-whisker plots of each neurocognitive subtest by whether the pregnancy was multifetal or singleton.[1] All neurocognitive Z-scores are adjusted to population norms.*

Table 1.

Characteristics of mothers and children of multifetal and singleton pregnancies who survived to 10 years and had or did not have a DAS-II IQ assessment at 10 years. These are column percepts except where noted.

		DAS-II IQ at 10 years			No DAS-II IQ at 10 years		
		Pregnancies		**Row N**	**Pregnancies**		**Row N**
Maternal characteristics		**Multifetal**	**Singleton**		**Multifetal**	**Singleton**	
Racial identity	White	77*	56	450	73*	44	137
	Black	16	31	202	18	35	90
	Other	6	13	86	8	21	52
Hispanic	Yes	8	12	79	10*	22	57
Age, years	< 21	5*	18	108	12	20	53
	21–35	73	35	489	67	66	191
	> 35	22	18	143	22	14	44
Education, years	12	32*	47	321	43*	57	146
	> 12, < 16	24	23	174	21	25	65
	16	44	30	245	36	19	59
Single marital status	Yes	27*	48	316	35*	57	153
Public insurance	Yes	24*	43	281	33*	60	154
Any conception assistance	Yes	49*	7	124	43*	4	29
Ovulation stimulation [1]	Yes	87	90	109	85	89	25
Fetal/delivery room death of co-twin or triplet	Yes	8	----	13	12	---	6
Maximum column N		172	568	740	51	237	288
Row Percent		22	88		21	89	
		Infants		**Row N**	**Infants**		**Row N**
Newborn characteristics		**Multifetal**	**Singleton**		**Multifetal**	**Singleton**	
Sex	Male	50	52	446	49	56	175
Gestational age (weeks)	23-24	21*	21	180	18	21	65
	25–26	40	48	396	44	50	157
	27	40	31	298	38	29	102
Birth weight, grams	750	34	39	323	33	35	113
	751–1000	46	42	379	37	50	141
	> 1000	20	20	172	30	19	70
Birth weight Z-score	< −2	4	7	51	5	3	11
	−2, < −1	12	14	116	8	13	37
	−1	85	79	707	87	84	276
Maximum column N		306	568	874	87	237	324
Row Percent		35	65		37	63	

*
Comparing pairs of adjacent multiple and singleton columns, p < 0.05 (Fisher's exact test)

[1] Among those undergoing conception assistance

Table 2.

Percent of multifetal and singleton children who have Z-scores ≤ −2 or > −2 and ≤ −1 on the intelligence, language, and achievement test assessments at age 10 years listed on the left. These are column percents.[1]

IQ	Z-score	Newborns		Total N
		Multiples	Singletons	
DAS-II Verbal reasoning	≤ −2	14	19	150
	> −2, ≤ −1	18	19	163
DAS-II Nonverbal reasoning	≤ −2	14	15	130
	> −2, ≤ −1	24	25	213
Language				
OWLS Listening comprehension	≤ −2	16	20	161
	> −2, ≤ −1	24	29	231
OWLS Oral expression	≤ −2	18	20	165
	> −2, ≤ −1	20	23	190
Academic Achievement				
WIAT-III Word reading	≤ −2	10	14	106
	> −2, ≤ −1	15	19	149
WIAT-III Pseudoword decoding	≤ −2	12[*]	16	126
	> −2, ≤ −1	14	18	145
WIAT-III Spelling	≤ −2	11	11	95
	> −2, ≤ −1	14	17	136
WIAT-III Numeric operations	≤ −2	16	16	141
	> −2, ≤ −1	19	25	199
Maximum column N		306 (35%)	568 (65%)	874

[*] Comparing adjacent multiple and singleton columns, $p < 0.05$ (Fisher's exact test)

[1] The table depicts column percent's, but does not convey the portion of the sample with scores greater than −1 standard deviations below the normative mean.

Table 3.

Percent of multifetal and singleton children who have Z-scores ≤ −2 or > −2 and ≤ −1 on executive function, processing speed, and visual perception assessments at age 10 years listed on the left. These are column percents.[1]

Executive Function	Z-score	Multiples	Singletons	Row N
DAS-II Working memory	≤ −2	15	19	156
	> −2, ≤ −1	18	17	153
NEPSY-II Auditory attention	≤ −2	21[*]	24	190
	> −2, ≤ −1	17	23	177
NEPSY-II Auditory response set	≤ −2	17	22	169
	> −2, ≤ −1	25	29	235
NEPSY-II Inhibition-Inhibition	≤ −2	29	36	287
	> −2, ≤ −1	25	22	199
NEPSY-II Inhibition-Switching	≤ −2	24	29	230
	> −2, ≤ −1	29	29	243
NEPSY-II Animal sorting	≤ −2	22[*]	32	246
	> −2, ≤ −1	31	30	263
Processing Speed				
NEPSY-II Inhibition-Naming	≤ −2	26	34	267
	> −2, ≤ −1	21	19	171
Visual Perception				
NEPSY-II Arrows	≤ −2	23	27	225
	> −2, ≤ −1	21	23	195
NEPSY-II Geometric puzzles	≤ −2	17	17	143
	> −2, ≤ −1	24	21	192
Fine Motor Function				
NEPSY-II Visuomotor precision	≤ −2	17	22	178
	> −2, ≤ −1	34	35	302
Maximum column N		306 (35%)	568 (65%)	874

[*] Comparing adjacent multiple and singleton columns, $p < 0.05$ (Fisher's exact test)

[1] The table depicts column percent's, but does not convey the portion of the sample with scores greater than −1 standard deviations blow the normative mean.

Table 4.

Odds ratios (95% confidence intervals) of a Z-score ≤−2 on the assessment listed on the left for multifetal compared to singleton children. Odds rations that are significantly different from 1.0 are bold (p < 0.05).

	Odds Ratios (95% Confidence Intervals) for Z-scores ≤−2		
	Unadjusted	**SES adjustment**	**Full adjustment**
General cognitive ability			
DAS-II Verbal	0.6 (0.3, 1.1)	1.0 (0.5, 1.8)	1.1 (0.6, 1.9)
DAS-II Nonverbal Reasoning	0.8 (0.6, 1.4)	1.1 (0.7, 1.9)	1.2 (0.7, 2.0)
Language			
OWLS Listening comprehension	0.7 (0.5, 1.1)	1.0 (0.6, 1.6)	1.1 (0.7, 1.8)
OWLS Oral expression	0.8 (0.4, 1.4)	1.2 (0.7, 2.1)	1.3 (0.7, 2.2)
Academic Achievement			
WIAT-III Word reading	0.7 (0.4 1.2)	1.0 (0.6, 1.7)	1.1 (0.7, 1.8)
WIAT-III Pseudoword decoding	0.7 (0.4, 1.1)	1.0 (0.6, 1.5)	1.0 (0.7, 1.6)
WIAT-III Spelling	1.1 (0.6, 2.1)	1.5 (0.5, 2.8)	1.7 (0.9, 3.1)
WIAT-III Numeric operations	1.0 (0.6, 1.8)	1.5 (0.9, 2.7)	1.7 (0.95, 2.9)
Executive Function			
DAS-II Working Memory	0.7 (0.4, 1.2)	1.1 (0.6, 1.6)	1.1 (0.7, 1.8)
NEPSY-II Auditory Attention	0.8 (0.6, 1.2)	0.9 (0.6, 1.4)	1.0 (0.7, 1.4)
NEPSY-II Auditory Response	0.7 (0.5, 1.1)	0.9 (0.6, 1.3)	0.9 (0.6, 1.4)
NEPSY-II Inhibition-Inhibition	*0.7 (0.5, 0.98)*	0.8 (0.6, 1.3)	0.9 (0.6, 1.3)
NEPSY-II Inhibition-Switching	0.7 (0.5, 1.2)	1.0 (0.7, 1.6)	1.1 (0.7, 1.7)
NEPSY-II Animal Sorting	*0.6 (0.4, 0.8)*	0.8 (0.5, 1.1)	0.8 (0.6, 1.1)
Processing Speed			
NEPSY-II Inhibition-Naming	*0.6 (0.4, 0.96)*	0.8 (0.6, 1.2)	0.9 (0.6, 1.3)
Visual Perception			
NEPSY-II Arrows	0.8 (0.5, 1.2)	1.1 (0.7, 1.6)	1.2 (0.8, 1.7)
NEPSY-II Geometric Puzzles	1.0 (0.6, 1.6)	1.2 (0.7, 1.9)	1.2 (0.8, 2.0)
Fine Motor Function			
NEPSY-II Visuomotor Precision	0.7 (0.5, 1.1)	0.8 (0.5, 1.3)	0.9 (0.6, 1.4)
Maximum column N	874 children from 740 pregnancies		

[1]This table compares the proportion of multi-fetal pregnancies with Z-scores ≤−2 to that of singletons with a Z-score ≤−2. The first column includes unadjusted odds ratios, the second column includes odds ratios adjusted for socio-economic status (maternal education ≤12 and 13-15 years, non-white race, and single marital status) only, and the last column includes odds ratios adjusted for maternal education (≤12 and 13-15 years, non-white race, and single marital status)), gestational age category, sex, and birth weight Z-score <−2. All models account for correlation between children from the same pregnancy.