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Early life risk factors of motor, cognitive, and language development: a pooled analysis of studies from low-and middle-income countries

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Abbreviations:
AGA= Appropriate for gestational age
BSID=Bayley Scales of Infant and Toddler Development
IUGR= intra-uterine growth restriction
LBW= Low birth weight, <2500 grams
LMIC= Low-and-middle income countries
LMP= last menstrual period
ECD=Early childhood development
SDGs=Sustainable Development Goals
SMDs=standardized mean differences
SGA=Small-for-gestational age

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Authors' contributions:

Ayesha Sania conceptualized the study, conducted the literature review, data analysis and drafted the manuscript. Christopher Sudfeld, and Wafaie Fawzi conceptualized the study and drafted the manuscript. Goodarz Danaei, Günther Fink, Dana Charles McCoy, Mary C. Smith Fawzi and Majid Ezzati provided critical input in the study design, interpretation of results and reviewed the manuscript. Zhaozhong Zhu participated in literature review and data analysis for the study. Mehmet Akman, Shams Arifeen, Aluísio J. D. Barros, David Bellinger, Maureen Black, Alemtsehay Bogale, Joseph Braun, Nynke van den Broek, Verena Ilona Carrara, Paulita Duazo, Christopher P. Duggan, Lia Fernald, Melissa Gladstone, Jena Hamadani, Alexis J. Handal, Siobán Harlow, Melissa Hidrobo, Christopher W. Kuzawa, Ingrid Kvestad, Lindsey Locks, Karim Manji, Honorati Masanja, Alicia Matijasevich, Christine McDonald, Rose McGready, Arjumand Rizvi, Darci Santos, Leticia Santos, Dilsad Save, Roger Shapiro, Barbara J. Stoecker, Tor A. Strand, Sunita Taneja, Martha-Maria Tellez-Rojo, Fahmida Tofail, and Aisha K.Yousafzai contributed data to the study, analyzed data and reviewed the manuscript. All authors had full access to their respective study data and to all statistical reports and tables of the pooled analyses, and can take responsibility for the integrity of the data and accuracy of data analyses. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Abstract:

Objective: To determine the magnitude of relationships of early life factors with child development in LMICs.

Design: Meta-analyses of standardized mean differences (SMD) estimated from published and unpublished data.

Data sources: We searched Medline, bibliographies of key articles and reviews, and grey literature to identify studies from LMICs that collected data on early life exposures and child development. We then invited the first authors of the publications and investigators of unpublished studies to participate in the study.

Eligibility criteria for selecting studies: Studies that assessed at least one domain of child development in at least 100 children under 7 years of age, and collected at least one early life factor of interest were included in the study.

Analyses: Linear regression models were used to assess SMDs in child development by parental and child factors within each study. We then produced pooled estimates across studies using random effects meta-analyses.

Results: We retrieved data from 21 studies including 20,882 children across 13 LMICs, to assess the associations of exposure to 14 major risk factors with child development. Children of mothers with secondary schooling had 0.14 SD (95% Confidence Interval, CI: 0.05, 0.25) higher cognitive scores compared to children whose mothers had primary education. Preterm birth was associated with 0.14 SD (-0.24, -0.05) and 0.23 SD (-0.42, -0.03) reductions in cognitive and motor scores, respectively. Maternal short stature, anemia in infancy, and lack of access to clean water and sanitation had significant negative associations with cognitive and motor development with effects ranging from -0.18 to -0.10 SDs.

Conclusions: Differential parental, environmental, and nutritional factors contribute to disparities in child development across LMICs. Targeting these factors from pre-pregnancy through childhood may improve health and development of children.

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Strengths and Limitations of this study:

- Pooling data from 21 studies, this study provides the most comprehensive analysis of early life risk factors of child development in low-and middle-income countries
- The study cohorts were selected from 13 countries across the globe
- Uniform classifications of early life exposures and statistical analyses applied across studies
- 14 major risk factors, - parental, environmental and nutritional factors are included
- Data on important risk factors such as exposure to environmental neurotoxicants, responsive parenting behaviors, and child stimulation were not available

Introduction:

More than 250 million children under age 5 years in low-and middle-income countries (LMICs) are at risk of not attaining their full development potential.[1-3] The first 1000 days (from conception through 24 months of age) is critical for children's development, as the plasticity of the rapidly developing brain makes it vulnerable to harmful exposures as well as receptive to positive stimuli during this period.[4 5] Suboptimal development in early childhood may have long-term detrimental effects on education[6] and income attainment,[7] which in turn contribute to poverty and inequality across the lifecycle, and possibly also across generations.[8] Disadvantaged children with developmental deficits lose an estimated 19.8% of adult income yearly,[9] with an estimated global cost of US$ 177 billion for physical growth delays alone.[10] In recognition of the high burden and cost associated with early life disadvantage, the 2030 Sustainable Development Goals (SDGs) directly target early childhood development under SDG 4,[11] which calls for ensuring access to quality early childhood development care and pre-primary education for all children.

The relative importance of exposures to nutritional, socioeconomic and environmental risk factors in early life on different domains of child development in LMICs is poorly understood Studies systematically reviewing the evidence linking early life risk factors to child outcomes primarily focused on growth (e.g., stunting),[9 12] identifying iodine deficiency, iron deficiency anemia, intrauterine growth restriction, maternal depression, exposure to violence, HIV infection as risk factors, and cognitive stimulation, maternal education, breastfeeding as protective factors.[13 14] However, the independent pathways from these risks to cognitive, motor and language development are not fully elucidated yet.[15 16] Consequently, priority risk factors and

interventions for improving cognitive, language, and motor development may differ from those designed to improve physical development in LMICs.

To determine the magnitude of the relationships linking early life exposures with child development in LMICs, we pooled data from 21 studies conducted in LMICs. We then examined the associations of early life risk factors on cognitive, motor and language development among children aged less than 7 years across studies. These pooled observational estimates are intended to inform the design of individual and packaged intervention studies to promote early child development in LMICs.

Methods

Study identification:

We searched Medline, bibliographies of key articles and reviews, and grey literature to identify studies from low-income and middle-income countries (LMICs) that collected data on early life exposures and child development. Search terms included a list of risk factors, terms related to motor, cognitive, language and socioemotional development, and a list of low and middle income countries (list of search terms, appendix 1). We also identified studies via personal communication with researchers of published studies. We initially contacted 50 first authors of the publications and investigators of unpublished studies, of whom 33 (66%) responded to participate in the present study (figure 1).

We then asked researchers to complete a survey that included questions about child development assessment tools used, age of developmental assessment and details on the early life factors measured in their study. The primary inclusion criterion for studies was the assessment of at least one domain of child development (cognitive, motor, language and socioemotional) using a standard child development assessment instrument in at least 100 children before 7 years of age, as well as the collection of at least one early life factor of interest as part of the study. Following the survey, 10 investigators declined to participate, 2 studies were excluded as the eligible sample size was less than 100 and 1 study was excluded as development was assessed after age 7 years. The investigators then shared results of pre-defined analyses on their data or shared data with researchers at the Harvard T.H. Chan School of Public Health to complete the analyses of individual studies and the meta-analyses.

Outcomes and early life factors:

We included cognitive, motor and language outcomes in the analyses, socioemotional outcomes were not measured in a sufficient number of studies. If a study measured child development on multiple occasions, we included the measurement obtained at the age closest to 24 months. Based on the survey responses we identified 14 early life factors for the pooled analyses and grouped them into parental factors: father's education (none <1 year; primary 1 - <6 years; secondary 6-<10 years; higher ≥10 years), mother's education (none <1 year; primary 1 - <6 years; secondary 6-<10 years; higher ≥10 years), maternal age (<15 years, 15-<20 years, 20-<35 years; ≥35 years), maternal height (<145 cm, 145-<150 cm, 150-<155 cm, >155 cm) maternal body mass index (BMI; <18.5 kg/m^2, 18.5-<25 kg/m^2, 25-<30 kg/m^2, ≥30 kg/m^2), hemoglobin level during pregnancy (normal ≥110 g/L; mild anemia 100-109 g/L ; moderate anemia 70-99 g/L) and child factors: birth weight (low birth weight <2500g; moderate low 2000-2500g; very low birth weight <2000g), preterm birth (preterm<37 weeks; late preterm 34-37 weeks; early preterm <34 weeks), small-for-gestational-age (SGA; <10 percentile; moderate SGA 3-<10 percentile; severe SGA <3 percentile) as determined by Alexander and Oken standards, exclusive breastfeeding until 6 months of age, hemoglobin levels in infancy (normal ≥110 g/L; mild anemia 100-109 g/L ; moderate anemia 70-99 g/L), access to clean water (yes, no), access to sanitation (yes, no) and diarrhea preceding the 6 months before development assessment (yes, no). Details on the definition and categories of the risk factors are included in appendix 2. We also enquired about data on birth spacing, maternal HIV infection, malaria, intimate partner violence and depression, but a limited number of studies had data on these factors.

Analyses of individual studies:

Within each study, linear regression models were used to assess standardized mean differences (SMDs) in cognitive, motor, and language scores for selected risk factors. Multivariable models were adjusted for child's age and sex, maternal education and a measure of socioeconomic status (e.g. household income or wealth index). In addition, estimates for preterm birth and gestation-specific birth weight category (SGA and appropriate-for-gestational-age) were adjusted for each other. If a study was a randomized trial, intervention assignment was also included in the adjusted model. The missing indicator method was used for covariates when <10% of the data were missing; if more than 10% were missing the covariate was excluded from the analyses.

Meta-analysis:

Meta-analysis for a given risk factor was conducted if estimates from at least four studies were available. To account for the variation in tools used for measuring development we only pooled the means and standard errors of the standardized outcomes scores. As multivariable adjustment substantially changed the effect estimates, we used the adjusted effect estimates for meta-analysis. Given that heterogeneous effects seemed likely across the large variety of contexts studied, random effects meta-analysis was conducted using the DerSimonian and Larid method.[17] Heterogeneity was assessed using I^2 statistics. All analyses were conducted using the metaan commands in Stata 12.0 (StataCorp, College Station, TX)

Ethical consideration:

The pooled study was approved by the Harvard T.H. Chan School of Public Health (IRB16-0256).

Results:

Table 1 shows the characteristics of the studies included in the analyses. We included 21 data sets with developmental measurements on 20,882 children of which 8 were from Asia,[18-25] 7 were from sub-Saharan Africa,[26-32] 5 were from Latin America and 1 from Europe.[33-38] The majority of studies (n=18), including 12 randomized trials,[18-22 25 26 29-32 38] followed up the participants prospectively. The Bayley Scales of Infant and Toddler Development (BSID) was used to assess child development in most of the studies with, BSID-III administered in 5 studies,[23 26 30-32] BSID-II in 5 studies,[18-21 29] and BSID I in 1 study.[38] The Ages and Stages questionnaire was used in 2 studies,[22 36] and a few studies used local adaptations of standard tools.[28 35] The majority of the studies had data on both motor and cognitive development,[18-24 26-38] 1 study had data on motor development only[25] and 6 studies provided data on language development.[28 30-33] Development was assessed before age 2 years in most studies,[18-26 28-34 37 38] except for 3 studies that assessed development at ages between 3-6 years. [27 35 36]

Parental factors:

Pooled estimates for the association of parental factors with child cognitive, motor, and language development are presented in Table 2. Higher attained maternal education was associated with improved cognitive, motor, and language development scores. Children whose mothers attended or completed secondary school had 0.14 SD (95% CI: 0.05, 0.25), 0.12 SD (95% CI: 0.06, 0.18), and 0.13 SD (95% CI: 0.04, 0.21) higher cognitive, motor and language scores, respectively, as compared to children whose mothers only had primary school education. Compared to children of mothers with primary education, children of mothers with $\geq$ ten years of education scored 0.36 SD (95% CI: 0.19, 0.48), 0.26 SD (95% CI: 0.14, 0.38) and 0.21 SD (95% CI 0.09, 0.33) higher

in cognitive, motor and language scores, respectively. Children of mothers with no formal schooling scored lowest in cognitive, motor and language scores. There was a significant positive association between father's education and cognitive and motor development after adjusting for maternal education, although the magnitude of the effect sizes was smaller than for those of maternal education. We found no significant relationships between maternal age at birth and cognitive, motor, or language development.

Children of mothers with short stature (height <155 cm) tended to have lower cognitive, motor, and language scores as compared with a maternal height >155cm. Children whose mothers were <145cm scored 0.10 SD (95% CI -0.20, -0.004), 0.11 SD (95% CI: -0.19, -0.03), and 0.11 SD (95% CI: -0.31, 0.09) lower on cognitive, motor, and language development, respectively. Low maternal BMI (<18.5 kg/m^2) was significantly associated with lower cognitive development scores (SD: -0.10; 95% CI -0.19, -0.02), but not motor or language development. There was no significant association of maternal hemoglobin with child cognition.

Child factors:

Pooled estimates for the association of child factors with development are presented in Table 3. Compared to children born with normal birth weight, children born with low birth weight (<2500g) had significantly poorer cognitive and motor scores. Children with birthweights <2000g had on average 0.27 SD (95% CI: -0.49, -0.07) lower cognitive, 0.26 SD (95% CI: -0.40, -0.12) lower motor and 0.28 SD (95% CI: -0.60, 0.05) lower language scores, compared with normal birthweight children (≥2500 g). Compared to term and appropriate for gestational age (AGA) infants, preterm-AGA infants had 0.14 SD (95% CI: -0.24, -0.05) and 0.23 SD (95% CI:

-0.42, -0.03) lower cognitive and motor scores, respectively. Term-SGA infants had poorer developmental scores in some studies, but the pooled effect estimates for term-SGA, adjusted for preterm birth, were not statistically significant.

Anemia in infancy was significantly and negatively associated with both motor and cognitive development scores. Combined effect sizes of moderate anemia were -0.18 SD (95% CI -0.27, -0.09) for motor and -0.11 SD (95% CI -0.12, - 0.10) for cognitive scores. Compared to children residing in households with access to clean water, children without access had 0.10 SD (95% CI: -0.12, -0.09) lower cognitive and 0.07 SD (95% CI: -0.16, 0.01) lower motor and 0.15 SD (95% CI: -0.35, -0.05) lower language scores. Children without access to clean sanitation had 0.13 SD (95% CI: -0.18, -0.07) lower cognitive and 0.10 SD (95% CI: -0.19, -0.01) lower motor scores. In the pooled analyses, exclusive breastfeeding until 6 months of age and diarrhea during the preceding 6-month of development assessment did not have significant associations with either cognitive or motor development.

Figure 2 presents effect sizes of all risk factors included in the analyses. Forests plots of metanalysis of individual risk factors are included in appendix 2.

Discussion:

This pooled analysis of development assessment of 20,882 children from 21 LMIC studies determined that low maternal and paternal education, short maternal stature, low birth weight, preterm birth, anemia in infancy, and lack of access to clean water and sanitation were associated with lower child development scores among children < 7 years of age. We did not find significant associations of maternal anemia, fetal growth restriction, exclusive breastfeeding, or childhood diarrhea with development scores.

We observed a dose-response relationship between parental education and child development. While a large body of literature supports the consistent role of maternal education in promoting children's language and cognitive developments, evidence on the role of paternal education is more limited.[34 39 40] Recent reports suggest advanced language and cognitive development among children of more educated fathers that persisted after adjustment for family income and mothers' education.[41] Maternal education is associated with more warm, responsive, and stimulating home environments, which in turn are predictive of more positive developmental outcomes for children.[42] High maternal education is also linked with protective factors like good feeding and hygiene practices and frequent utilization of antenatal care and child immunization.[43 44] In addition, low maternal education is associated with known risk factors of poor child development such as malnutrition in children, and depression and stress in mothers.[45 46] Although prior work suggests that less educated mothers tend to be less receptive to early childhood development (ECD) messages, research also shows that their children may benefit more from ECD interventions.[47] Therefore, adopting a 2-generational intervention approach to empower parents and improve parenting capacity are likely to generate long-term benefits for child development.

Due to the availability of maternal education data, low maternal education can serve as a simple risk marker to target children in need of ECD intervention.[48]

We found significant negative associations of preterm birth with cognitive and motor development but not with language development. Meta-analyses of studies conducted in developed countries reported lower IQ scores and cognitive functioning, [49-51] along with deficits in motor [52], language [53], and visual-spatial abilities[54] in preterm infants. Reduction of the intrauterine period interrupts the trajectory of neurodevelopmental processes such as synapse formation and myelination, which often leads to neurocognitive deficits.[55] Although most preterm infants catch up in physical growth[56], this deficit in neurocognitive development often persists into childhood and adolescence.[57 58] Given the high incidence of preterm delivery in LMIC[59] and the increased survival of preterm infants with medical advances, the burden of the developmental deficits caused by preterm birth in LMIC may be increasing. There are currently few interventions to prevent preterm birth[60]; however, a variety of psychosocial interventions to alleviate the adverse neurodevelopmental effects of preterm birth implemented at different points in early childhood have shown modest short-term benefits.[61]

We found that fetal growth restriction, assessed via SGA, was not significantly associated with child development. This agrees with several reports from developed countries[62-64] whereas others have reported adverse effects of SGA on cognitive and motor functioning[31 65 66]. These disparate findings could be caused by different definitions of SGA and/or timing of the developmental assessment. Most studies from LMICs used LBW (as marker of SGA), which is also caused by prematurity, a major risk predictor of child development. There is some evidence that with

adequate nutrition, the developmental deficit in SGA infants is often compensated with age, although the gap in physical growth remains[67]. This finding underscores the potentially differential roles and separate causal mechanisms of effects of early life risk factors for physical and mental development. It is important to note that the effect size for SGA may be biased downwards considering the heterogeneity in outcome and the measurement error due to the use of last menstrual period (LMP) date for the estimation of gestational age in most the studies. We found significant negative associations between short maternal stature (<145 cm) and low BMI (<18.5 kg/m2)[68] on cognitive function, which may indicate the role of chronic malnutrition of mothers over their life course on pregnancy health and development of fetus. These are also known risk factors of SGA,[68] suggesting that adverse effects of fetal growth restriction on child development are possible. Further research is needed to quantify the effects of fetal growth restriction on children's development and evaluate the effects of interventions to alleviate the negative impacts of SGA on development.

We found an adverse role of anemia in infancy with motor and cognitive development. Prior studies reported significant effects of anemia on cognitive, motor and socioemotional development that persisted into middle childhood during longitudinal follow-up[69]. Worldwide, the predominant cause of anemia for infants and children is iron deficiency[70], which can interfere with myelination, synapse formation and protein expression during sensitive periods of neurodevelopment[71]. Meta-analyses of randomized trials of infant iron supplementation have not established an effect on child development; however statistical power to detect effect sizes of < 0.2 SD as our analysis predicts is limited due to few trials with large enough sample sizes.[72 73] In our pooled analyses, maternal anemia during pregnancy, an important determinant of anemia in

infancy[74], was not significantly associated with children's development. We also did not find a significant association between exclusive breastfeeding until 6 months of age and children's development. Nevertheless, few studies included in our pooled analyses had a sufficient number of infants who were exclusively breastfed until six months to allow for a well-powered analysis. Because of the multidimensional benefits of breastfeeding from infection prevention to fostering mother-infant bonding and infant attachment, significant positive effects of exclusive breastfeeding on child development are plausible. Meta-analyses of studies of effects of breastfeeding on children's development reported significant increases in intelligence and cognitive scores[75 76]; however some studies have attributed these associations entirely to the presence of confounding by socioeconomic status and stimulation at home.[77]

This study is among the first to report on the associations between lack of access to safe water and sanitation and child cognitive development. The burden of developmental deficit attributed to these risk factors is likely very high as a large proportion of the population in LMICs reside in unhygienic environments with limited access to safe water. The effects of poor sanitation and unsafe water on child cognitive development are potentially mediated through childhood anemia, inflammation and undernutrition resulting from frequent enteric infections[78]. However, in the pooled analyses, we did not find any significant adverse associations between diarrhea and development, which is different from previously published evidence[22 79 80]. One potential explanation for the lack of association found in this study may be measurement error: diarrhea is inherently complex and hard to measure; variations in the definitions of episodes as well as parental inability to correctly report diarrhea may have led to the failure to detect potential effects of diarrhea on cognitive, motor and language development in this study.

The strengths of this pooled study include the global coverage of the cohorts, the large sample size, and uniform classifications of early life exposures and statistical analyses across studies. Nevertheless, there are also several limitations, including the lack of data on exposure to environmental neurotoxicants, maternal depression, responsive parenting behaviors, and child stimulation and early education. A recent meta-analysis determined that the potential effect of responsive stimulation on cognitive development at 2 years of age was +0.42SD (95% CI: 0.36, 0.48)[81], which is larger than all risk factors examined in our analysis. Thus, comprehensive packages of environmental, nutrition, and stimulation interventions may produce larger effect sizes than interventions targeting single risks. In addition, due to the observational nature of the studies included in this analysis, we are unable to determine a causal relationship between parental and child factors with child development. Although we have adjusted for major confounders the potential for residual confounding remains. Last, there was moderate to high levels of heterogeneity, as indicated by the I^2 values, in some of our pooled estimates. The magnitude of the relationship for maternal education, prematurity, birthweight, SGA, and access to water and sanitation appeared to vary by study cohort. Accordingly, future intervention studies should be conducted among diverse study populations as their effect may importantly differ by setting.

In summary, in a pooled study of 21 studies in LMICs, we determined that multiple risk factors classically associated with child morbidity and mortality also appear to have negative associations with cognitive, motor, and language development. As a result, our study suggests that interventions that span pre-pregnancy through early and middle childhood may be necessary to provide optimal child development in LMICs. Future research should focus on determining the effectiveness of, and delivery strategies for comprehensive intervention packages to promote child development.

Key Words:

Motor development
cognitive development
Language development
Early life risk factors
Preterm
SGA
Maternal education
Paternal education
Maternal short stature
Maternal anemia
anemia in infancy,
Access to clean water
Access to sanitation
Breastfeeding
Diarrhea

Figure Legends

Figure 1: flow chart of study selection

Figure 2- Panel A: Pooled estimates of association between maternal factors and development

Panel B: Pooled estimates of association between child factors and development

Table 1: Characteristics of the included studies

	Study	Setting	Primary study design	Study population	N (data on child development)	Child development tool used	Child age in years at assessment (mean±SD)
Asia							
1	Black (2004)[18]	Bangladesh	randomized controlled trial	birth cohort	221	Bayley Scales of Infant and Toddler Development, 2nd edition (BSID-II) and the Home Observation for Measurement of the Environment (HOME) Inventory	1.06±0.03
2	Tofail (2008)[19]	Bangladesh	randomized controlled trial	birth cohort	2853 total (2116 tested)	2 problem-solving tests, motor index of Bayley Scales of Infant and Toddler Development, 2nd edition (BSID-II) and Wolke's behavior ratings	0.61±0.02
3	Tofail (2012)[20]	Bangladesh	randomized controlled trial	prospective, community-based cohort	249	Bayley Scales of Infant and Toddler Development, 2nd edition (BSID-II)	0.84±0.01
4	Taneja (2005)[21]	India	randomized placebo-controlled trial	Prospective, community-based cohort	571	Bayley Scales of Infant and Toddler Development, 2nd edition (BSID-II)	1.25±0.16
5	Kvestad (2015)[22]	India	randomized placebo-controlled trial	prospective, community-based cohort	422	Ages and Stages Questionnaire, 3rd edition (ASQ-3)	1.37±0.60
6	Yousafzai (2014)[23]	Pakistan	community-based cluster-randomized effectiveness trial	prospective, community-based cohort	1357	Bayley Scales of Infant and Toddler Development, 3rd edition (BSID-III)	11.6 ±0.83
7	Duazo (2010)[24]	Philippines	longitudinal program evaluation	birth cohort	4904	Philippines Revised Early Childhood Development Checklist (REC)	1.62±0.88
8	McGready (2007)[25]	Thailand	randomized controlled trial	prospective, facility-based cohort	503	Shoklo Developmental Test	1.62±0.02
Sub-Saharan Africa							
9	Shapiro (2013)[26]	Botswana	randomized controlled trial	prospective, community-based cohort	224	Bayley Scales of Infant and Toddler Development, 3rd edition (BSID-III)	2.03±0.08
10	Alemtsehay (2009)[27]	Ethiopia	cross-sectional study	cross-sectional, community-based cohort	100	Raven's Colored Progressive Matrices (CPM) and Kaufman Assessment Battery for Children-II (KABC-II)	5.11±0.24
11	Gladstone (2011)[28]	Malawi	cross-sectional community-based cohort study	community-based cohort	840	Ten Question Questionnaire [TQQ] and Malawi Developmental Assessment Tool [MDAT]	1.74±0.33
12	McDonald (2013)[29]	Tanzania	randomized placebo-controlled trial	birth cohort	305	Bayley Scales of Infant and Toddler Development, 2nd edition (BSID-II)	1.28±0.04
13	Manji (2014)[30]	Tanzania	randomized placebo-controlled trial	birth cohort	206	Bayley Scales of Infant and Toddler Development, 3rd edition (BSID-III)	1.28±0.04
14	Sudfeld (2015)[31]	Tanzania	randomized placebo-controlled trial	birth cohort	958	Bayley Scales of Infant and Toddler Development, 3rd edition (BSID-III)	2.25±0.52
15	Locks	Tanzania	randomized placebo-	birth cohort	248	Bayley Scales of Infant and Toddler	1.21±0.03

	Study	Setting	Primary study design	Study population	N (data on child development)	Child development tool used	Child age in years at assessment (mean±SD)
	(2016)[32]		controlled trial			Development, 3rd edition (BSID-III)	
Latin America							
16	Santos IS (2011)[33]	Brazil	longitudinal birth cohort survey	2004 Pelotas birth cohort	3868	Battelle Screening Developmental Inventory (BSDI)	1.99 ± 0.05
17	Santos (2008)[34]	Brazil	longitudinal birth cohort survey	Longitudinal, community-based cohort	365	Wechsler Pre-School and Primary Scale of Intelligence-Revised (WPPSI-R)	5.80±3.02
18	Fernald (2011)[35]	Ecuador	randomized effectiveness trial	Prospective, community-based cohort	1265	MacArthur-Bates Communicative Development Inventory, short form, Spanish version	4.59±0.87
19	Handal (2008)[36]	Ecuador	cross-sectional	Community based, selected using door-to-door survey	283	Ages and Stages Questionnaire (ASQ)	2.46±1.46
20	Braun (2012)[37]	Mexico	prospective cohort study	prospective, facility-based cohort	1032	Bayley Scales of Infant and Toddler Development, 2nd edition (BSID-II) McCarthy Scales of Children's Abilities (MSCA)	2.02±0.03
Europe							
21	Akman (2004)[38]	Europe-Turkey	randomized clinical trial	facility-based hospital	108	Bayley Scales of Infant and Toddler Development, 1st edition (BSID-I)	1.42±0.59

Table 2: Summary results of meta-analysis of associations of parental factors and cognitive, motor and language developments

Risk Factor	Cognitive				Motor				Language			
	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)
Mother's education												
No education (<1 years)	15	-0.12 (-0.24, -0.008)	0.05	50.8	18	-0.07 (-0.13, -0.01)	0.03	18.2	5	-0.06 (-0.21, -0.09)	0.49	35.5
Primary (1- <6 years)		Reference				Reference				Reference		
Secondary (6- <10 years)	17	0.14 (0.05, 0.24)	< 0.01	59.7	19	0.12 (0.06, 0.18)	< 0.01	51.8	5	0.13 (0.04, 0.21)	0.04	0.0
Higher (≥10 years)	17	0.36 (0.19, 0.48)	< 0.01	65.8	19	0.26 (0.14, 0.38)	< 0.01	70.6	5	0.21 (0.09, 0.33)	0.03	0.0
Father's education												
No education (<1 years)	13	-0.005 (-0.08, 0.07)	0.91	0.0	17	-0.08 (-0.11, -0.04)	< 0.01	0.0	4	0.02 (-0.15, 0.20)	0.80	30.0
Primary (1- <6 years)		Reference				Reference				Reference		
Secondary (6- <10 years)	15	0.06 (0.015, 0.11)	0.02	0.0	17	0.08 (0.03, 0.13)	< 0.01	30.3	4	0.09 (0.02, 0.16)	0.08	0.0
Higher (≥10 years)	15	0.15 (0.08, 0.21)	< 0.01	0.0	17	0.18 (0.10, 0.26)	< 0.01	42.3	4	0.22 (0.11, 0.32)	0.03	17.9
Mother's age												
<15 years	5	-0.06 (-0.13, 0.25)	0.57	0.0	5	0.12 (-0.06, 0.30)	0.25	0.0	2	n/a	n/a	n/a
15-<20 years	18	-0.007 (-0.06, 0.05)	0.80	10.7	20	-0.02 (-0.11, 0.08)	0.75	83.6	6	0.01 (-0.09, 0.11)	0.85	37.0
20-34 years		Reference				Reference				Reference		
≥35 years	18	-0.01 (-0.06, 0.04)	0.58	0.0	20	-0.006 (-0.07, 0.05)	0.85	50.1	6	0.02 (-0.05, 0.09)	0.59	0.0
Mother's height												
<145 cm	11	-0.10 (-0.20, -0.004)	0.07	0.0	13	-0.11 (-0.19, -0.03)	0.02	21.5	5	-0.11 (-0.31, 0.09)	0.35	0.0
145 -<150 cm	13	-0.11 (-0.19, -0.02)	0.03	27.1	15	-0.07 (-0.16, 0.03)	0.17	71.1	5	-0.06 (-0.13, 0.06)	0.52	0.0
150- <155 cm	13	-0.09 (-0.14, -0.04)	< 0.01	3.3	15	-0.04 (-0.09, 0.009)	0.14	31.5	5	-0.05 (-0.12, 0.02)	0.22	0.0
>155 cm		Reference				Reference				Reference		
Mother's BMI (kg/m^2)												

Risk Factor	Cognitive				Motor				Language			
	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)
<18.5	11	-0.11 (-0.20, -0.02)	0.03	12.7	13	-0.02 (-0.11, 0.07)	0.69	51.4	3	n/a	n/a	n/a
18.5 -<25		Reference				Reference				Reference		
25-<30	12	0.03 (-0.04, 0.09)	0.44	23.3	14	0.04 (-0.03, 0.11)	0.31	64.6	4	-0.04 (-0.21, 0.13)	0.70	61.0
≥30	12	-0.02 (-0.17, 0.14)	0.82	46.3	14	-0.02 (-0.14, 0.10)	0.77	63.6	4	-0.14 (-0.34, 0.06)	0.26	35.9
Mother's hemoglobin level (g/L)												
Normal (≥110 g/L))		Reference				Reference				Reference		
Mild anemia (100-109 g/L)	4	-0.06 (-0.15, 0.03)	0.28	0.0	11	0.06 (0.008, 0.11)	0.04	29.7	1	n/a	n/a	n/a
Moderate anemia (70-99 g/L)	4	-0.06 (-0.19, 0.06)	0.39	0.0	6	-0.01 (-0.06, 0.04)	0.68	16.3	1	n/a	n/a	n/a

[1]Adjusted for child's gender and age, mother's education and household wealth

Table 3: Summary results of meta-analysis of associations of child factors and cognitive, motor and language developments, standardized scores

Risk Factor	Cognitive				Motor				Language			
	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)
Birth weight (g)												
Normal (≥2500 g)		Reference				Reference				Reference		
Low (<2500 g)	14	-0.13 (-0.20, -0.07)	< 0.01	51.0	15	-0.14 (-0.23, -0.06)	< 0.01	66.5	5	-0.11 (-0.22, 0.00)	0.12	74.6
Moderate low (2000-2500 g)	14	-0.07 (-0.12, -0.03)	< 0.01	17.2	15	-0.11 (-0.20, -0.02)	0.03	64.0	5	-0.05 (-0.10, 0.01)	0.20	29.6
Very low (<2000 g)	14	-0.27 (-0.49, -0.07)	0.02	74.0	13	-0.26 (-0.40, -0.12)	< 0.01	74.9	5	-0.28 (-0.60, 0.05)	0.17	81.1
Gestational age (g)[2]												
Term (≥37 weeks)		Reference				Reference				Reference		
Late preterm (34-37 weeks)	8	-0.21 (-0.39, -0.04)	0.04	69.8	8	-0.14 (-0.33, 0.04)	0.17	74.5	5	-0.05 (-0.23, 0.13)	0.64	72.1
Early preterm (<34 weeks)	8	-0.16 (-0.34, 0.31)	0.15	53.5	7	-0.26 (-0.53, 0.006)	0.10	65.0	4	-0.20 (-0.55, 0.15)	0.35	75.4
Size for gestational age[3]												
AGA (≥10 percentile)		Reference				Reference				Reference		
Moderate SGA (3-<10 percentile)	8	-0.05 (-0.11, 0.12)	0.16	0.0	9	-0.01 (-0.10, 0.07)	0.77	36.6	4	-0.06 (-0.18, 0.06)	0.40	29.4
Severe SGA (<3 percentile)	8	-0.09 (-0.24, 0.07)	0.30	72.0	9	0.02 (-0.09, 0.12)	0.78	37.4	4	0.03 (-0.13, 0.19)	0.73	37.7
Gestational age and Size-for-gestational age												
Term-AGA		Reference				Reference				Reference		
Preterm-AGA	8	-0.14 (-0.24, -0.05)	0.02	17.0	9	-0.23 (-0.42, -0.03)	0.05	76.5	4	-0.02 (-0.23, 0.19)	0.87	78.0
Term-SGA	8	-0.02 (-0.10, 0.06)	0.66	44.6	9	-0.007 (-0.08, 0.06)	0.84	31.4	4	-0.03 (-0.12, 0.06)	0.55	9.3
Preterm-SGA	5	-0.17 (-0.29, -0.05)	0.05	0.0	5	-0.15 (-0.40, 0.09)	0.29	53.1	3	n/a	n/a	n/a
Exclusive breastfeeding												
Yes		Reference				Reference				Reference		
No	4	-0.02 (-0.08, 0.04)	0.60	0.0	4	-0.05 (-0.13, 0.04)	0.36	16.4	3	n/a	n/a	n/a

Risk Factor	Cognitive				Motor				Language			
	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)
Child hemoglobin level (g/L)												
Normal (≥110 g/L)		Reference				Reference				Reference		
Mild anemia (100-109 g/L)	9	-0.06 (-0.13, 0.01)	0.14	27.7	9	-0.03 (-0.13, 0.07)	0.54	51.2	3	n/a	n/a	n/a
Moderate anemia (70-99 g/L)	9	-0.11 (-0.12, -0.10)	< 0.01	0.0	9	-0.18 (-0.28, -0.09)	< 0.01	49.0	3	n/a	n/a	n/a
Access to clean water												
Yes		Reference				Reference				Reference		
No	8	-0.10 (-0.12, -0.09)	< 0.01	0.0	8	-0.07 (-0.16, 0.01)	0.14	71.0	4	-0.15 (-0.35, 0.05)	0.23	82.5
Access to sanitation												
Yes		Reference				Reference				Reference		
No	8	-0.13 (-0.18, -0.07)	< 0.01	47.5	8	-0.10 (-0.19, -0.01)	0.05	82.8	4	-0.12 (-0.27, 0.03)	0.21	92.4
Diarrhoea												
Yes	5	-0.02 (-0.16, 0.13)	0.84	66.8	5	-0.02 (-0.14, 0.09)	0.71	62.8	2	n/a	n/a	n/a
No		Reference				Reference				Reference		

[1]Adjusted for child's gender and age, mother's education and household wealth
[2]Adjusted for small for gestational age
[3]Adjusted for gestational age

AGA: Appropriate for Gestational Age
SGA: Small for Gestational Age

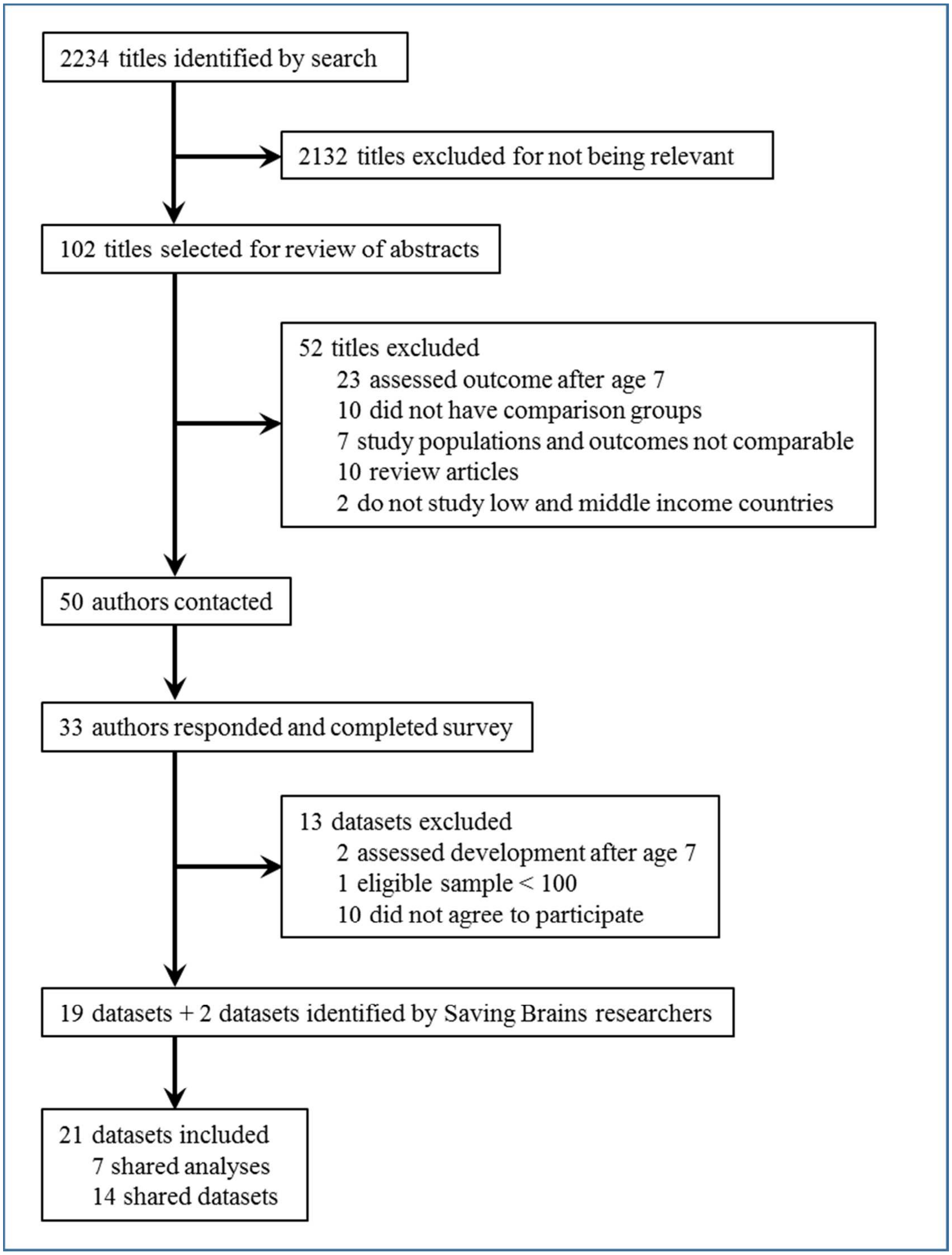

Figure 2: flow chart of study selection

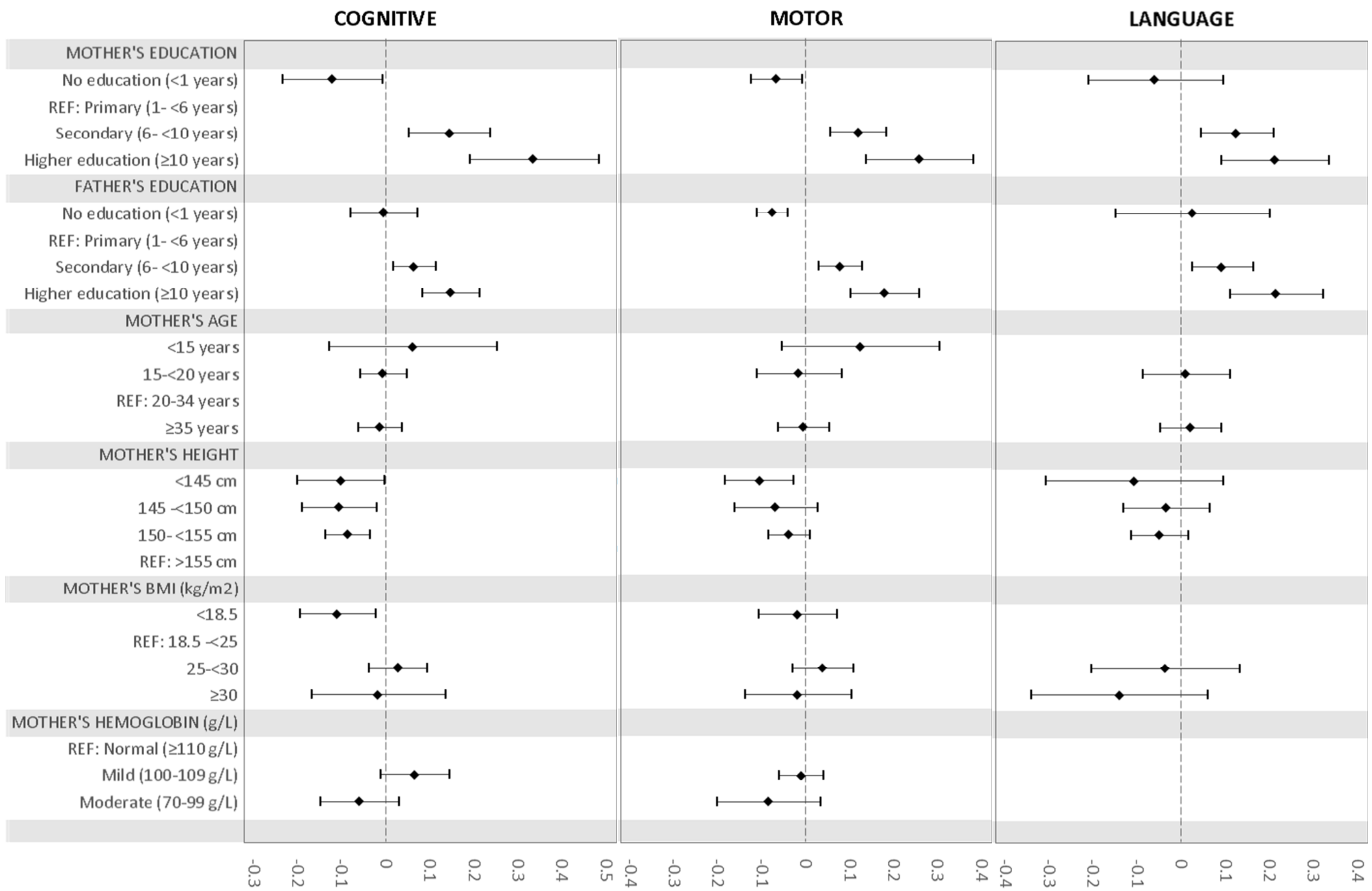

Figure 3, Panel A: Pooled estimates of association between maternal factors and development

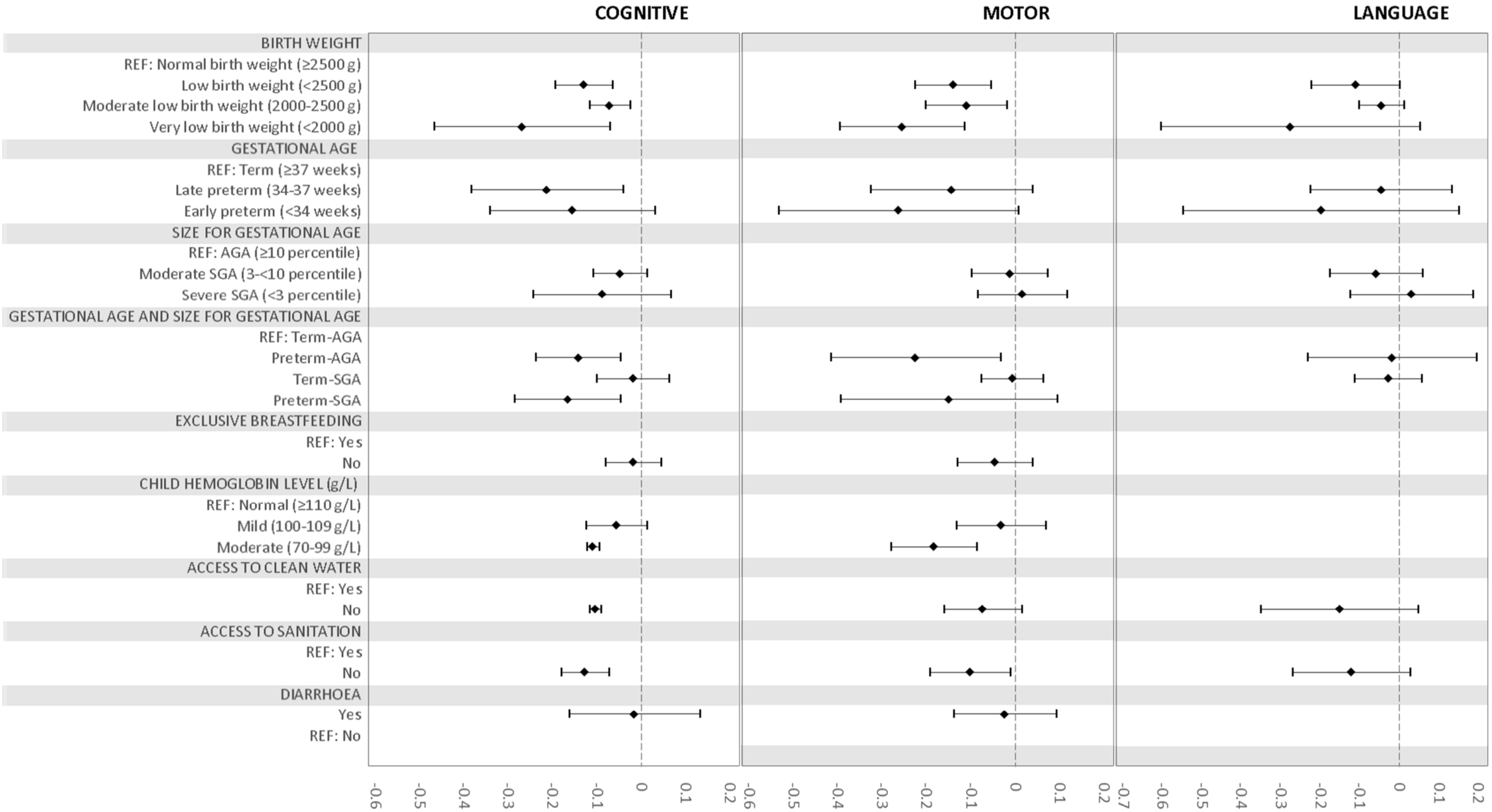

Figure 2, Panel B: Pooled estimates of association between child factors and development

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Appendix 1: Search terms

("child"[MeSH] OR "infant"[MeSH]) AND ("child development"[MeSH] OR "cognition"[MeSH] OR "psychomotor disorders"[MeSH] OR "psychomotor performance"[MeSH] OR "motor skills"[MeSH] OR "intelligence"[MeSH] OR "IQ"[All Fields] OR "executive function"[MeSH] OR "attention"[MeSH] OR "memory"[MeSH] OR "learning"[MeSH] OR "education"[MeSH] OR "reading"[MeSH] OR "mathematics"[MeSH] OR "learning disorders"[MeSH] OR "aptitude tests"[MeSH] OR "language tests"[MeSH] OR "mental health"[MeSH] OR "child behavior"[MeSH] OR "emotional intelligence"[MeSH] OR "emotions"[MeSH] OR "temperament"[MeSH] OR "self concept"[MeSH] OR "self efficacy"[MeSH] OR "mental competency"[MeSH] OR "aggression"[MeSH]) AND ("preterm"[All Fields] OR "low birth weight"[All Fields] OR “maternal height” OR “maternal underweight” OR “malaria” OR “birth spacing” OR “Teen pregnancy” OR “anemia” or “hemoglobin” OR “HIV” OR “iron supplement” OR “iron deficiency” OR “childhood diarrhea” OR “HIV” OR “zinc” OR “iodine” OR “sanitation” OR “clean water” OR “breastfeeding” OR “hookworms”) AND ("Armenia"[All Fields] OR "Azerbaijan"[All Fields] OR "Georgia"[All Fields] OR "Kazakhstan"[All Fields] OR "Kyrgyzstan"[All Fields] OR "Mongolia"[All Fields] OR "Tajikistan"[All Fields] OR "Turkmenistan"[All Fields] OR "Uzbekistan"[All Fields] OR "Afghanistan"[All Fields] OR "Bangladesh"[All Fields] OR "Bhutan"[All Fields] OR "India"[All Fields] OR "Nepal"[All Fields] OR "Pakistan"[All Fields] OR "Cambodia"[All Fields] OR "Indonesia"[All Fields] OR "Lao People's Democratic Republic"[All Fields] OR "Malaysia"[All Fields] OR "Maldives"[All Fields] OR "Mauritius"[All Fields] OR "Mayotte"[All Fields] OR "Myanmar"[All Fields] OR "Philippines"[All Fields] OR "Seychelles"[All Fields] OR "Sri Lanka"[All Fields] OR "Thailand"[All Fields] OR "Viet Nam"[All Fields] OR "Anguilla"[All Fields] OR "Antigua and Barbuda"[All Fields] OR "Aruba"[All Fields] OR "Bahamas"[All Fields] OR "Barbados"[All Fields] OR "Belize"[All Fields] OR "Bermuda"[All Fields] OR "British Virgin Islands"[All Fields] OR "Cayman Islands"[All Fields] OR "Cuba"[All Fields] OR "Turks and Caicos Islands"[All Fields] OR "Bolivia"[All Fields] OR "Ecuador"[All Fields] OR "Peru"[All Fields] OR "Colombia"[All Fields] OR "Costa Rica"[All Fields] OR "El Salvador"[All Fields] OR "Guatemala"[All Fields] OR "Honduras"[All Fields] OR "Mexico"[All Fields] OR "Nicaragua"[All Fields] OR "Panama"[All Fields] OR "Venezuela"[All Fields] OR "Argentina"[All Fields] OR "Chile"[All Fields] OR "Falkland Islands"[All Fields] OR "Malvinas"[All Fields] OR "Uruguay"[All Fields] OR "Brazil"[All Fields] OR "Paraguay"[All Fields] OR "Algeria"[All Fields] OR "Bahrain"[All Fields] OR "Egypt"[All Fields] OR "Iran"[All Fields] OR "Iraq"[All Fields] OR "Jordan"[All Fields] OR "Kuwait"[All Fields] OR "Lebanon"[All Fields] OR "Libyan Arab Jamahiriya"[All Fields] OR "Morocco"[All Fields] OR "Occupied Palestinian Territory"[All Fields] OR "Oman"[All Fields] OR "Qatar"[All Fields] OR "Saudi Arabia"[All Fields] OR "Syrian Arab Republic"[All Fields] OR "Tunisia"[All Fields] OR "Turkey"[All Fields] OR "United Arab Emirates"[All Fields] OR "Western Sahara"[All Fields] OR "Yemen"[All Fields] OR "American Samoa"[All Fields] OR "Cook Islands"[All Fields] OR "Fiji"[All Fields] OR "French Polynesia"[All Fields] OR "Guam"[All Fields] OR "Kiribati"[All Fields] OR "Marshall Islands"[All Fields] OR "Micronesia"[All Fields] OR "Nauru"[All Fields] OR "New Caledonia"[All Fields] OR "Niue"[All Fields] OR "Northern Mariana Islands"[All Fields] OR "Palau"[All Fields] OR "Papua New Guinea"[All Fields] OR "Pitcairn"[All Fields] OR "Samoa"[All Fields] OR "Solomon Islands"[All Fields] OR "Tokelau"[All Fields] OR "Tonga"[All Fields] OR "Tuvalu"[All Fields] OR "Vanuatu"[All Fields] OR "Wallis and Futuna Islands"[All Fields] OR "Angola"[All Fields] OR "Central African Republic"[All Fields] OR

"Congo"[All Fields] OR "Democratic Republic of the Congo"[All Fields] OR "Equatorial Guinea"[All Fields] OR "Gabon"[All Fields] OR "Burundi"[All Fields] OR "Comoros"[All Fields] OR "Djibouti"[All Fields] OR "Eritrea"[All Fields] OR "Ethiopia"[All Fields] OR "Kenya"[All Fields] OR "Madagascar"[All Fields] OR "Malawi"[All Fields] OR "Mozambique"[All Fields] OR "Rwanda"[All Fields] OR "Somalia"[All Fields] OR "Sudan"[All Fields] OR "Uganda"[All Fields] OR "United Republic of Tanzania"[All Fields] OR "Zambia"[All Fields] OR "Botswana"[All Fields] OR "Lesotho"[All Fields] OR "Namibia"[All Fields] OR "South Africa"[All Fields] OR "Swaziland"[All Fields] OR "Zimbabwe"[All Fields] OR "Benin"[All Fields] OR "Burkina Faso"[All Fields] OR "Cameroon"[All Fields] OR "Cape Verde"[All Fields] OR "Chad"[All Fields] OR "Cote d'Ivoire"[All Fields] OR "Gambia"[All Fields] OR "Ghana"[All Fields] OR "Guinea"[All Fields] OR "Guinea-Bissau"[All Fields] OR "Liberia"[All Fields] OR "Mali"[All Fields] OR "Mauritania"[All Fields] OR "Niger"[All Fields] OR "Nigeria"[All Fields] OR "Saint Helena"[All Fields] OR "Sao Tome and Principe"[All Fields] OR "Senegal"[All Fields] OR "Sierra Leone"[All Fields] OR "Togo"[All Fields])

Appendix 2: Forest plots

1. Child Risk Factors on Child's Cognitive Development

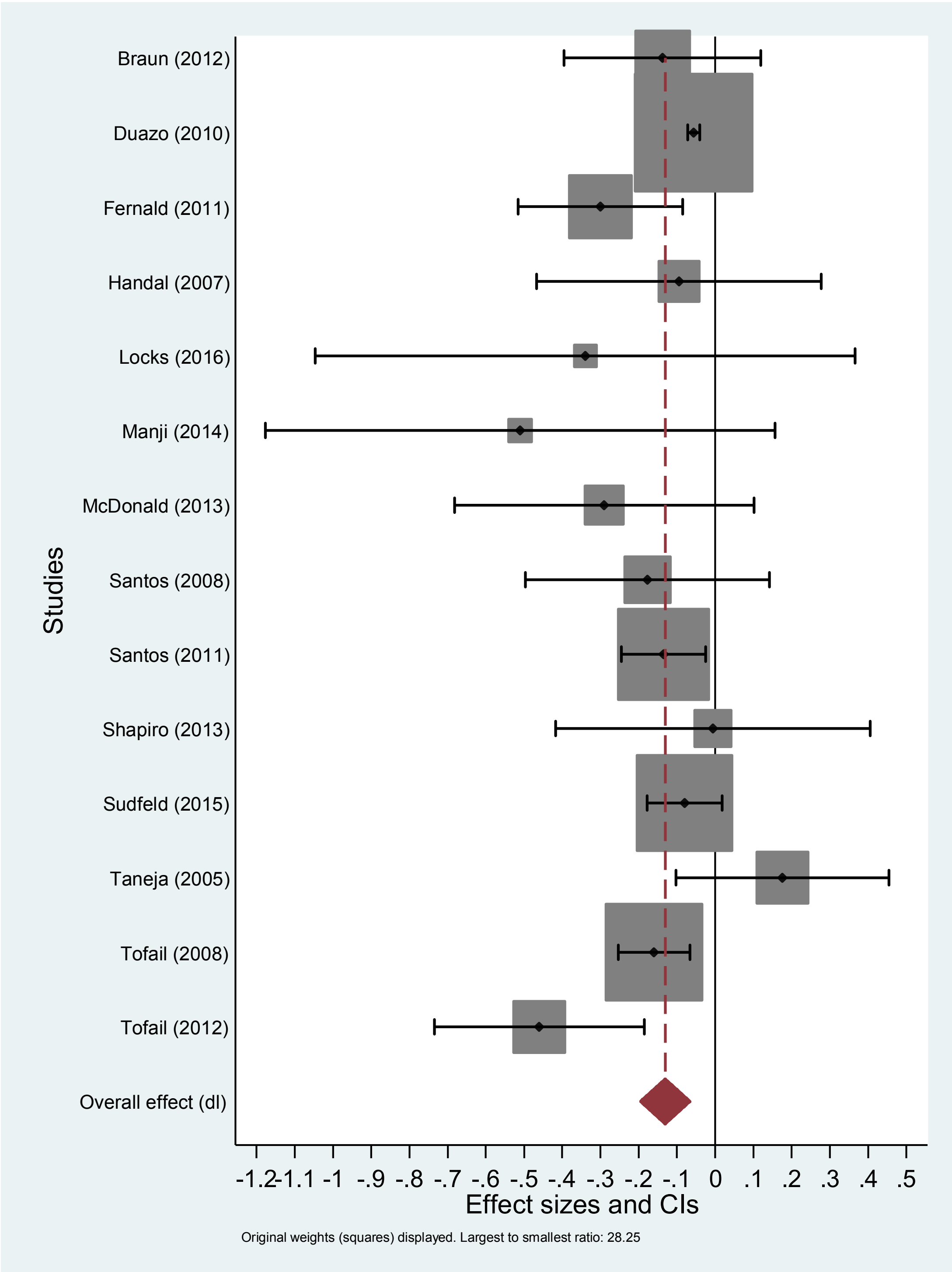

Figure 1: Association between low birth weight (LBW) and (reference: normal birth weight) and cognitive development.

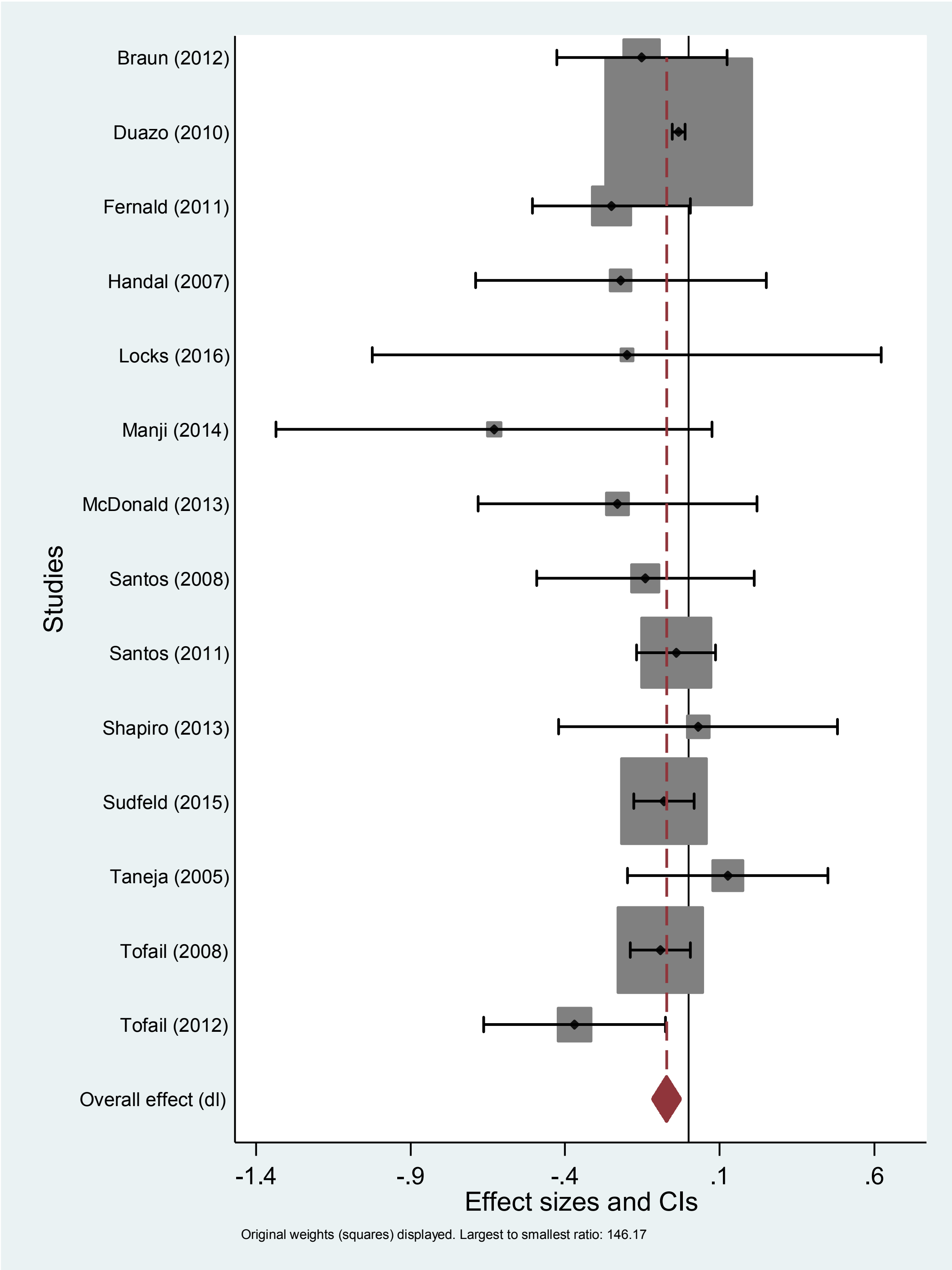

Figure 2: Association between Moderately low birth Weight (reference, normal birth weight) and cognitive development.

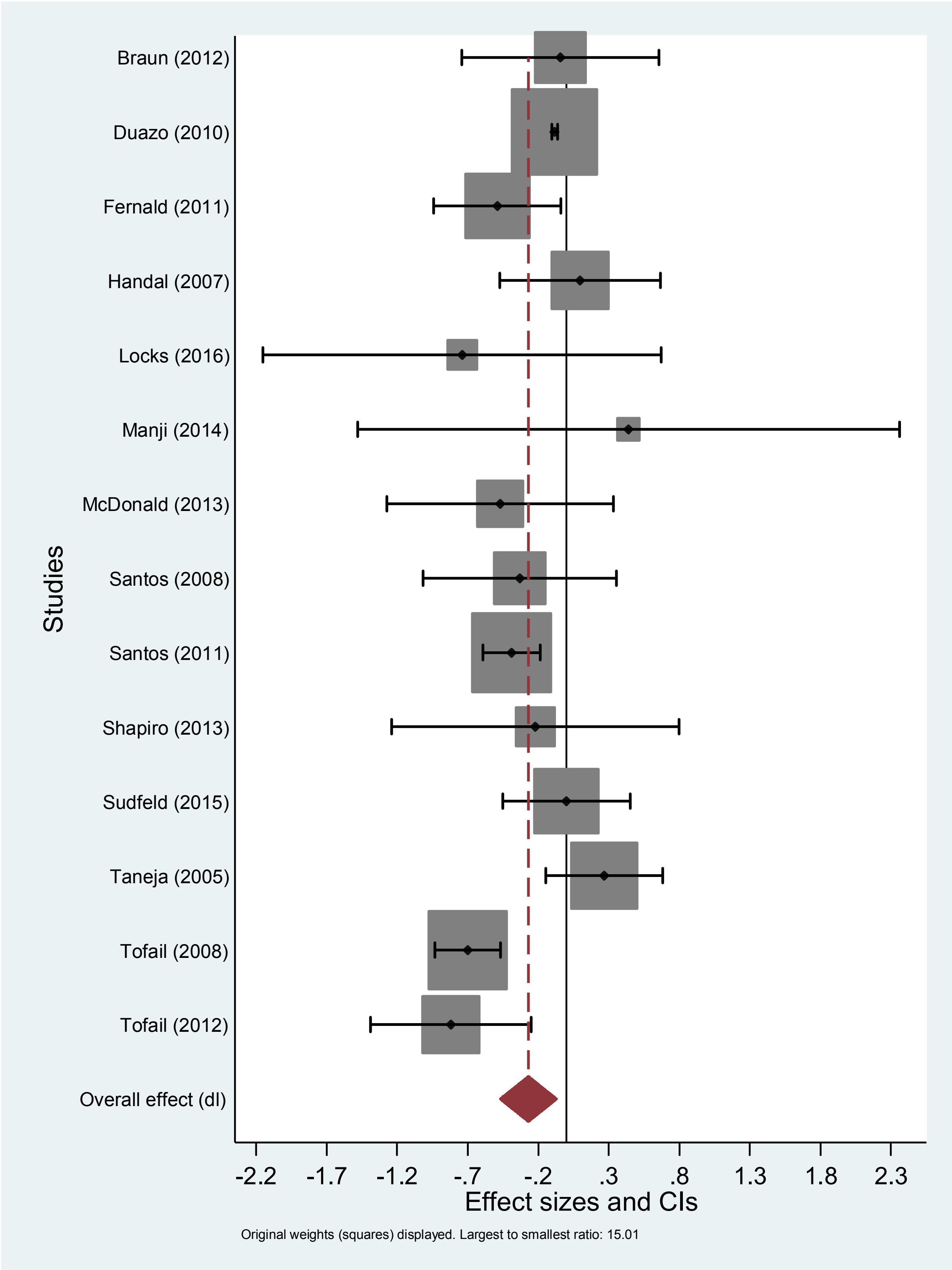

Figure 3: Association between very low Birth weight (reference: normal birth weight)) and cognitive development.

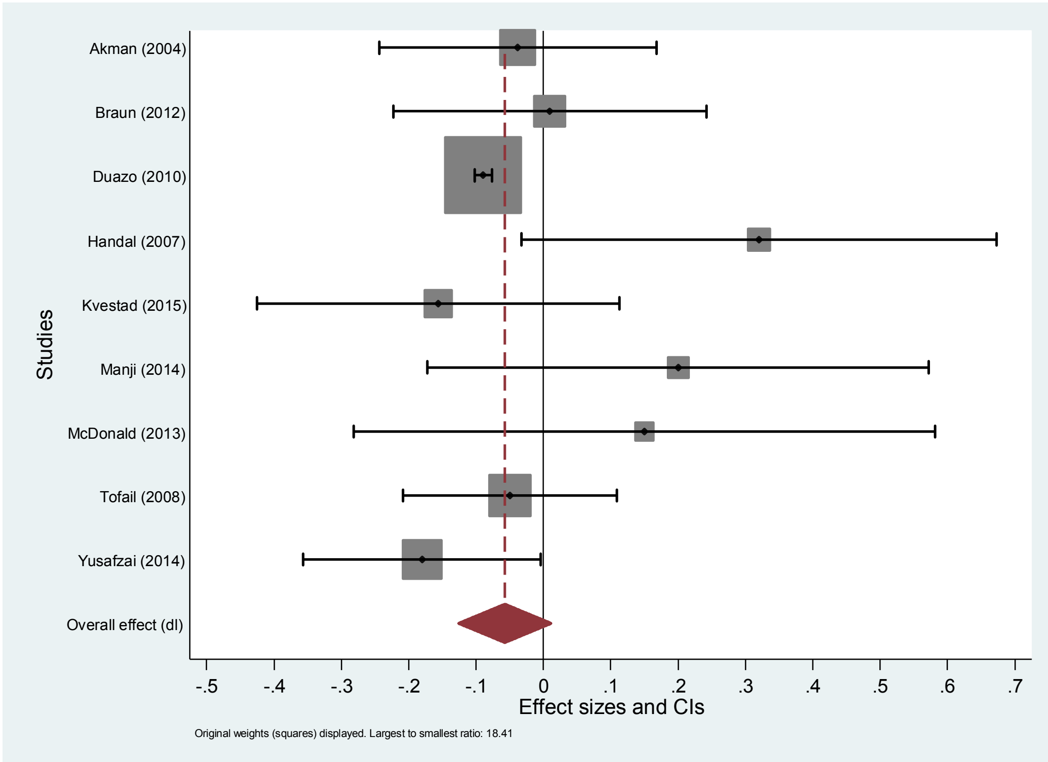

Figure 4: Association between child mild anemia (reference: no anemia) and cognitive development.

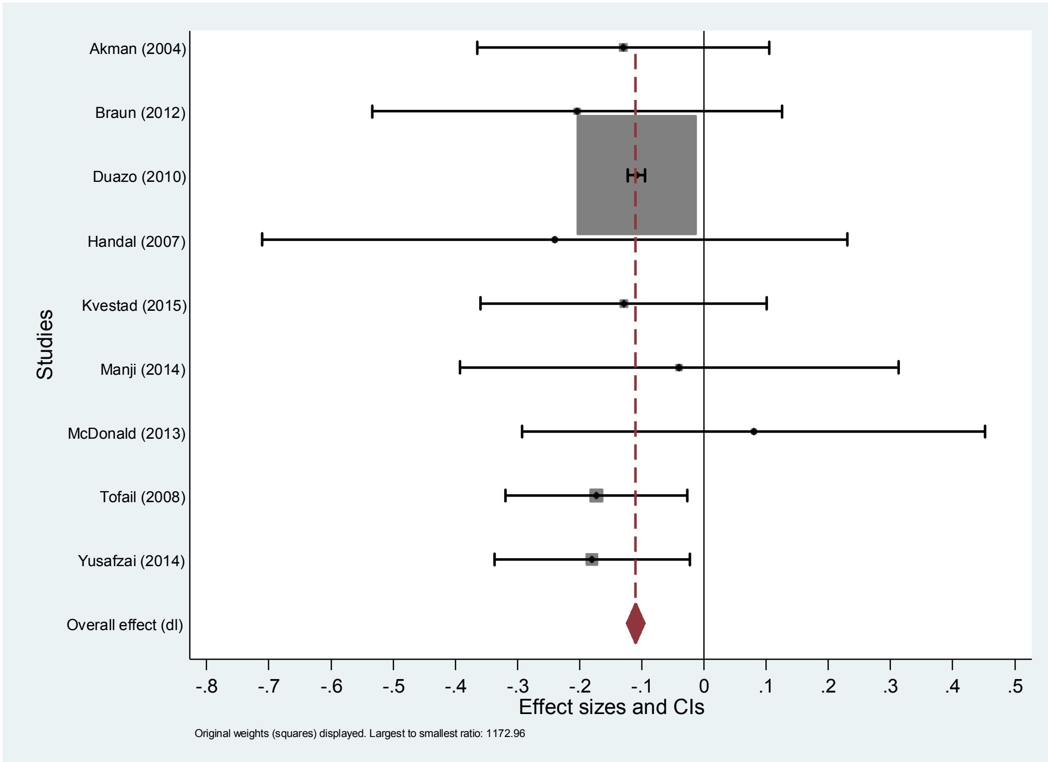

Figure 5: Association between child moderate anemia (reference: no anemia) and cognitive development.

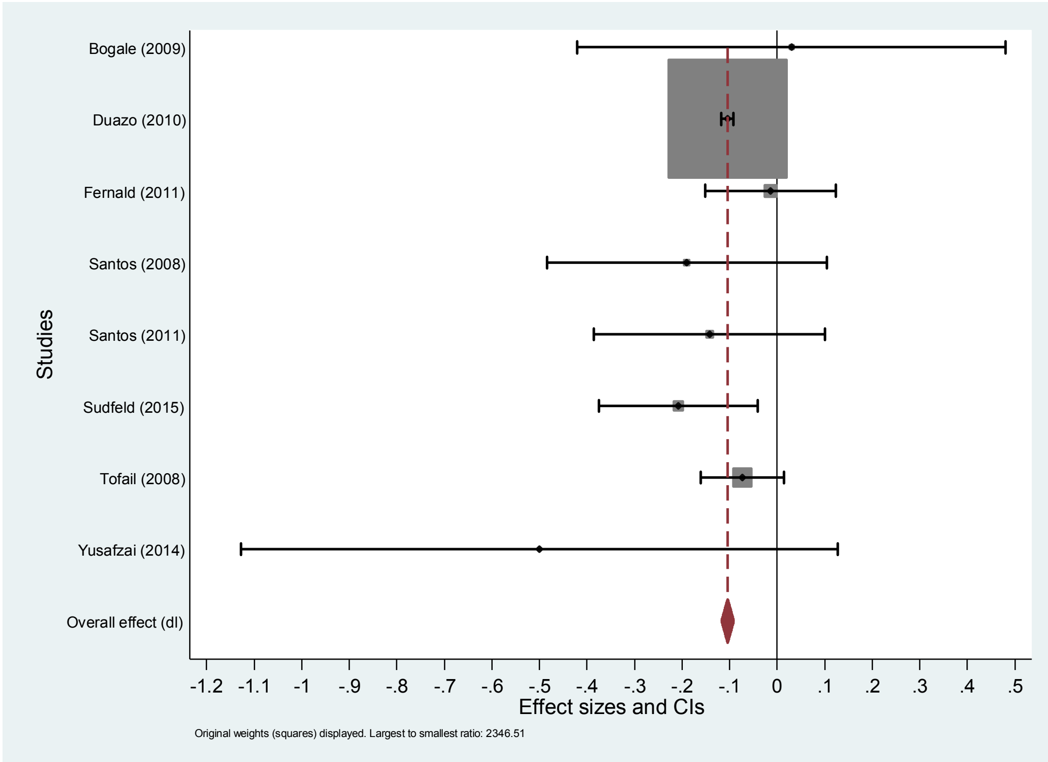

Figure 6: Association between lack of access to clean water (reference: access to clean water) and cognitive development.

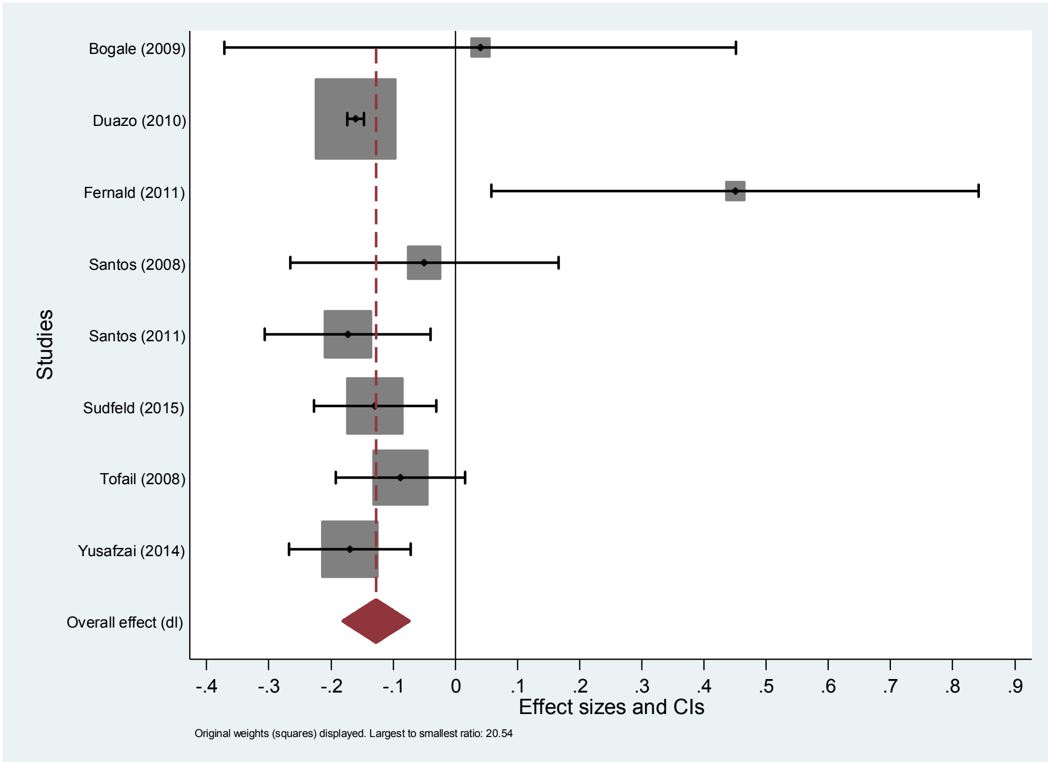

Figure 7: Association between lack of access to sanitation (reference: access to sanitation) and cognitive development.

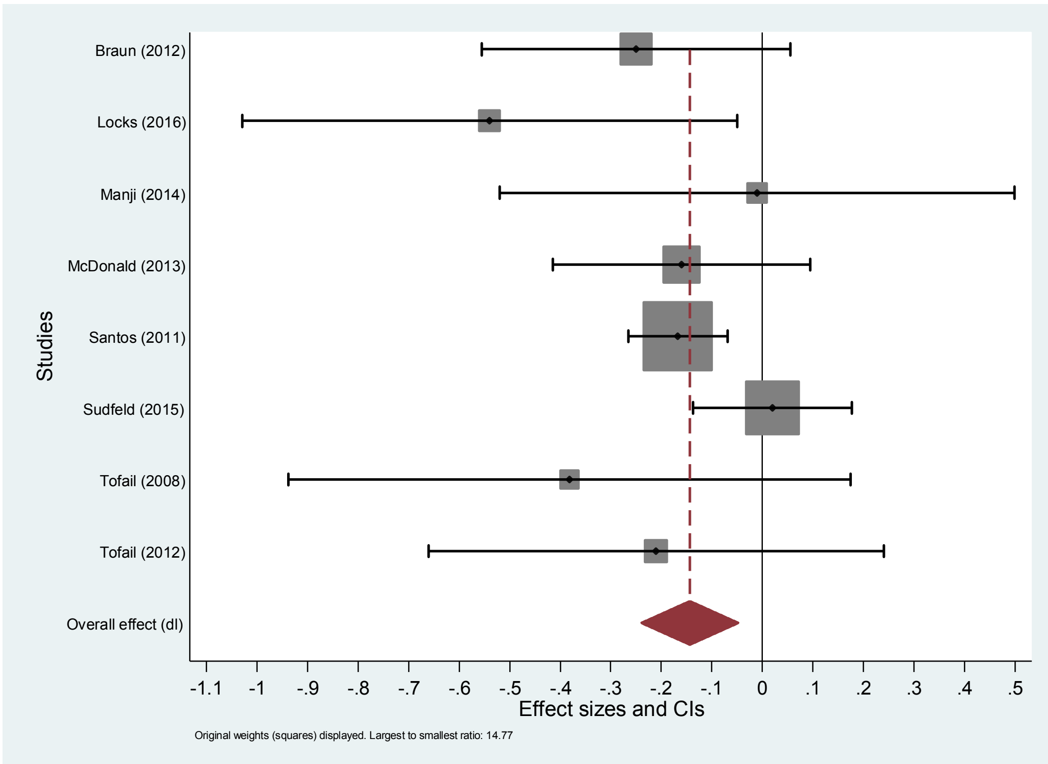

Figure 8: Association between preterm-AGA (reference: term-AGA) and cognitive development.

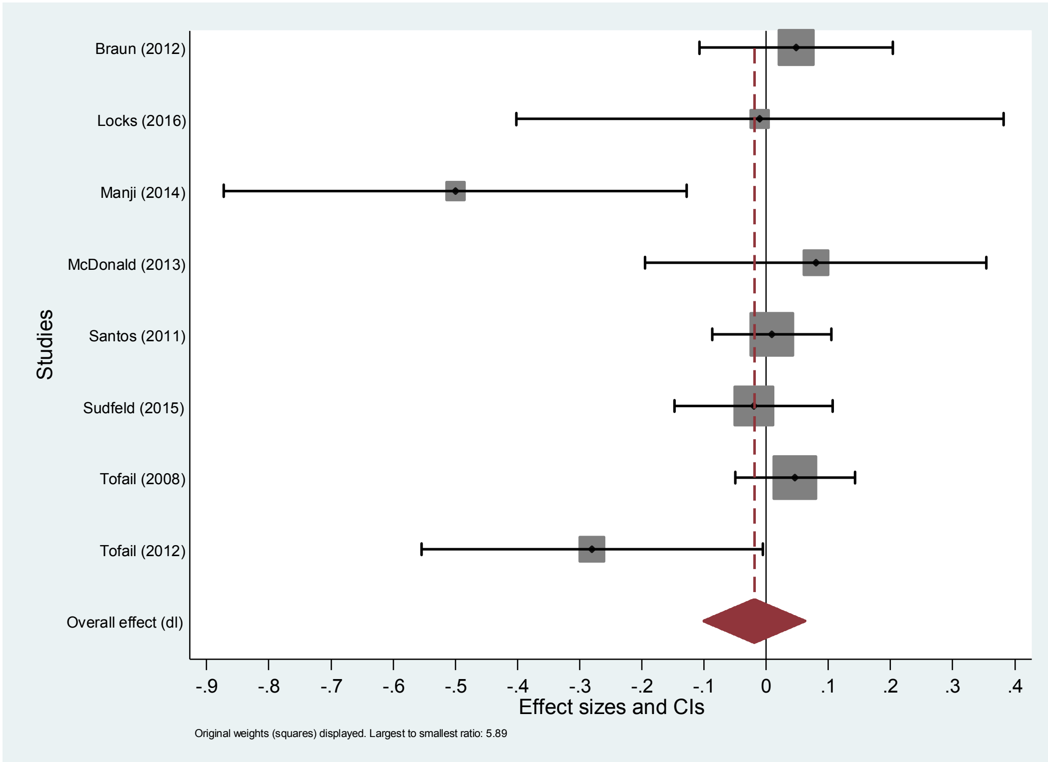

Figure 9: Association between term-SGA (reference: term-AGA) and cognitive development.

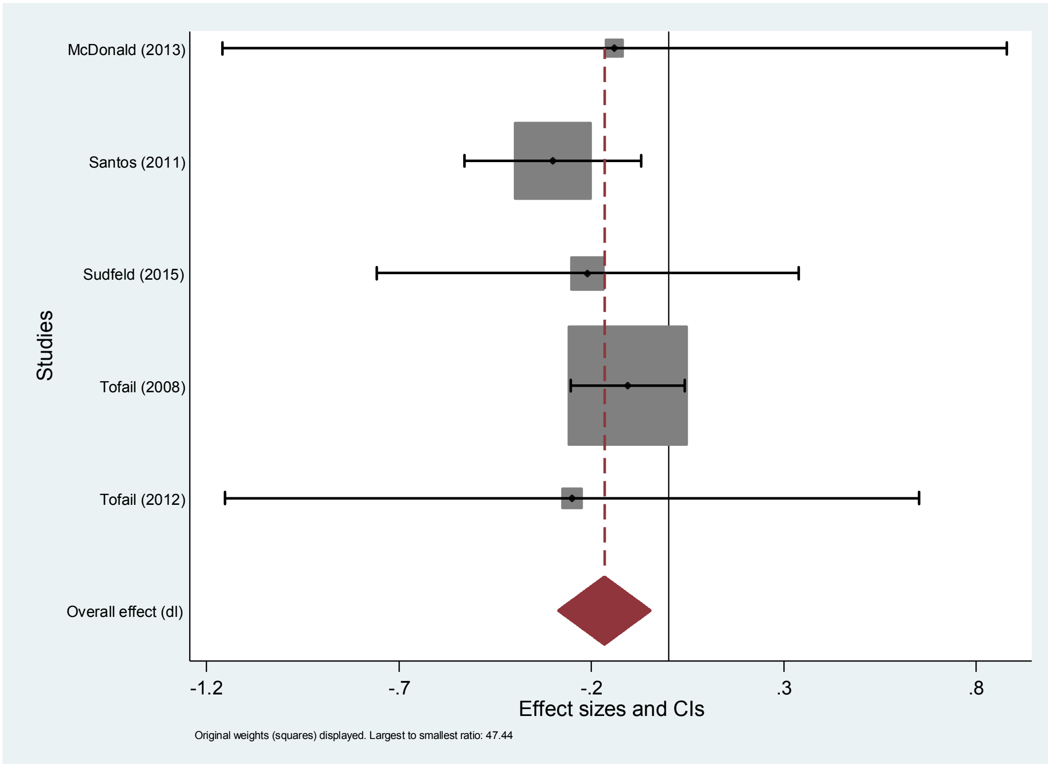

Figure 10: Association between preterm- SGA (reference: term-AGA) and cognitive development.

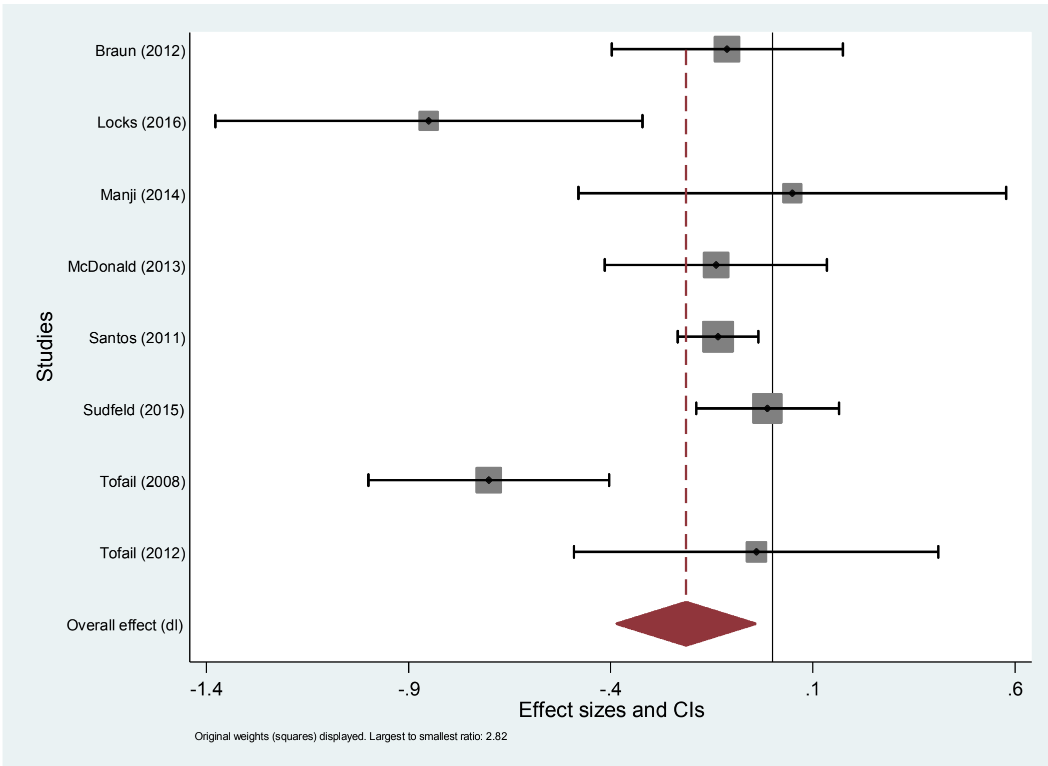

Figure 11: Association between late preterm birth, 34-37 weeks (reference: term) and cognitive development.

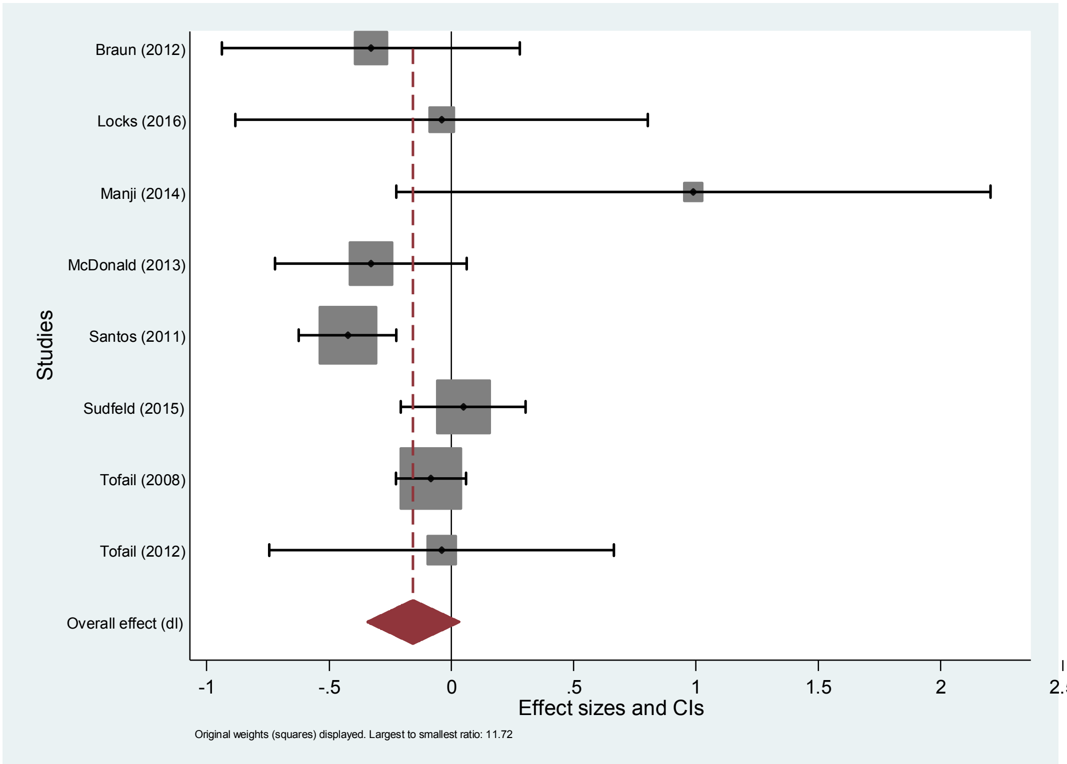

Figure 12: Association between early preterm birth, < 34 weeks (reference: term) and cognitive development.

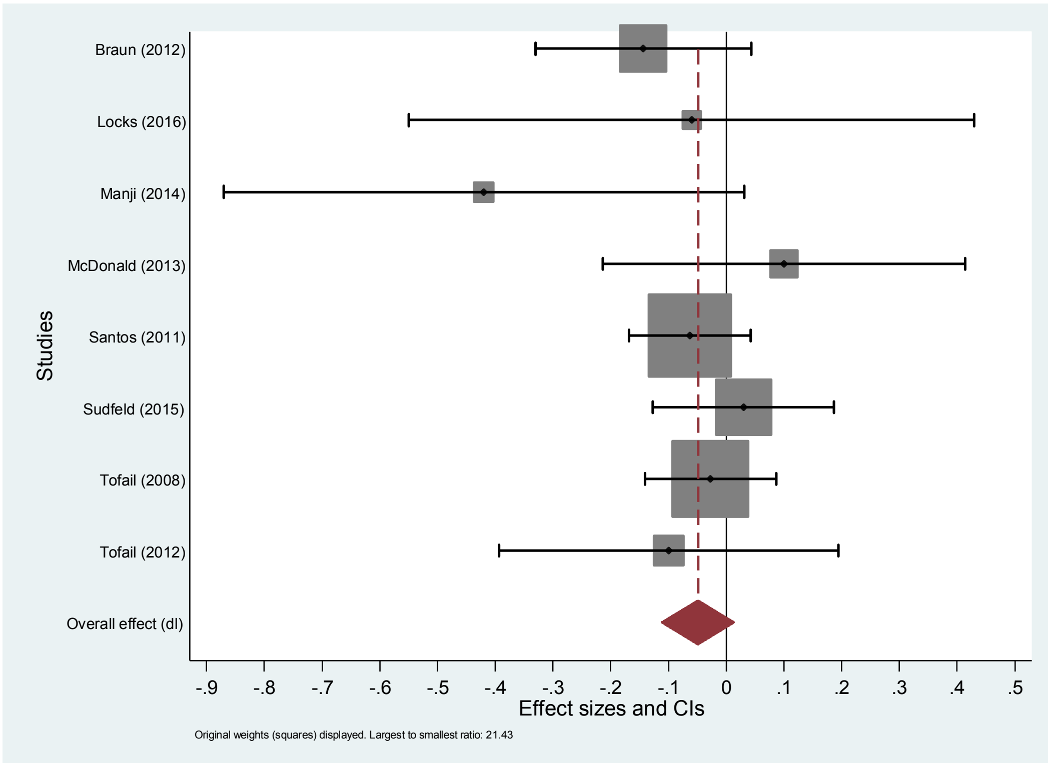

Figure 13: Association between moderate SGA (reference: AGA) and cognitive development.

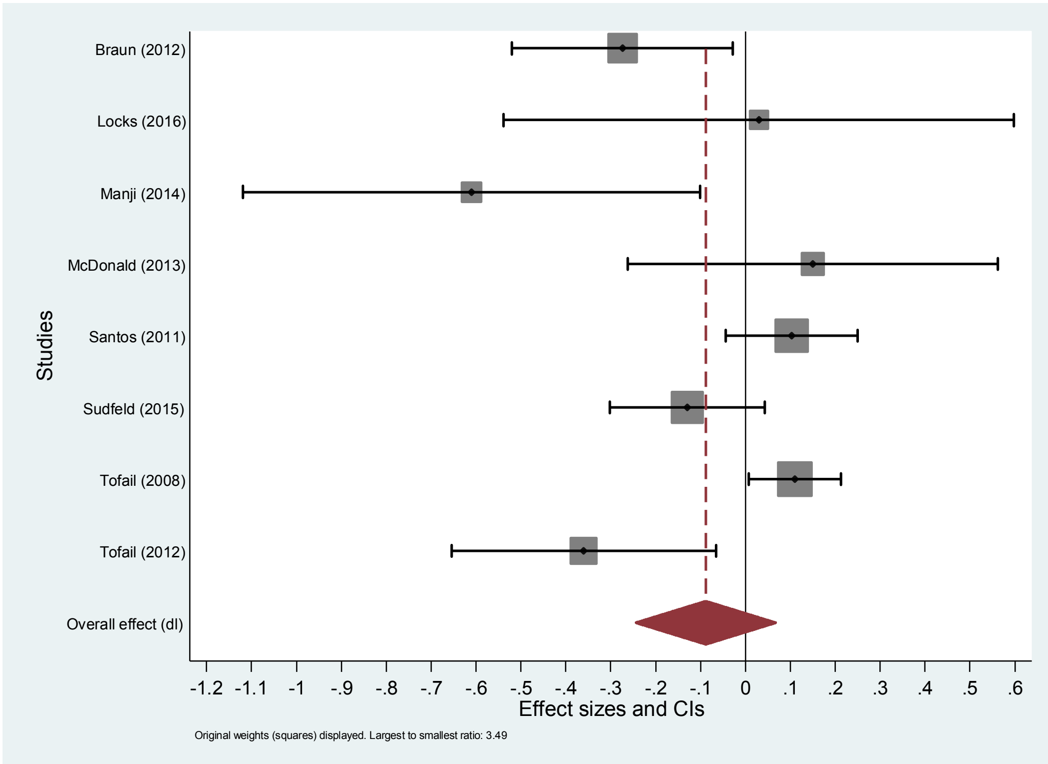

Figure 14: Association between severe SGA (reference: AGA) and cognitive development.

2. Child Risk Factors on Child's Motor Development

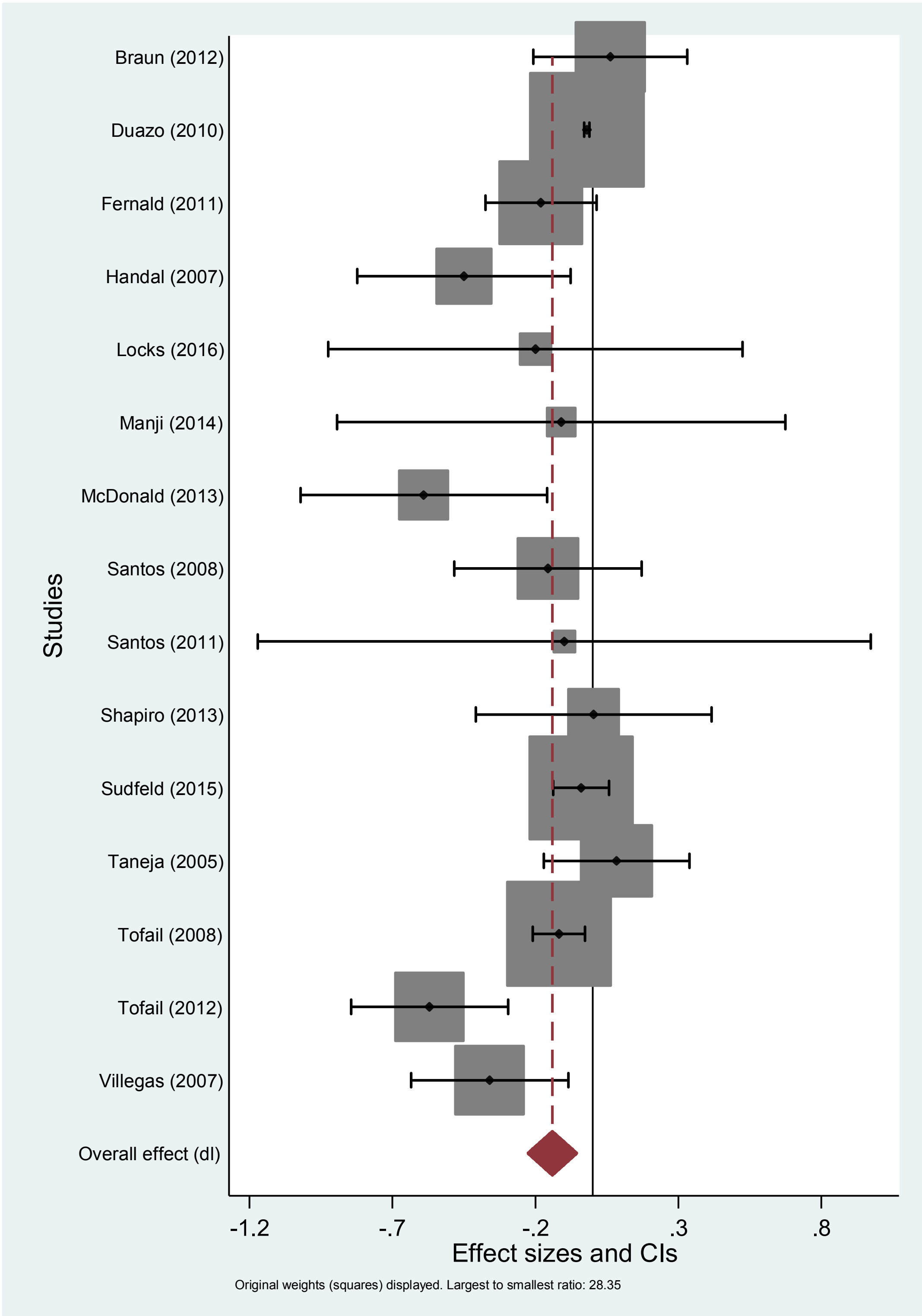

Figure 15: Association between low birth weight (reference: normal birth weight) and motor development.

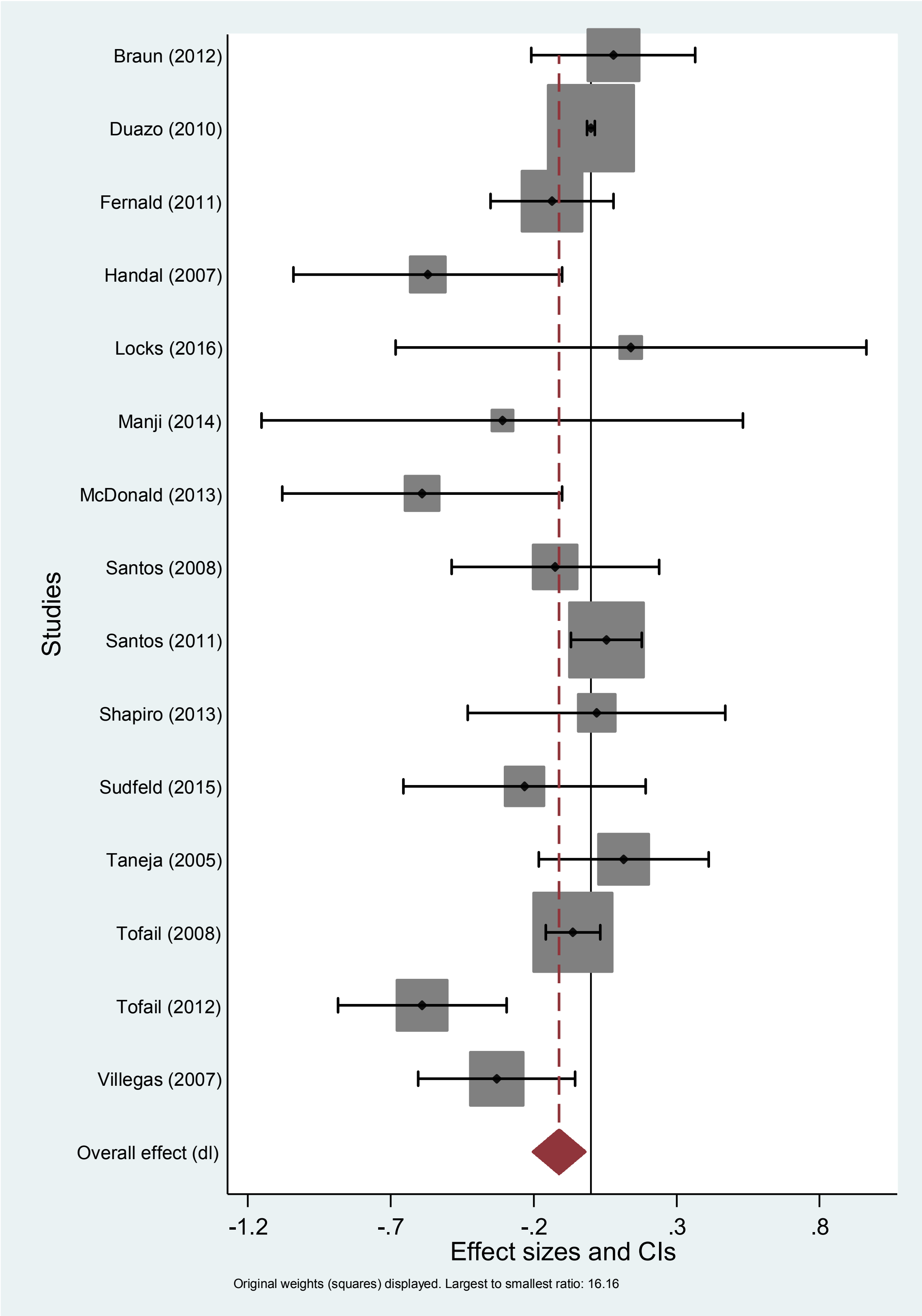

Figure 16: Association between moderately low birth weight (reference: normal birth weight) and motor development.

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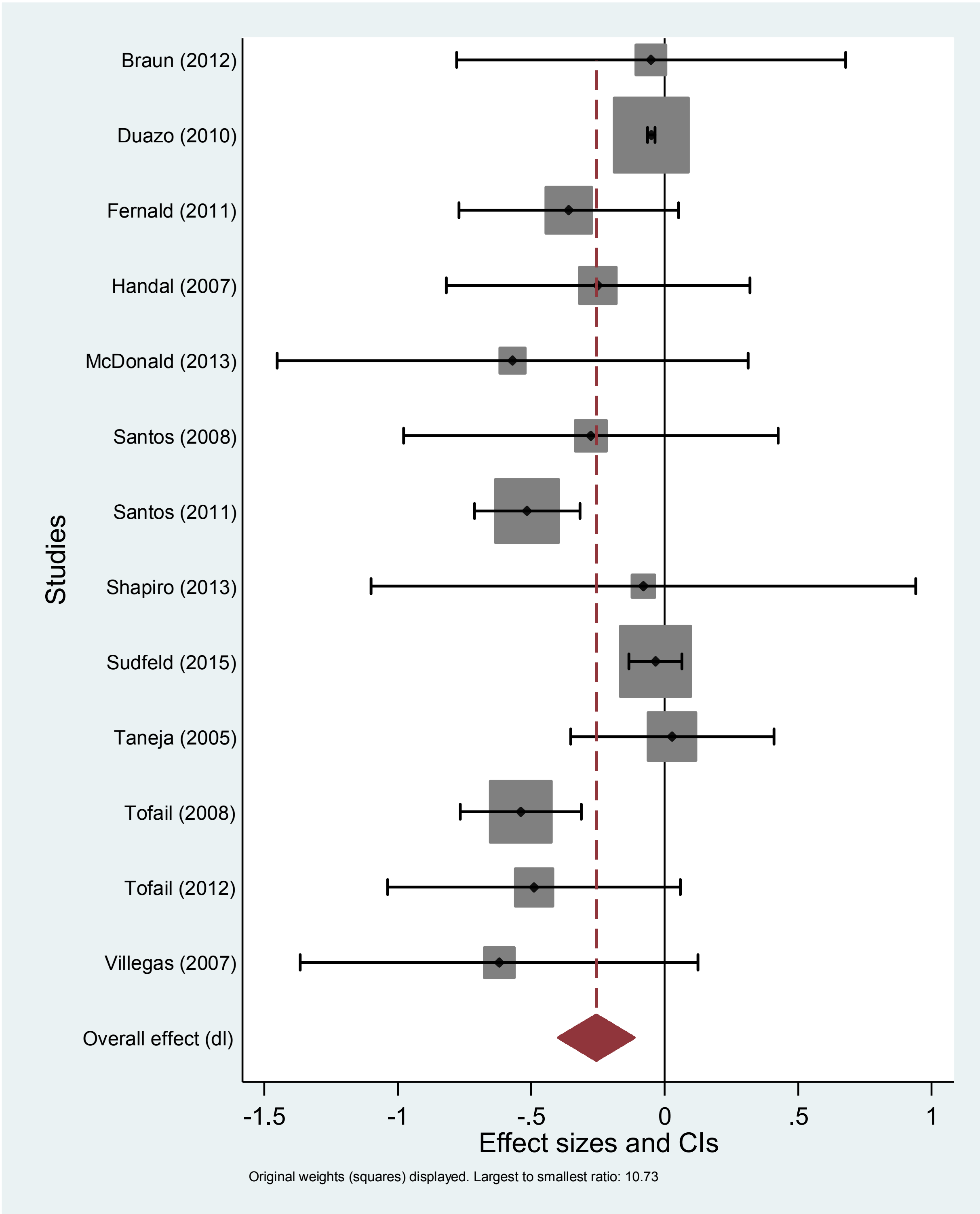

Figure 17: Association between very low birth weight (reference: normal birth weight) and motor development.

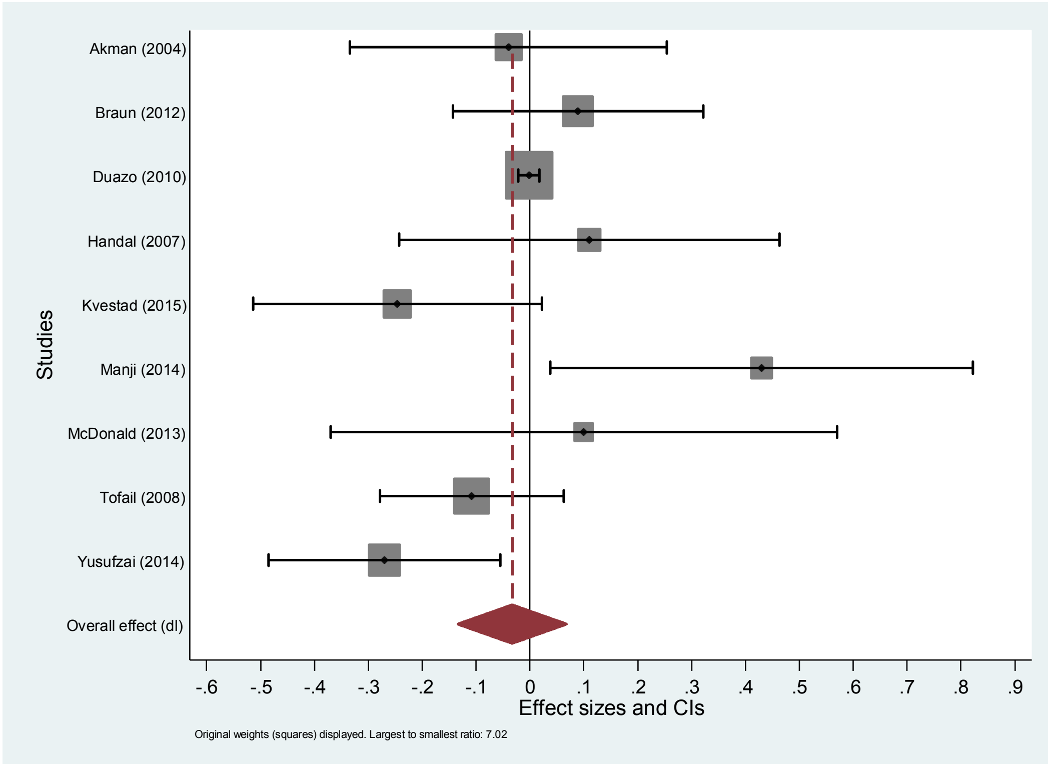

Figure 18: Association between child mild anemia (reference: no anemia) and motor development.

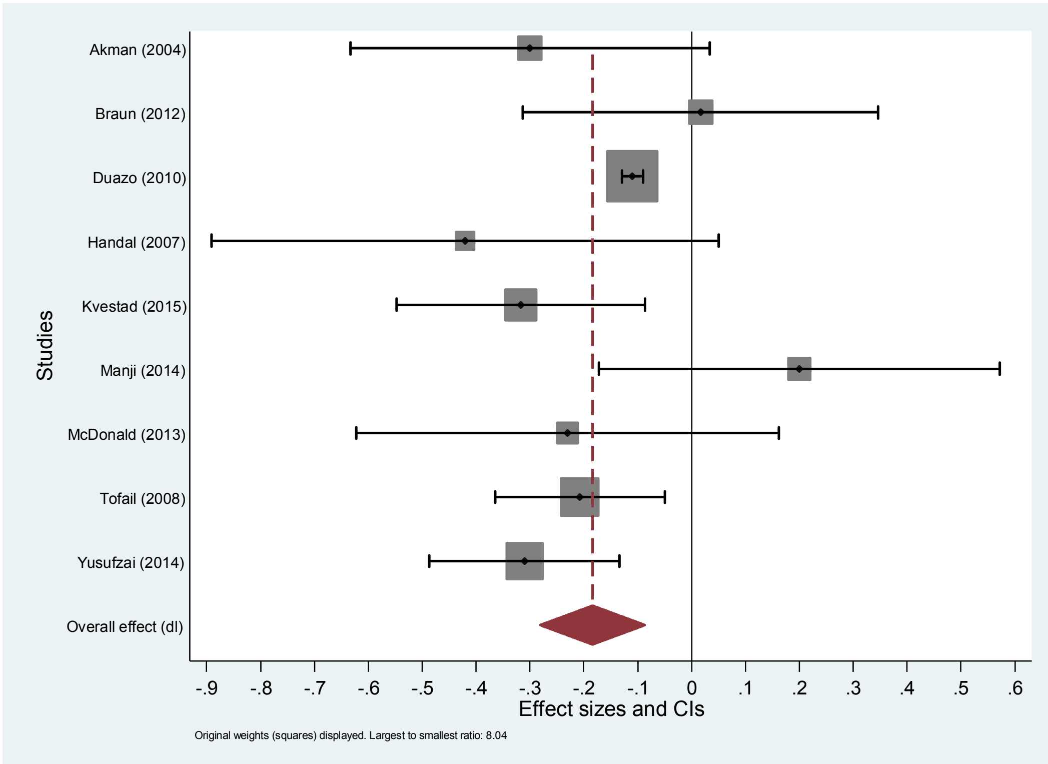

Figure 19: Association between child moderate anemia (reference: no anemia) and motor development.

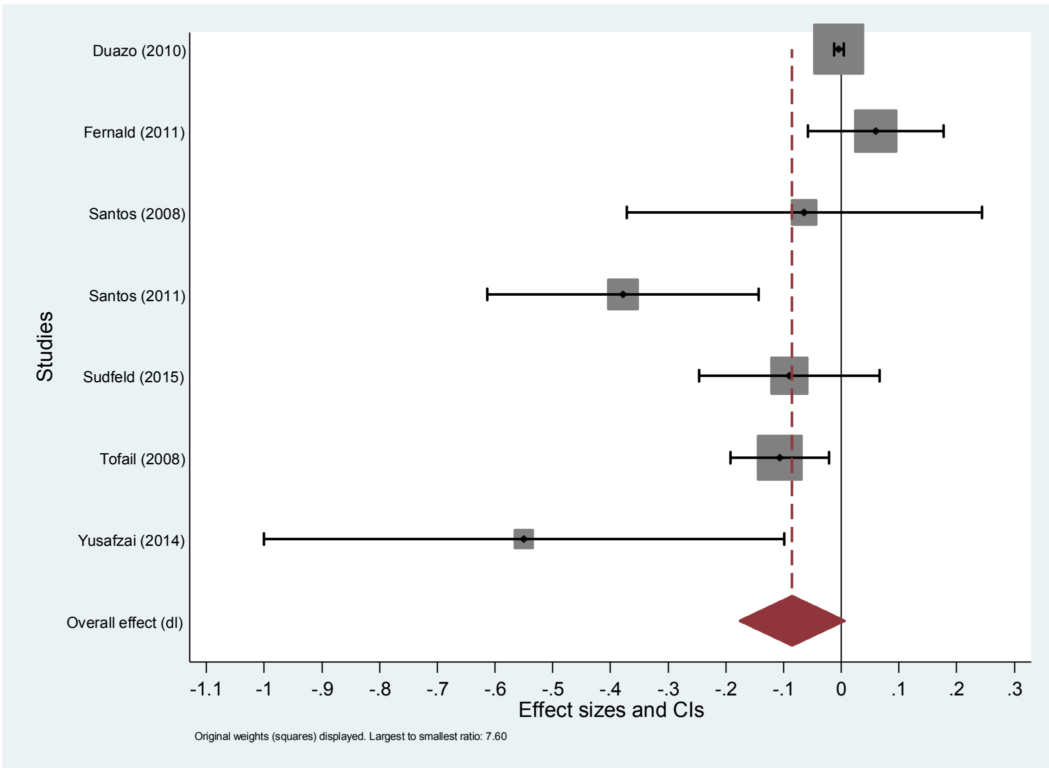

Figure 20: Association between lack of access to clean water (reference: access to clean water) and motor development.

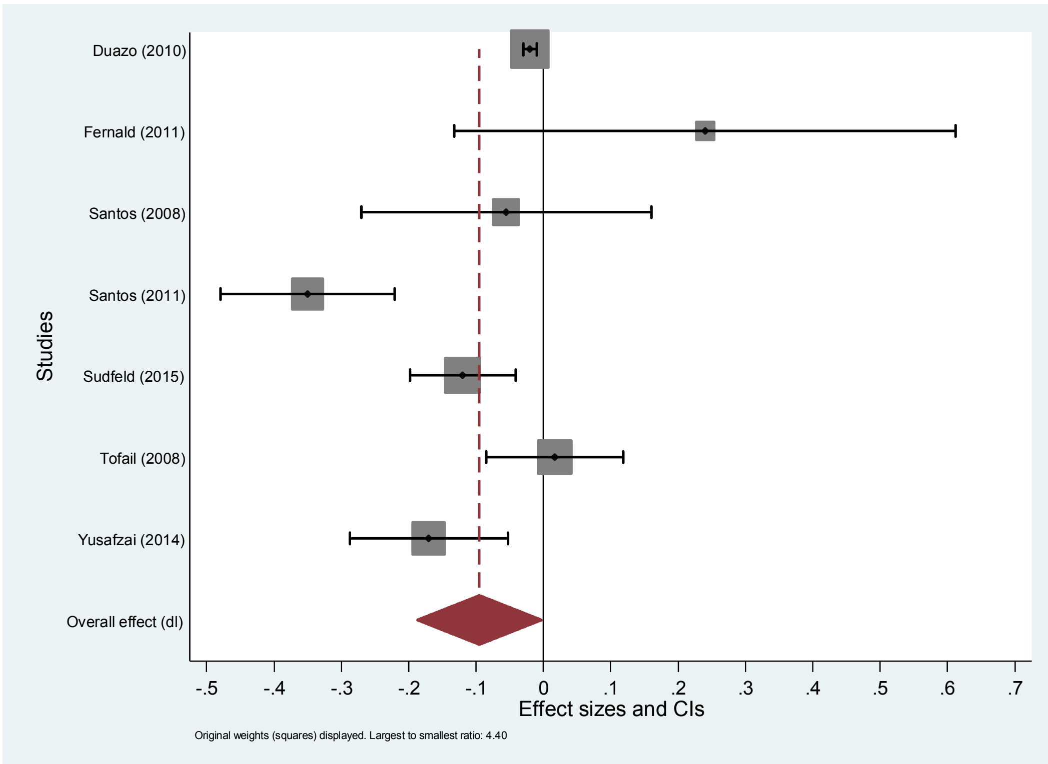

Figure 21: Association between lack of access to sanitation (reference: access to sanitation) and motor development.

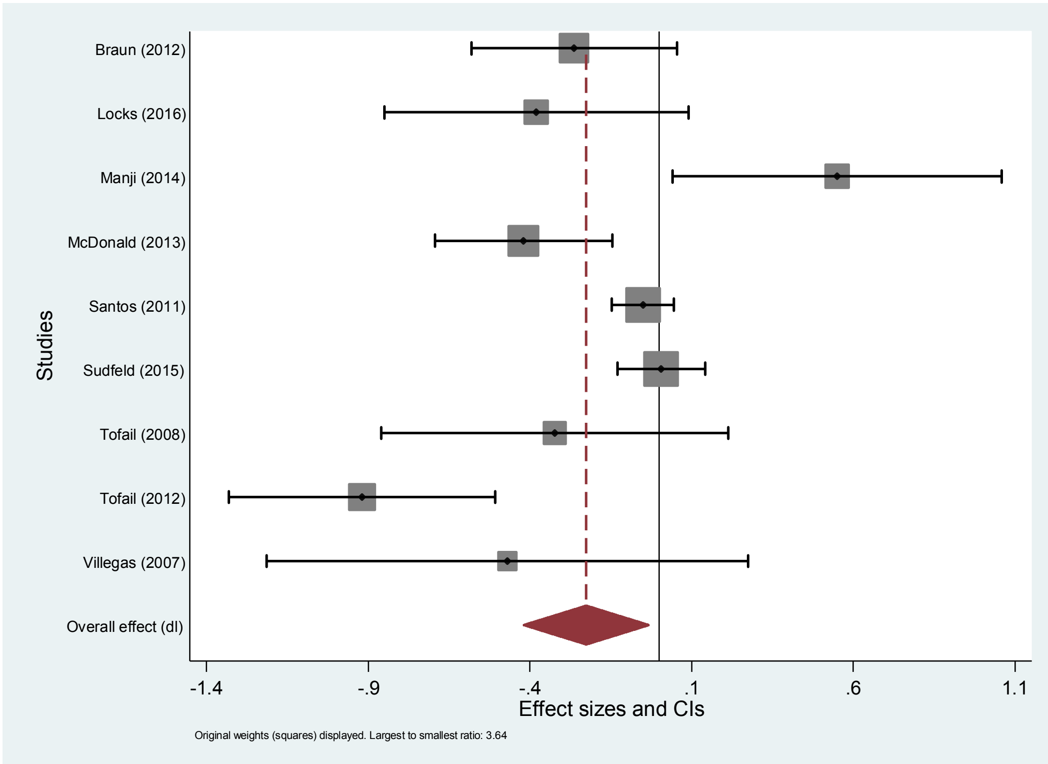

Figure 22: Association between preterm-AGA (reference: term-AGA) and motor development.

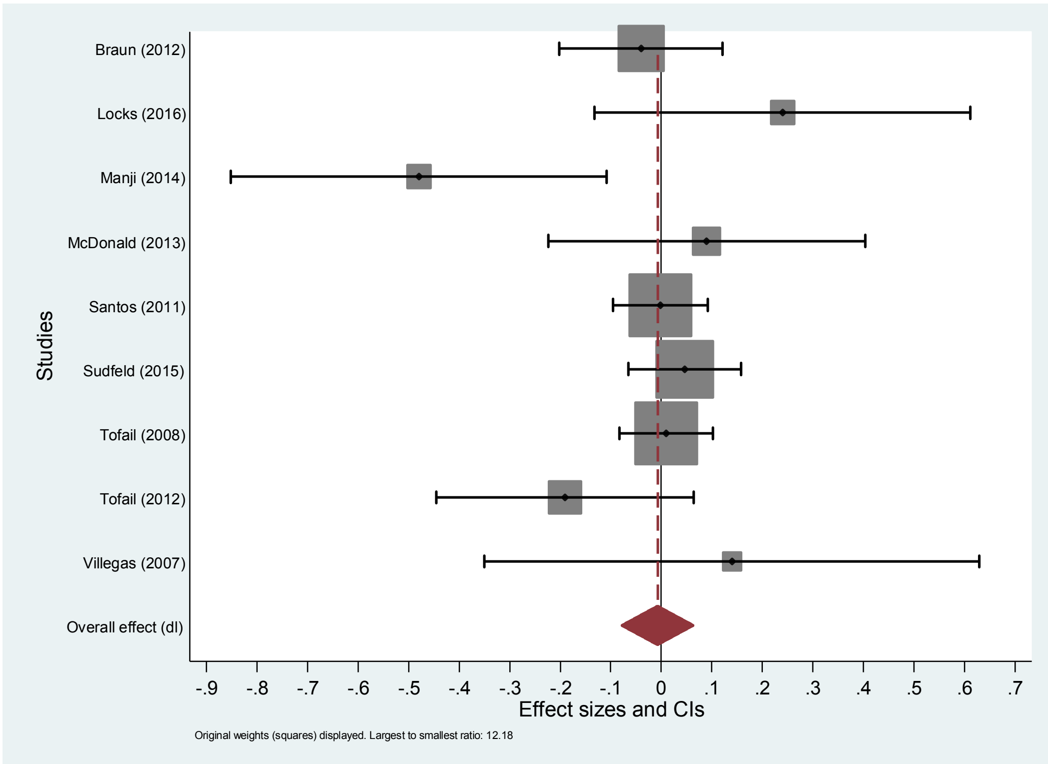

Figure 23: Association between term-SGA (reference: term-AGA) and motor development.

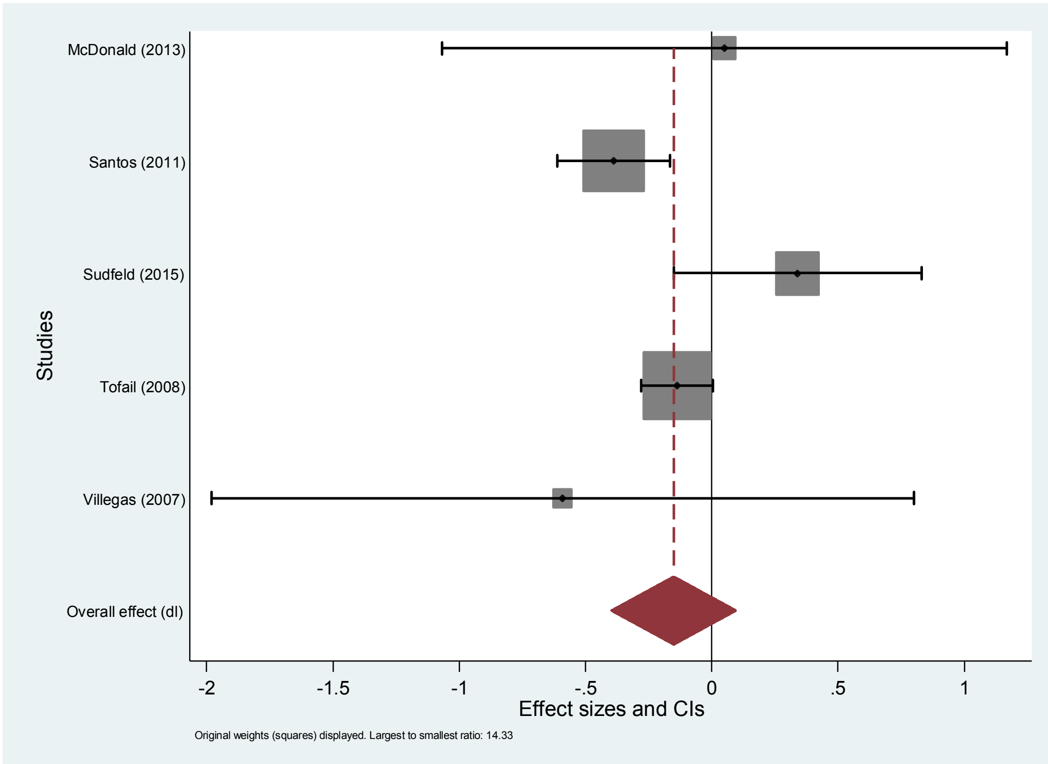

Figure 24: Association between preterm-SGA (reference: term-AGA) and motor development.

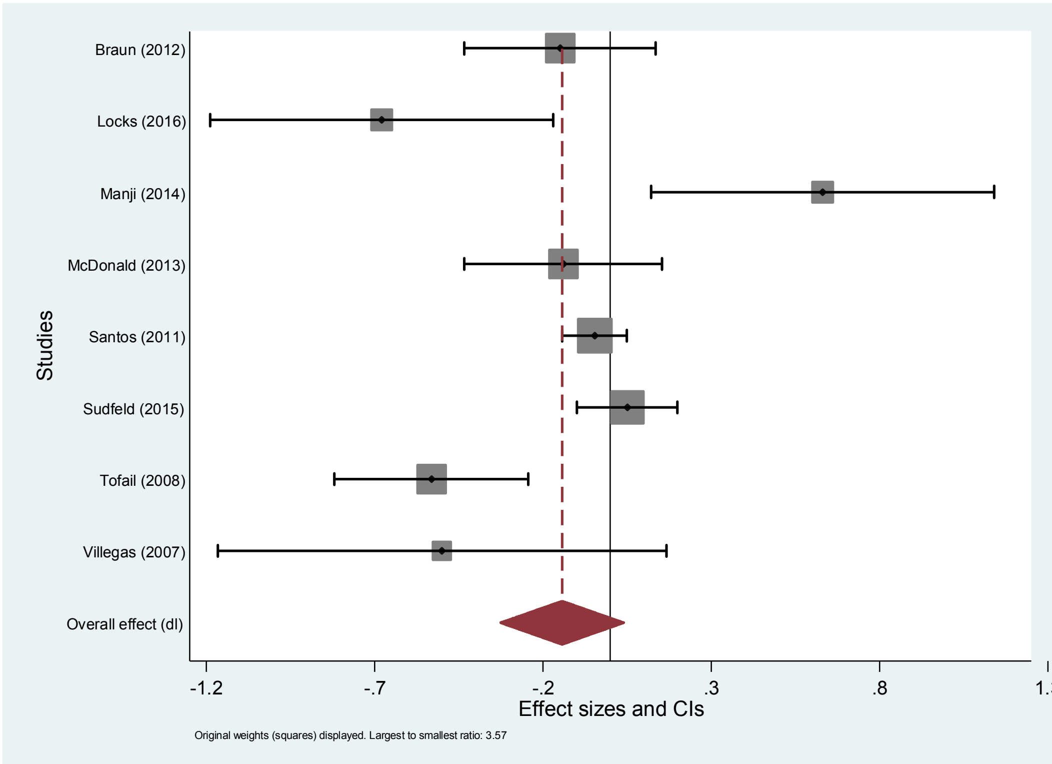

Figure 25: Association between late preterm birth, 34-37 weeks (reference: term) and motor development.

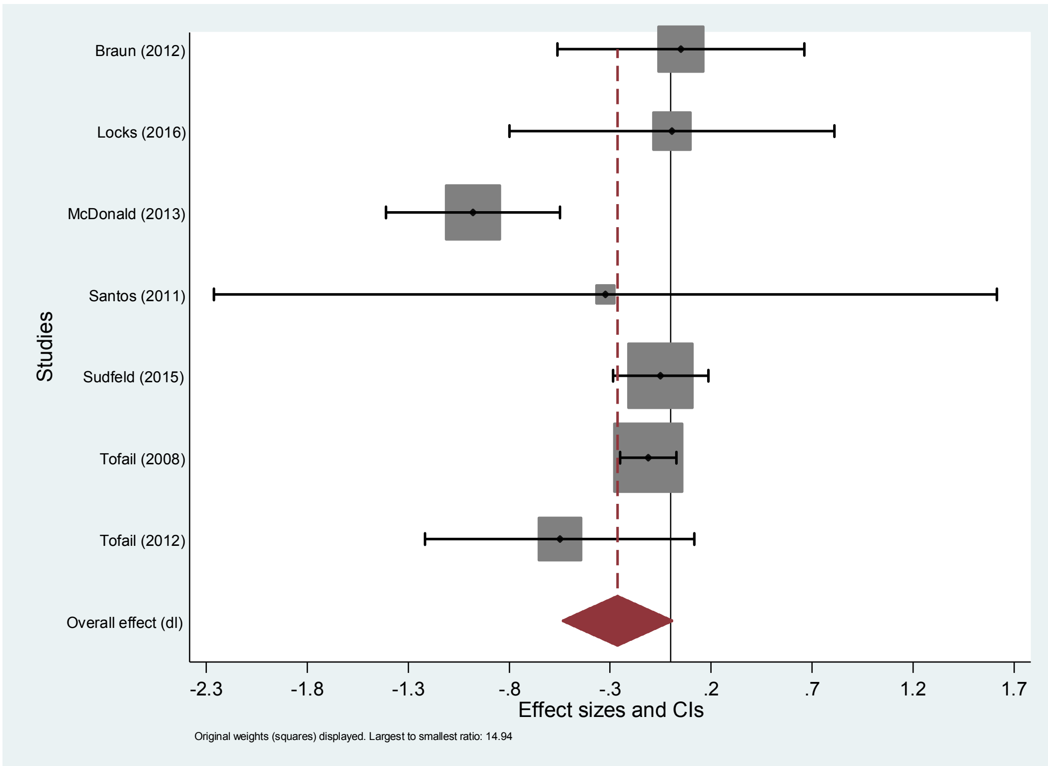

Figure 26: Association between early preterm birth, < 34 weeks (reference: term) and motor development.

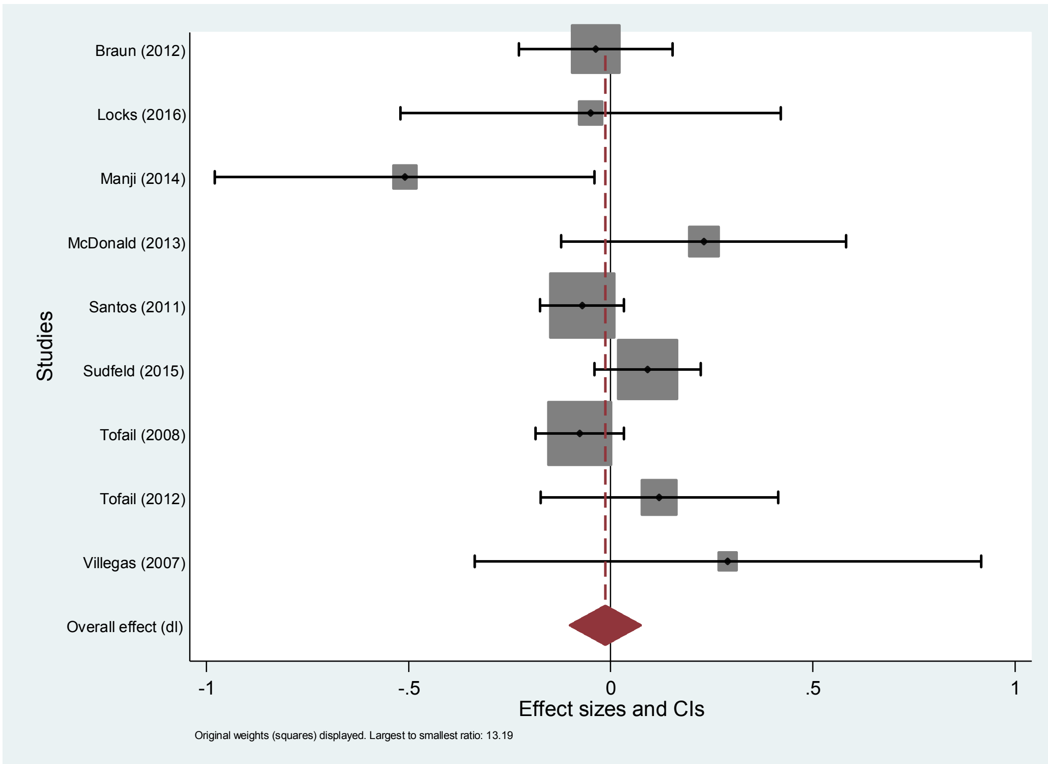

Figure 27: Association between moderate SGA (reference: AGA) and motor development.

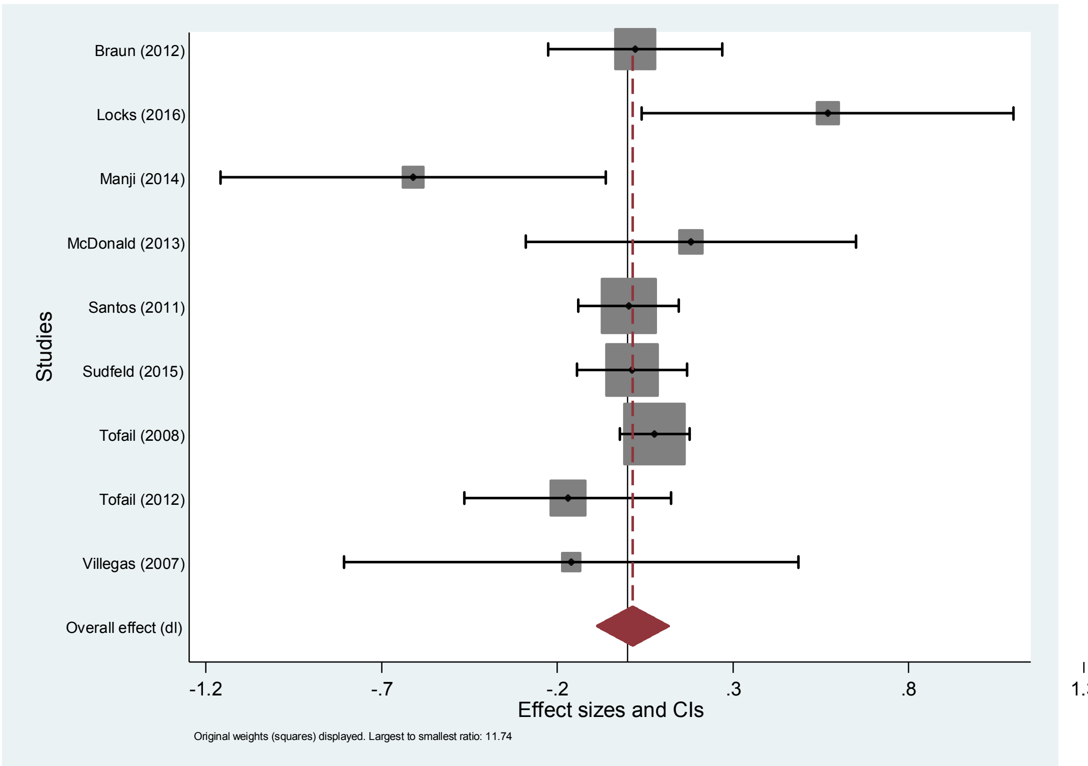

Figure 28: Association between severe SGA (reference: AGA) and motor development.

3. Child Risk Factors on Child's Language Development

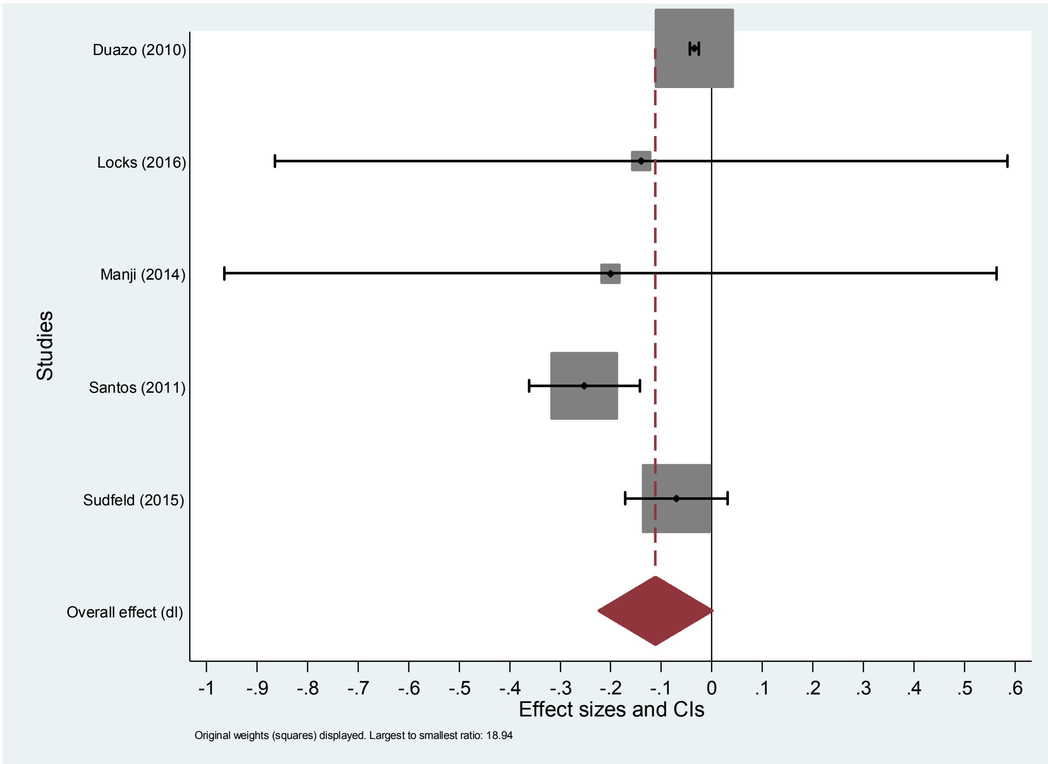

Figure 29: Association between low birth weight (LBW) and (reference: normal birth weight) and language development.

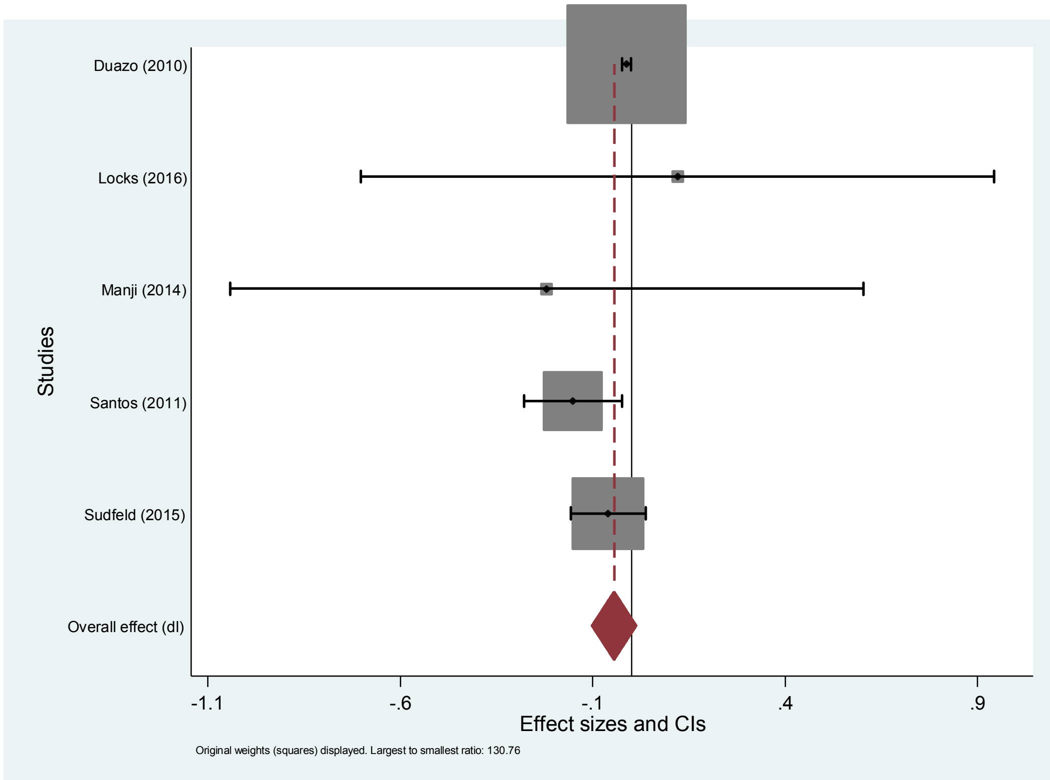

Figure 30: Association between moderately low birth weight and (reference: normal birth weight) and language development.

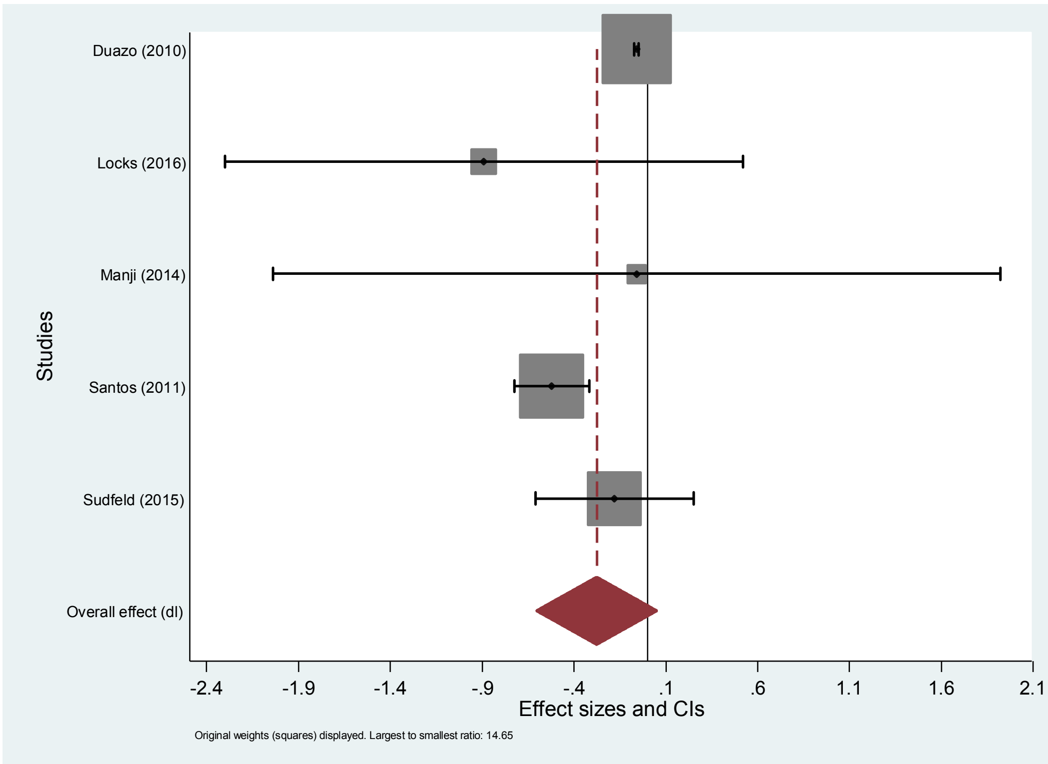

Figure 31: Association between very low birth weight and (reference: normal birth weight) and language development.

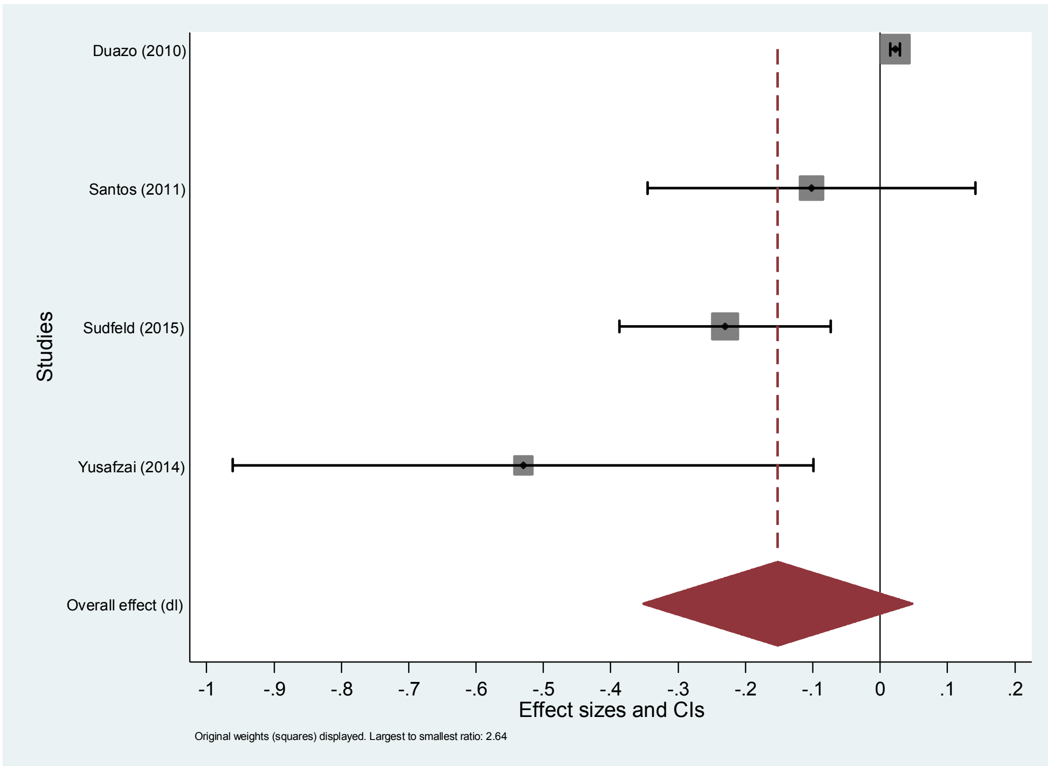

Figure 32: Association between lack of access to clean water (reference: access to clean water) and language development.

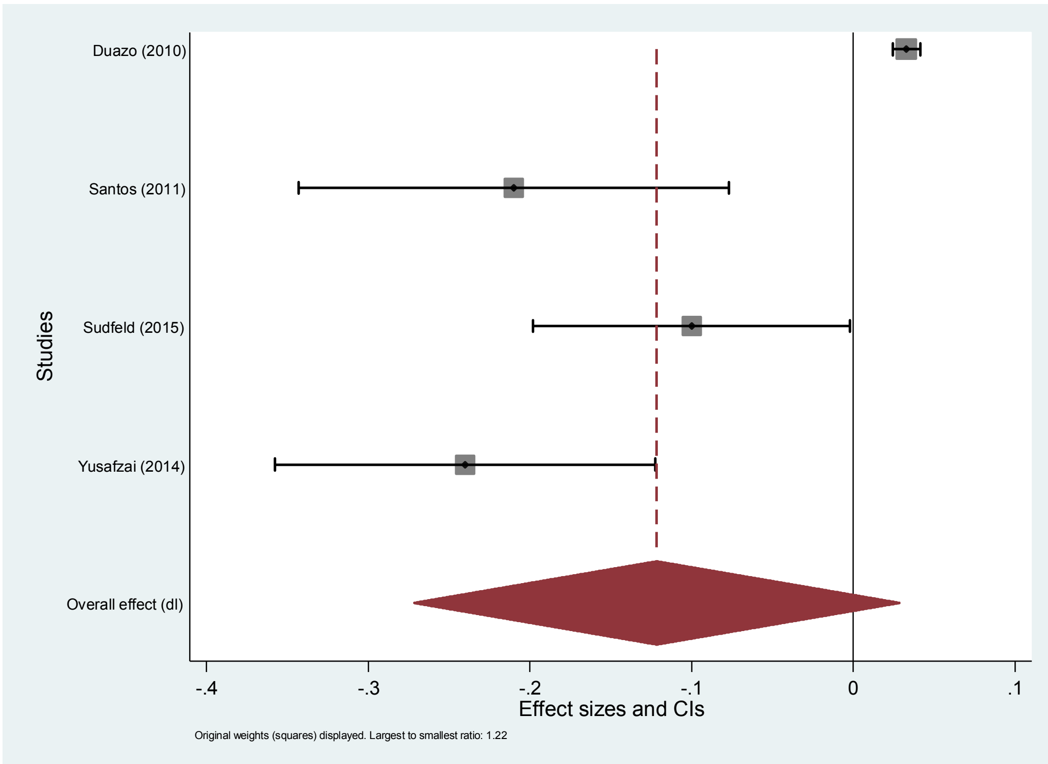

Figure 33: Association between lack of access to sanitation (reference: access to sanitation) and language development.

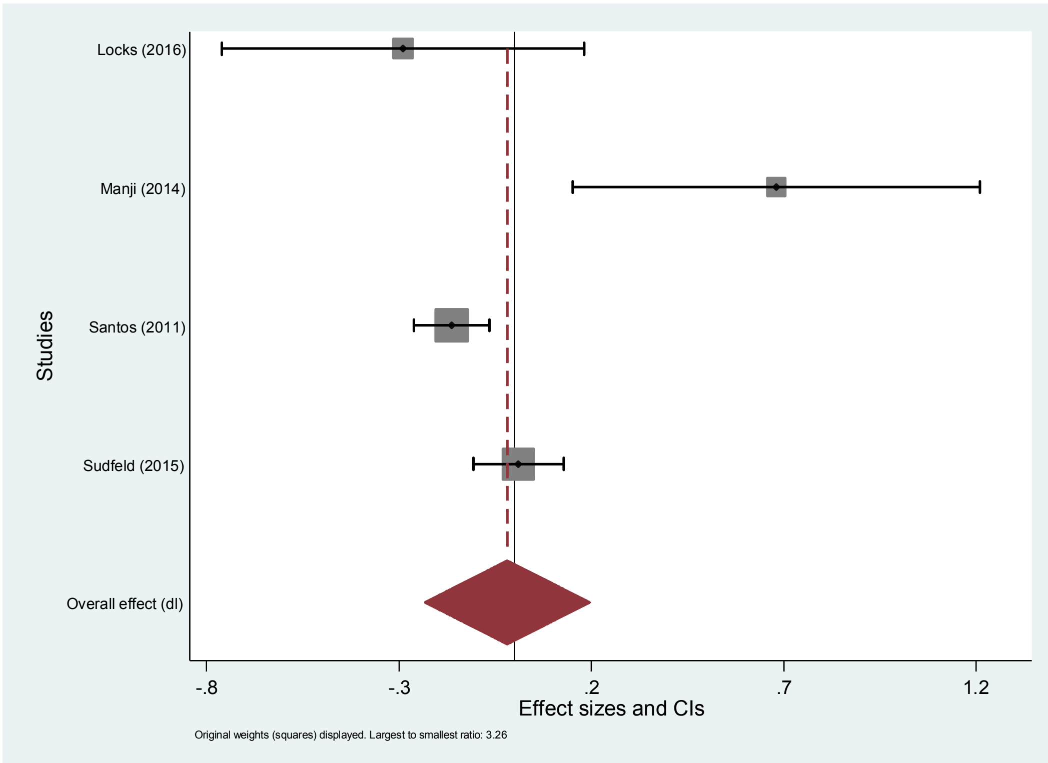

Figure 34: Association between preterm-AGA (reference: term-AGA) and language development.

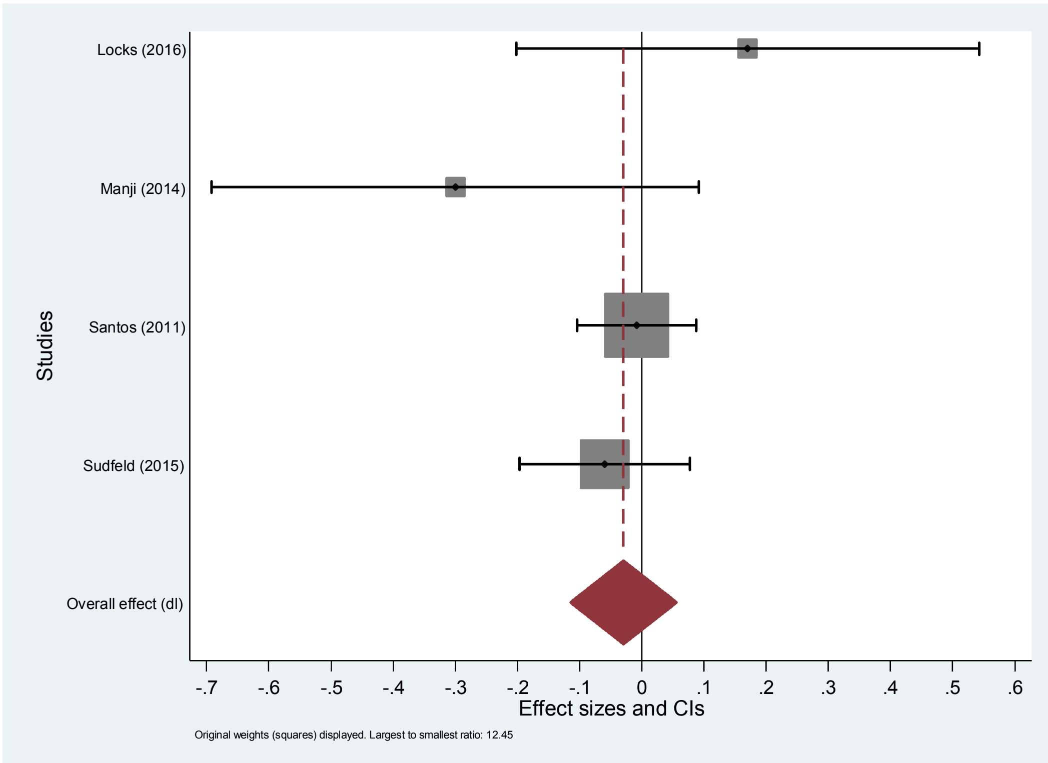

Figure 35: Association between term-SGA (reference: term-AGA) and language development.

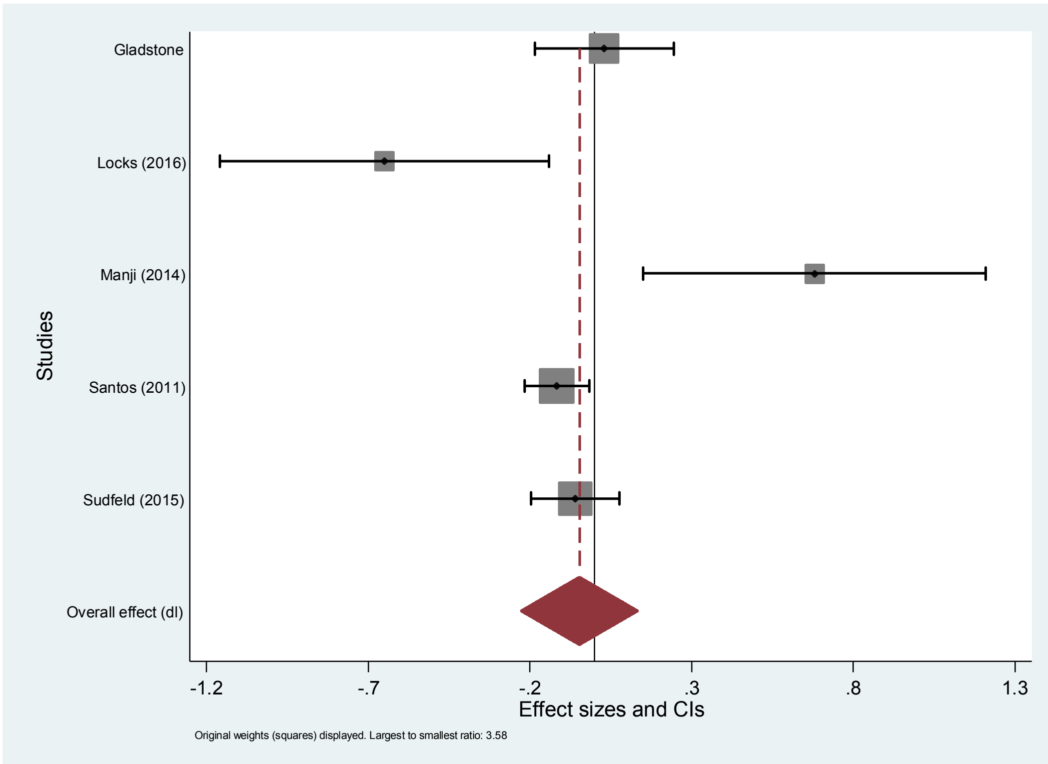

Figure 36: Association between late preterm birth, 34-37 weeks (reference: term) and language development.

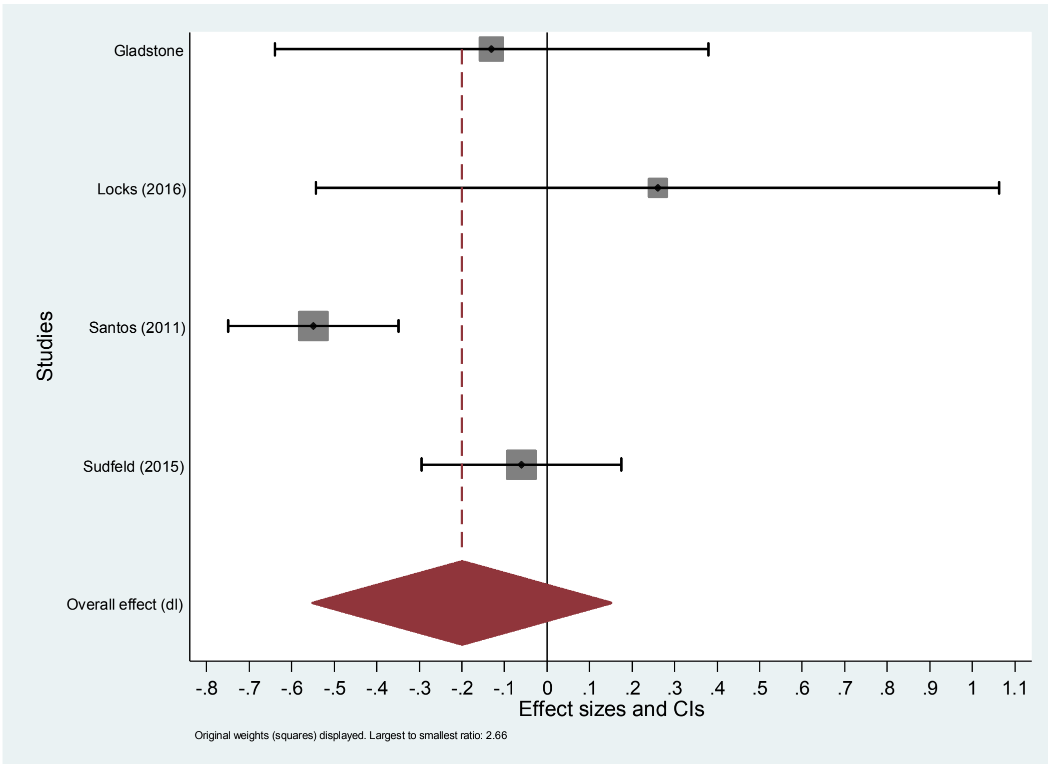

Figure 37: Association between early preterm birth, < 34 weeks (reference: term) and language development.

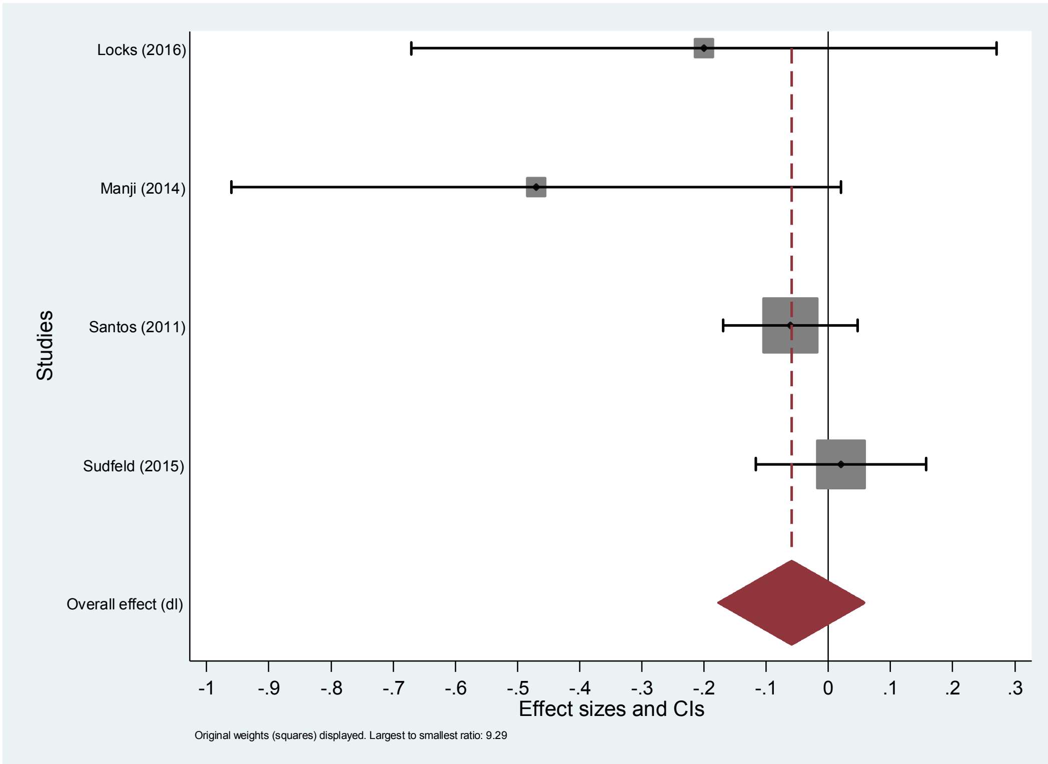

Figure 38: Association between moderate SGA (reference: AGA) and language development.

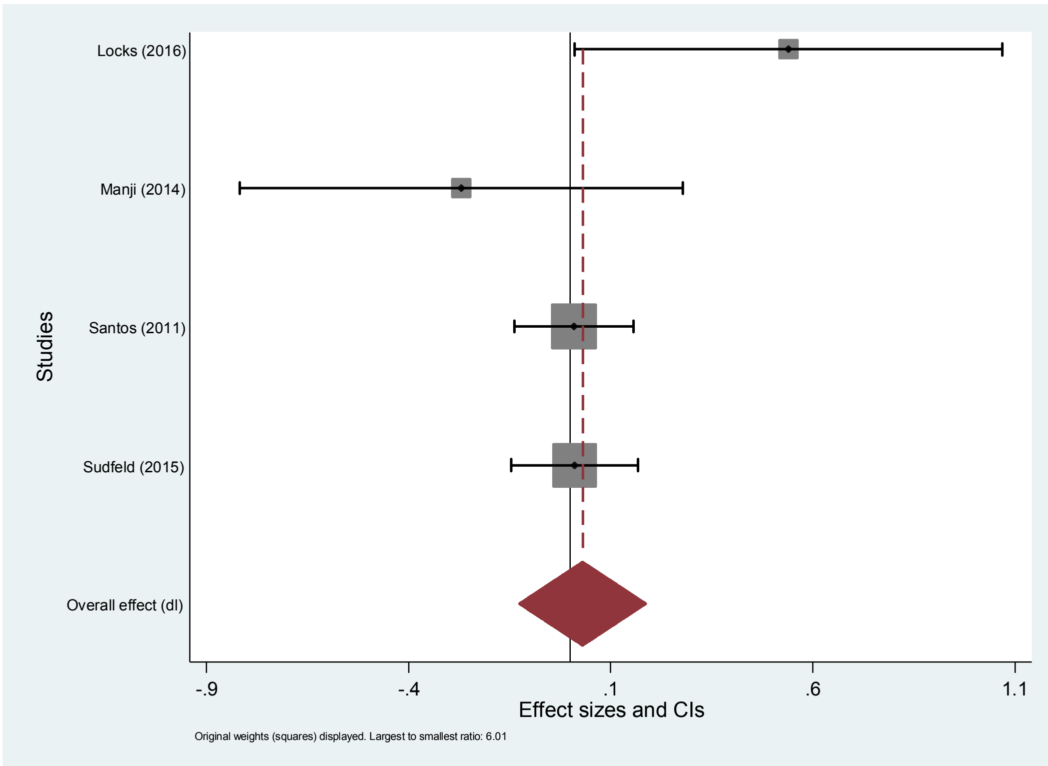

Figure 39: Association between severe SGA (reference: AGA) and language development.

4. Parental Risk Factors on Child's Cognitive Development

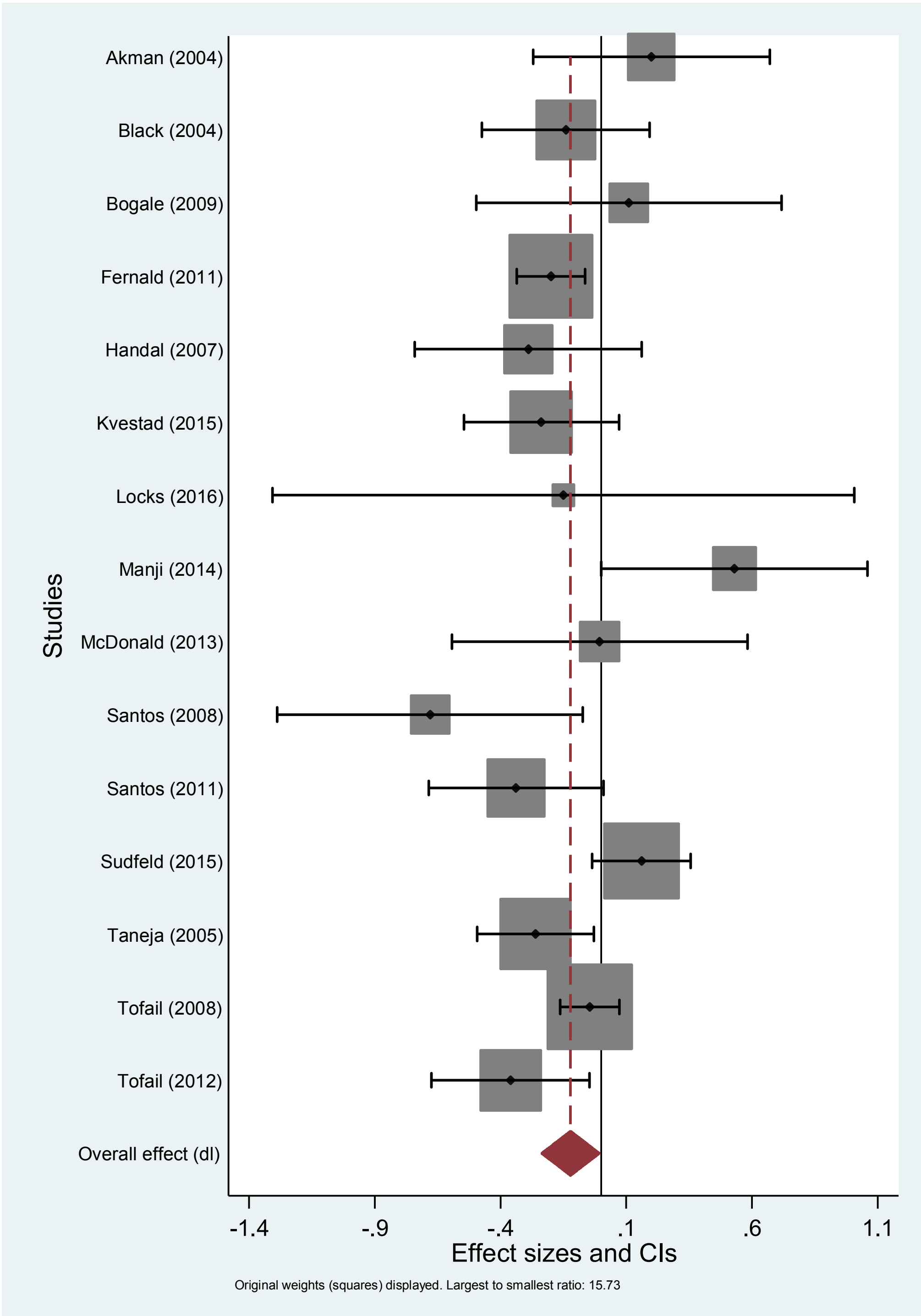

Figure 40: Association between no maternal education (reference: primary education) and cognitive development.

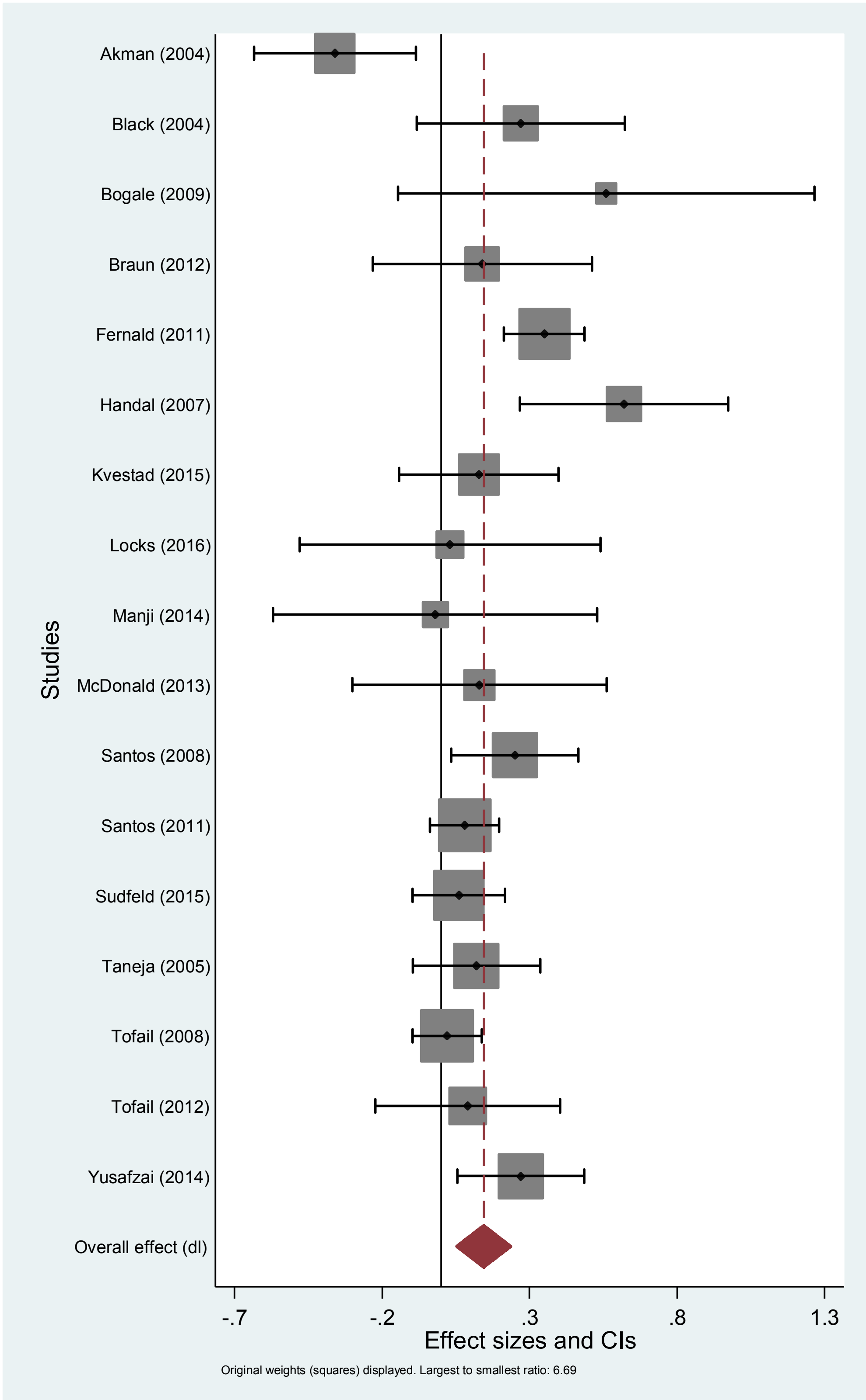

Figure 41: Association between maternal secondary education (reference: primary education) and cognitive development.

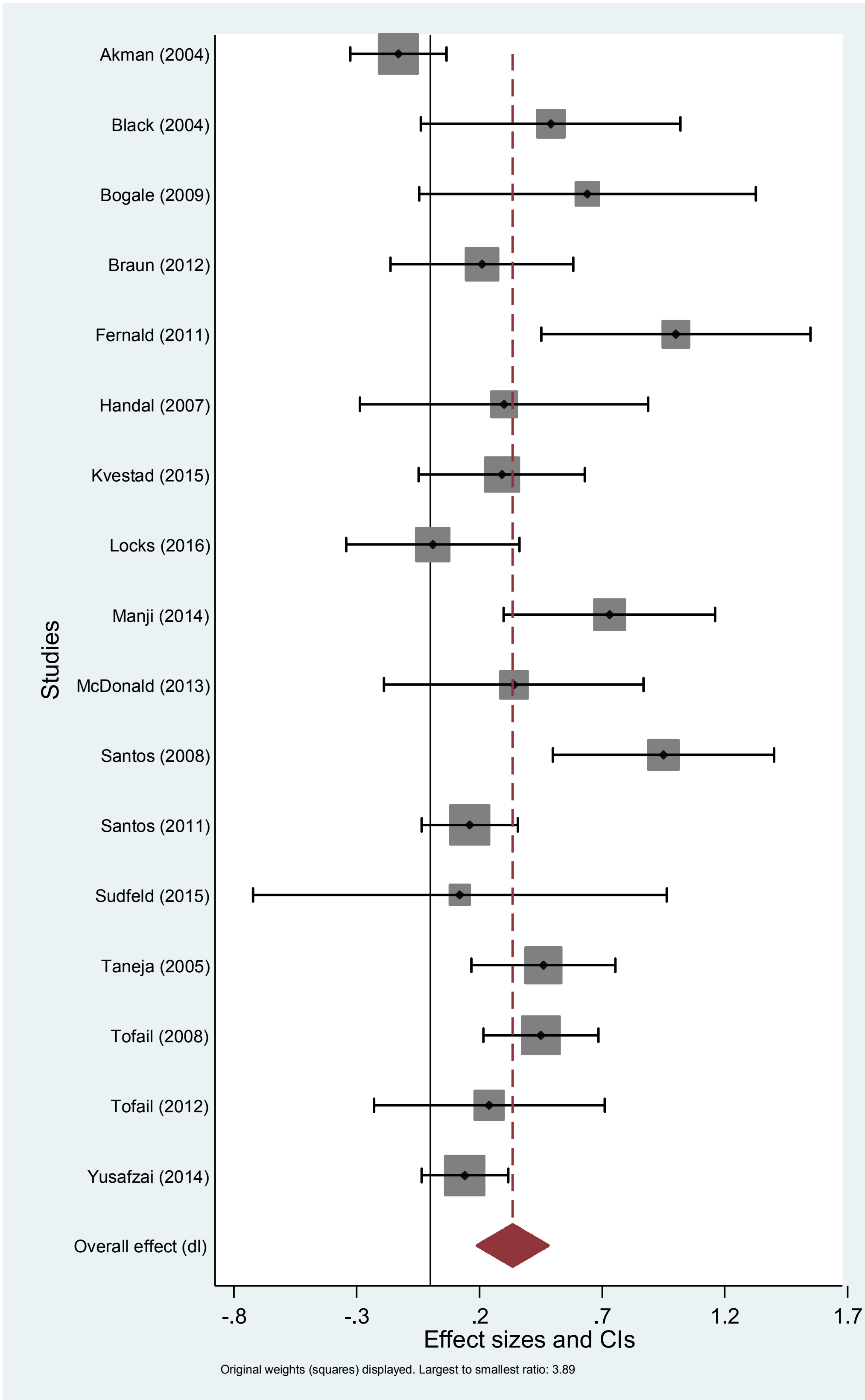

Figure 42: Association between maternal higher education (reference: primary education) and cognitive development.

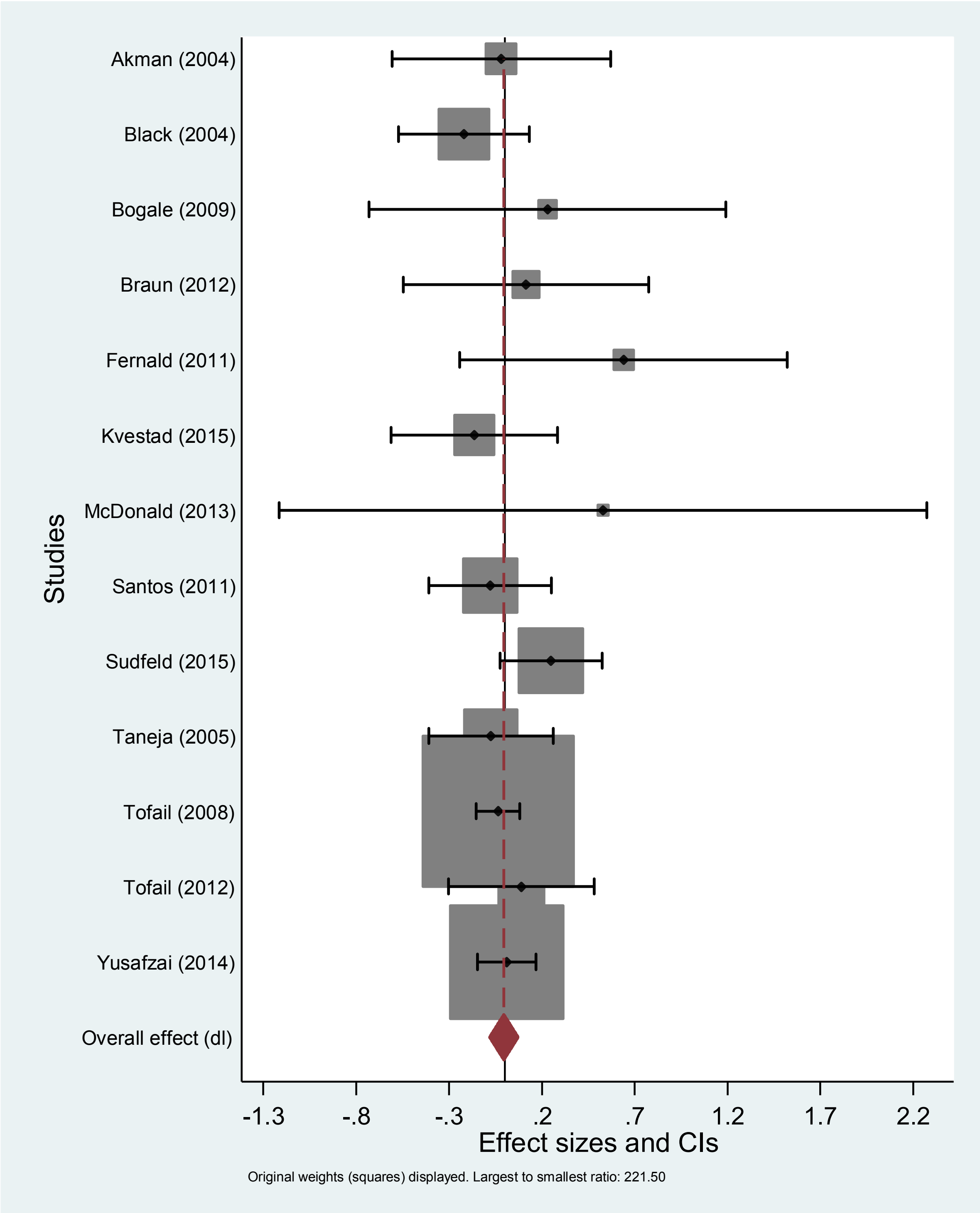

Figure 43: Association between no paternal education (reference: primary education) and cognitive development.

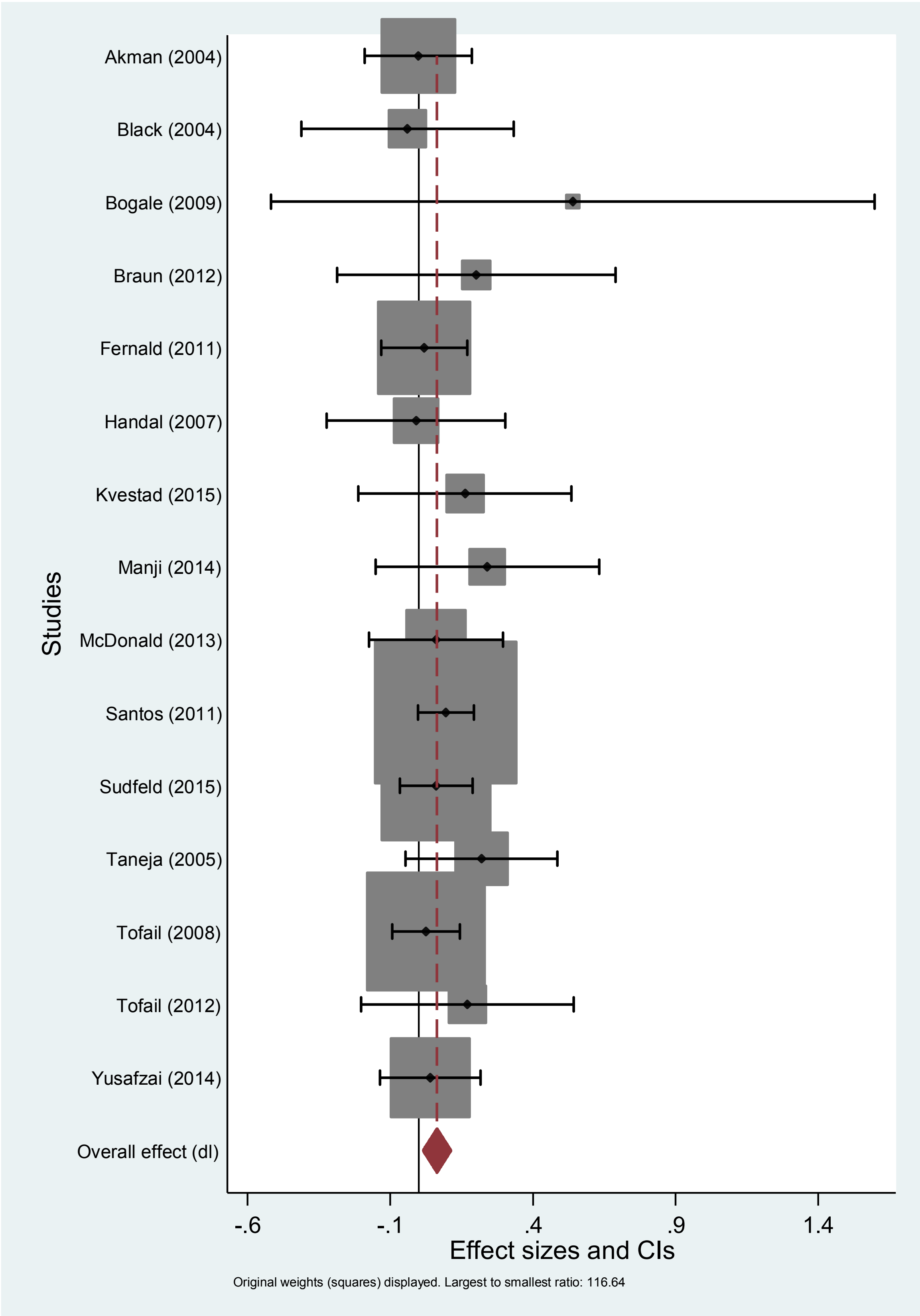

Figure 44: Association between paternal secondary education (reference: primary education) and cognitive development.

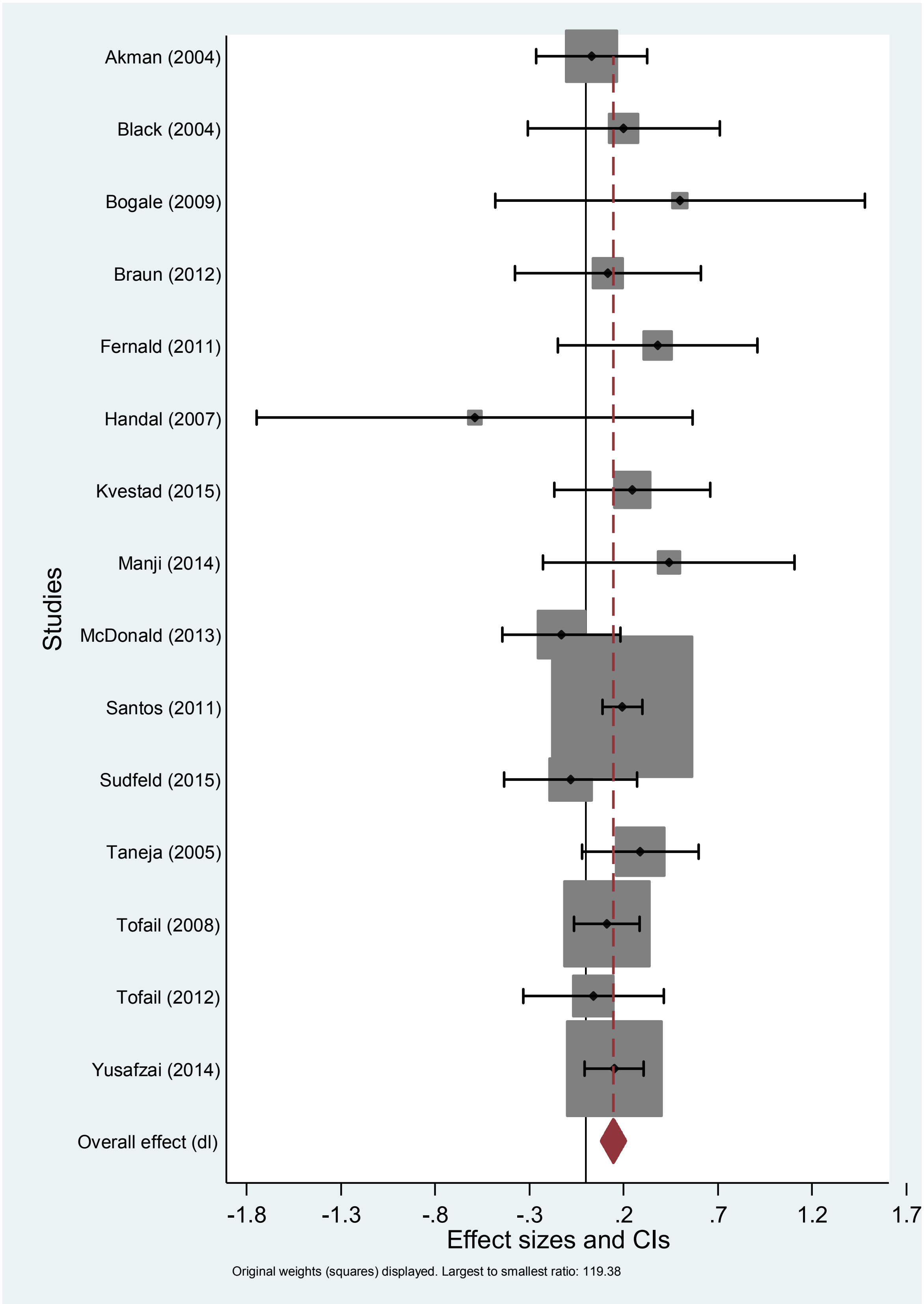

Figure 45: Association between paternal higher education (reference: primary education) and cognitive development.

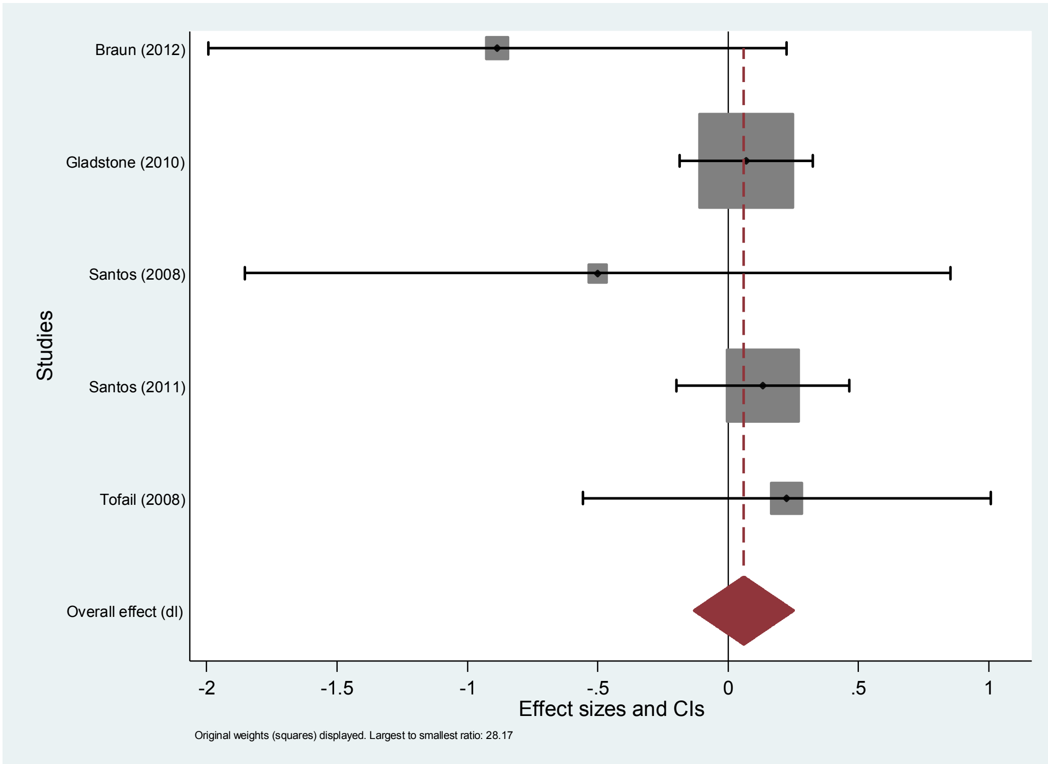

Figure 46: Association between maternal ages < 15 (reference: ages 20-34) and cognitive development.

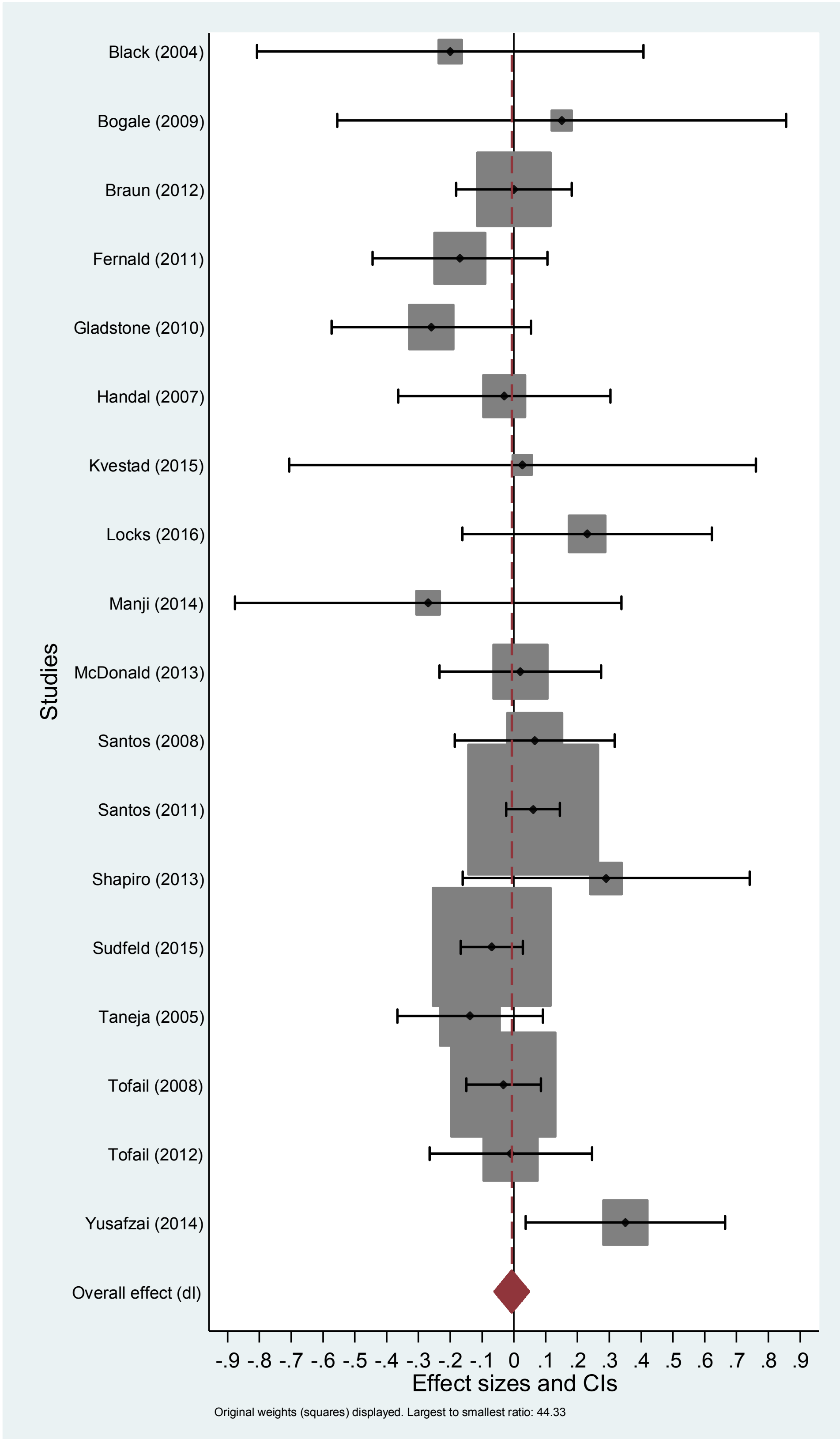

Figure 47: Association between maternal ages 15-20 (reference: ages 20-34) and cognitive development.

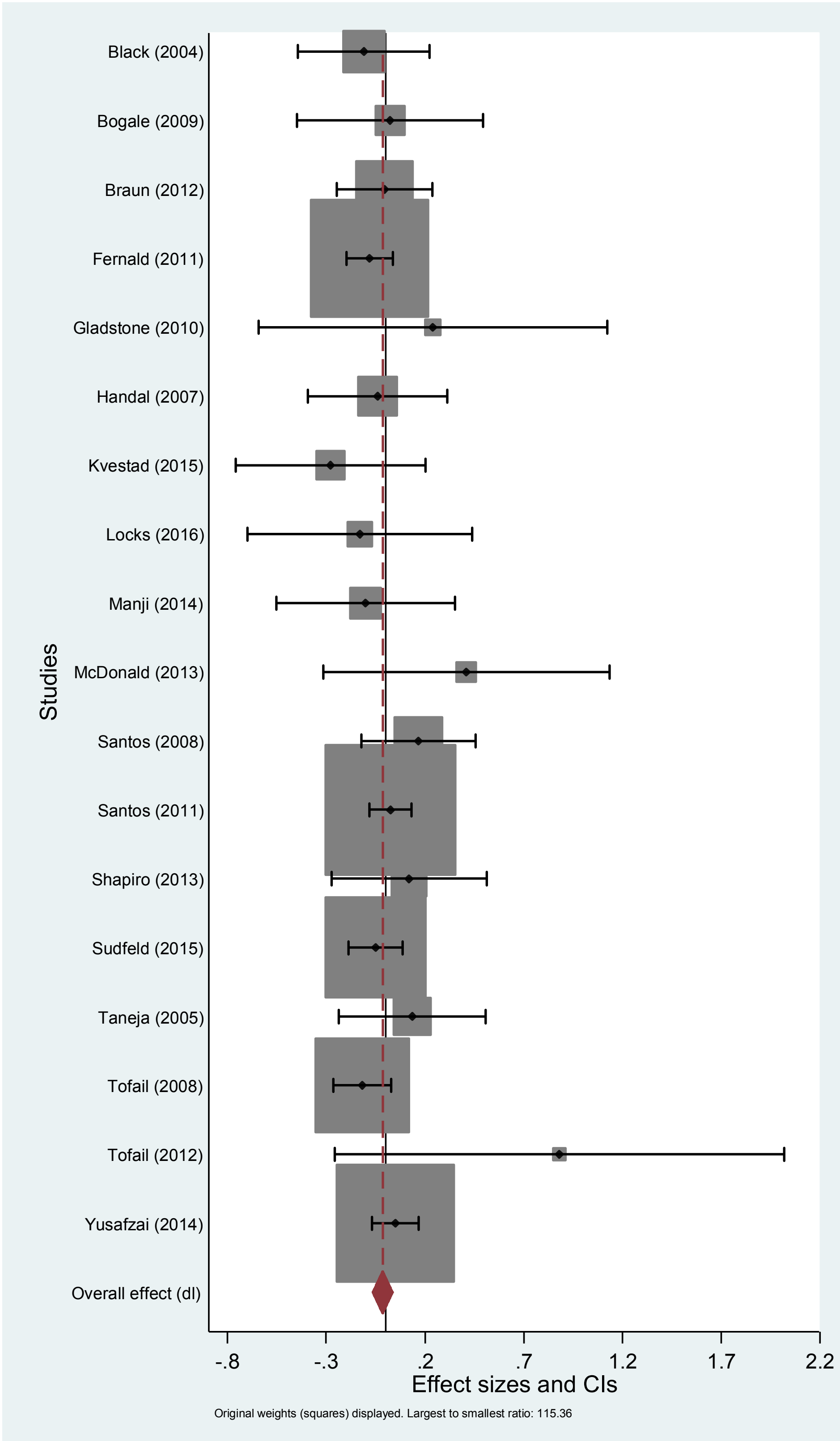

Figure 48: Association between maternal ages >35 (reference: ages 20-34) and cognitive development.

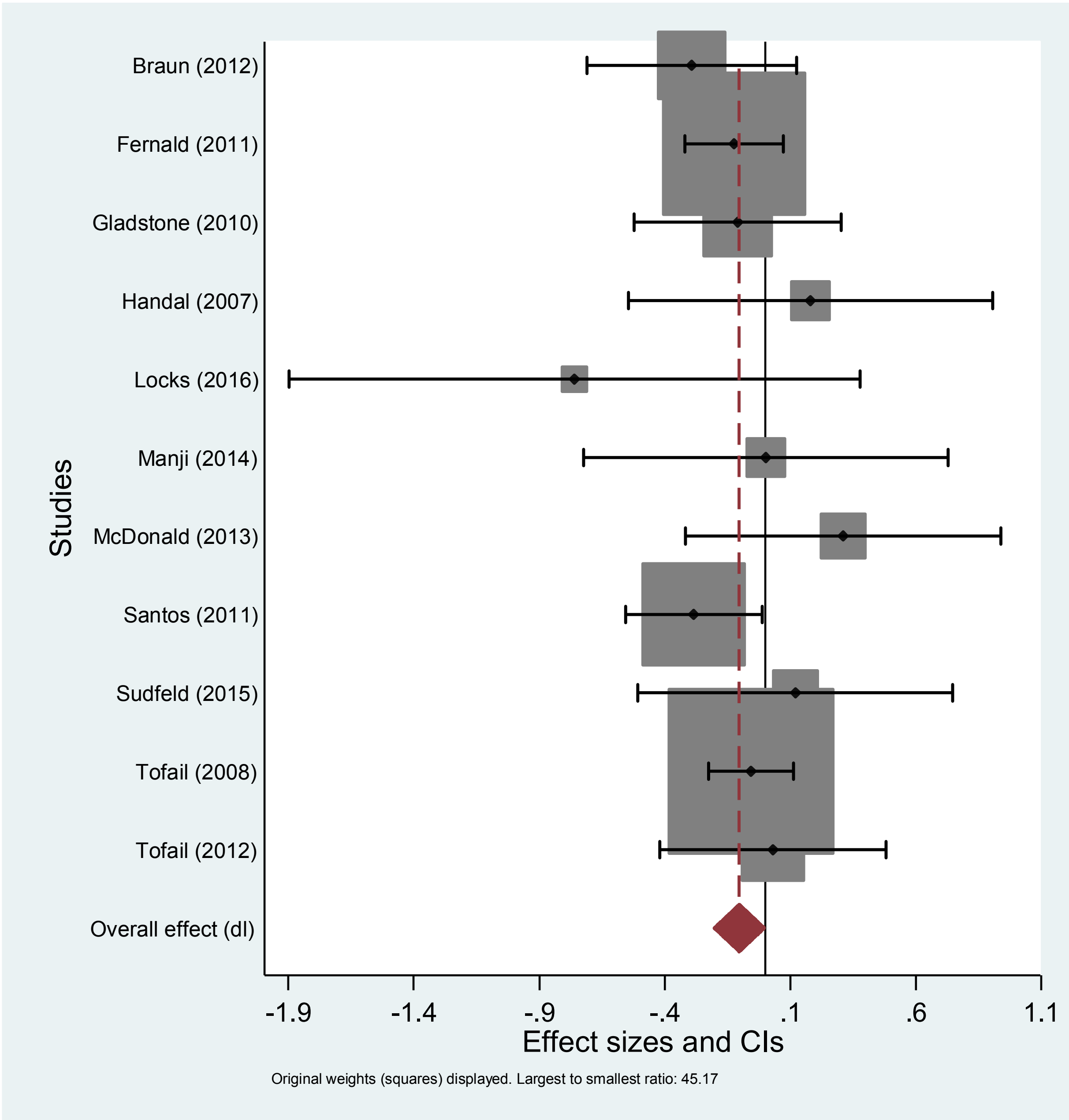

Figure 49: Association between maternal height < 145cm (reference: >155 cm) and cognitive development.

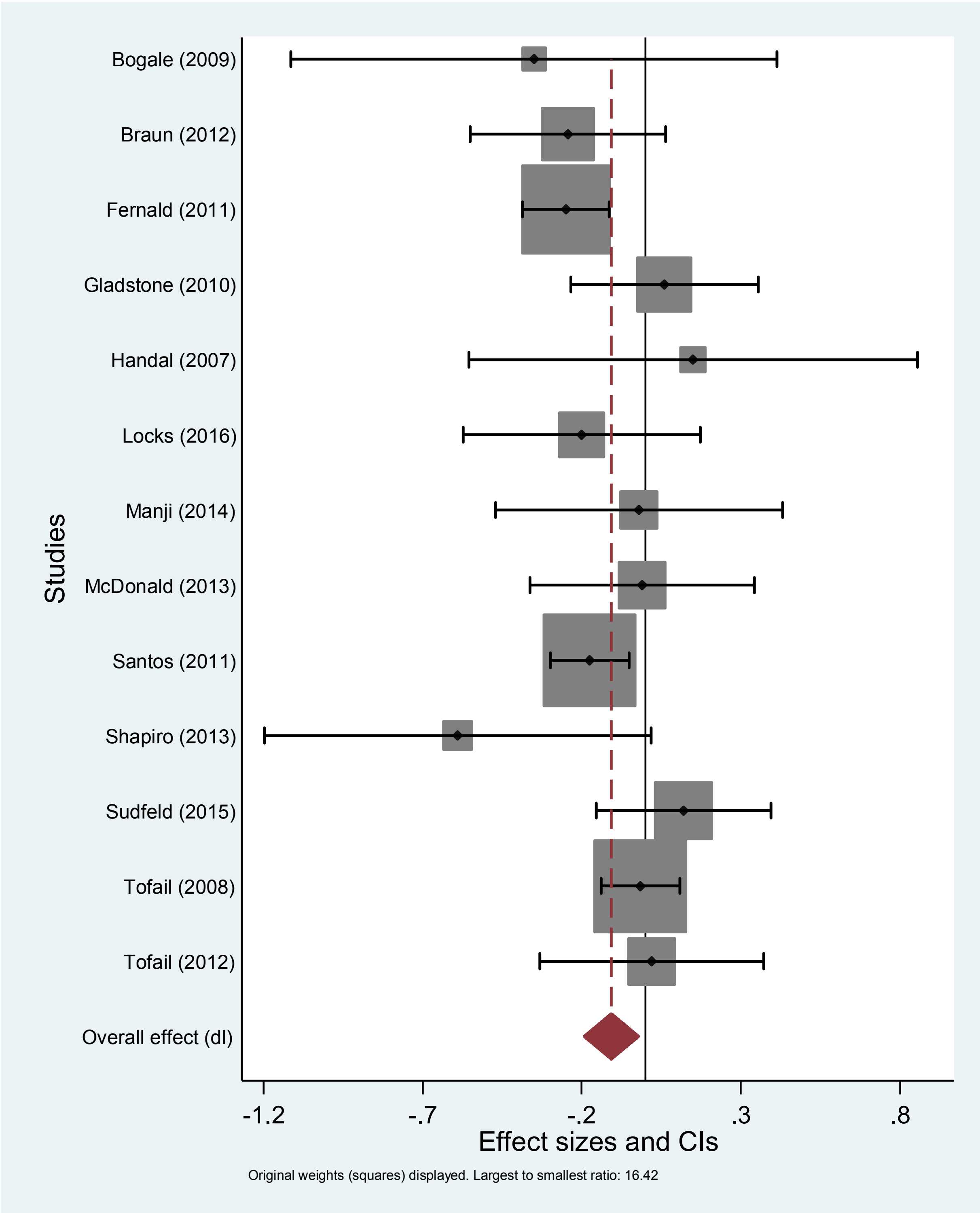

Figure 50: Association between maternal height 145-150cm (reference: >155 cm) and cognitive development.

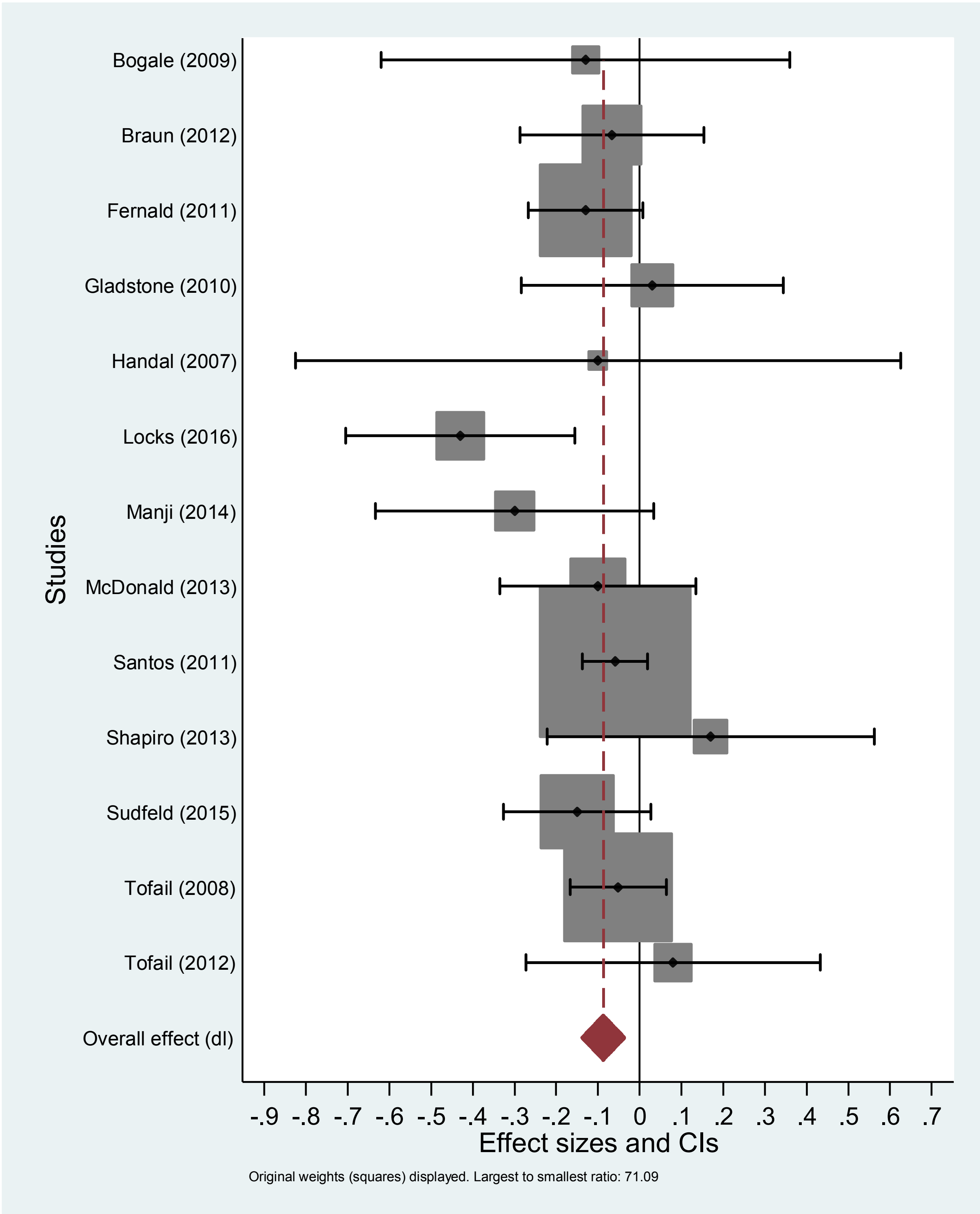

Figure 51: Association between maternal height 150-155 cm (reference: >155 cm) and cognitive development.

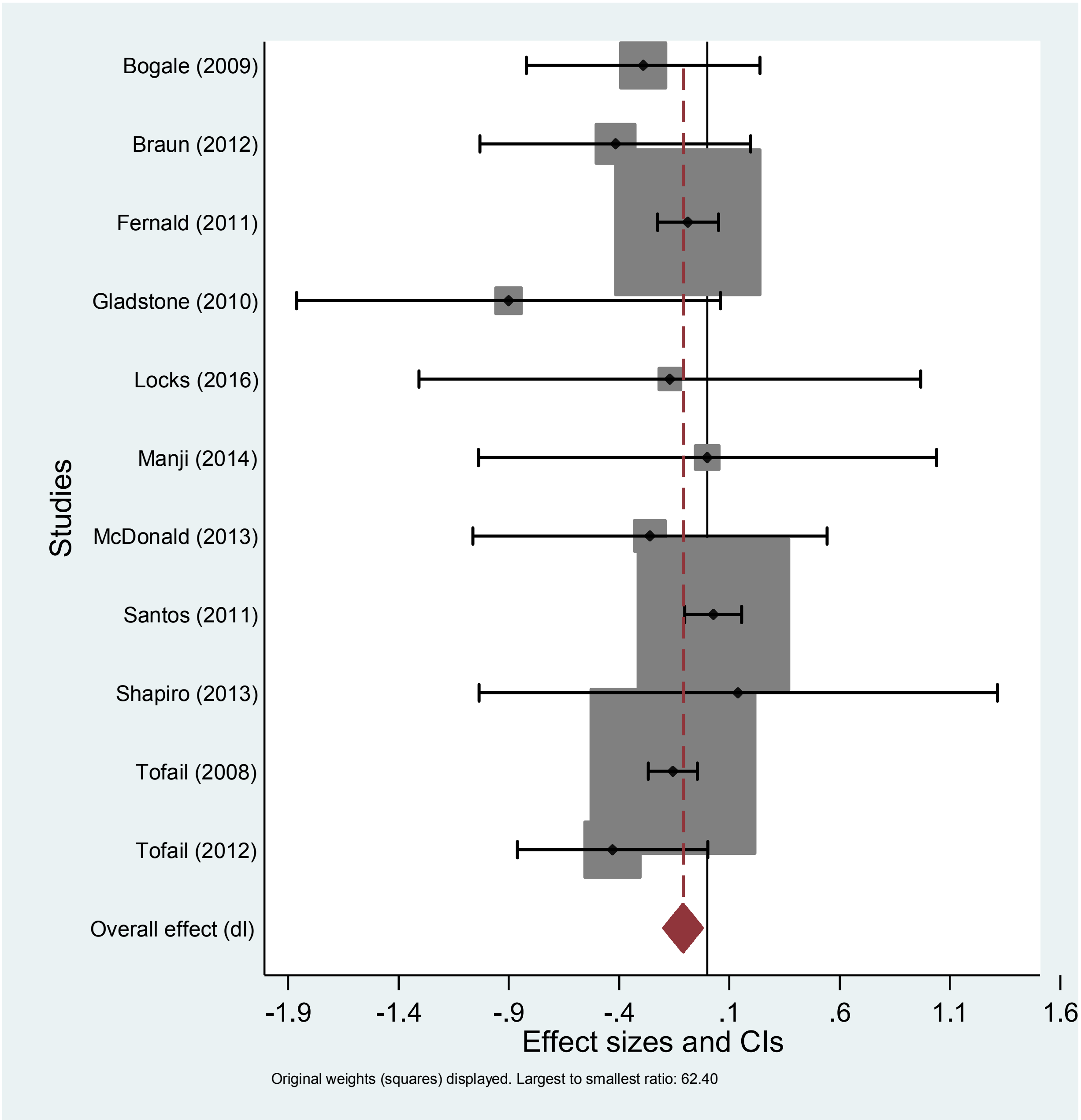

Figure 52: Association between maternal BMI <18.5 kg/m^2 (reference: 18.5-25) and cognitive development.

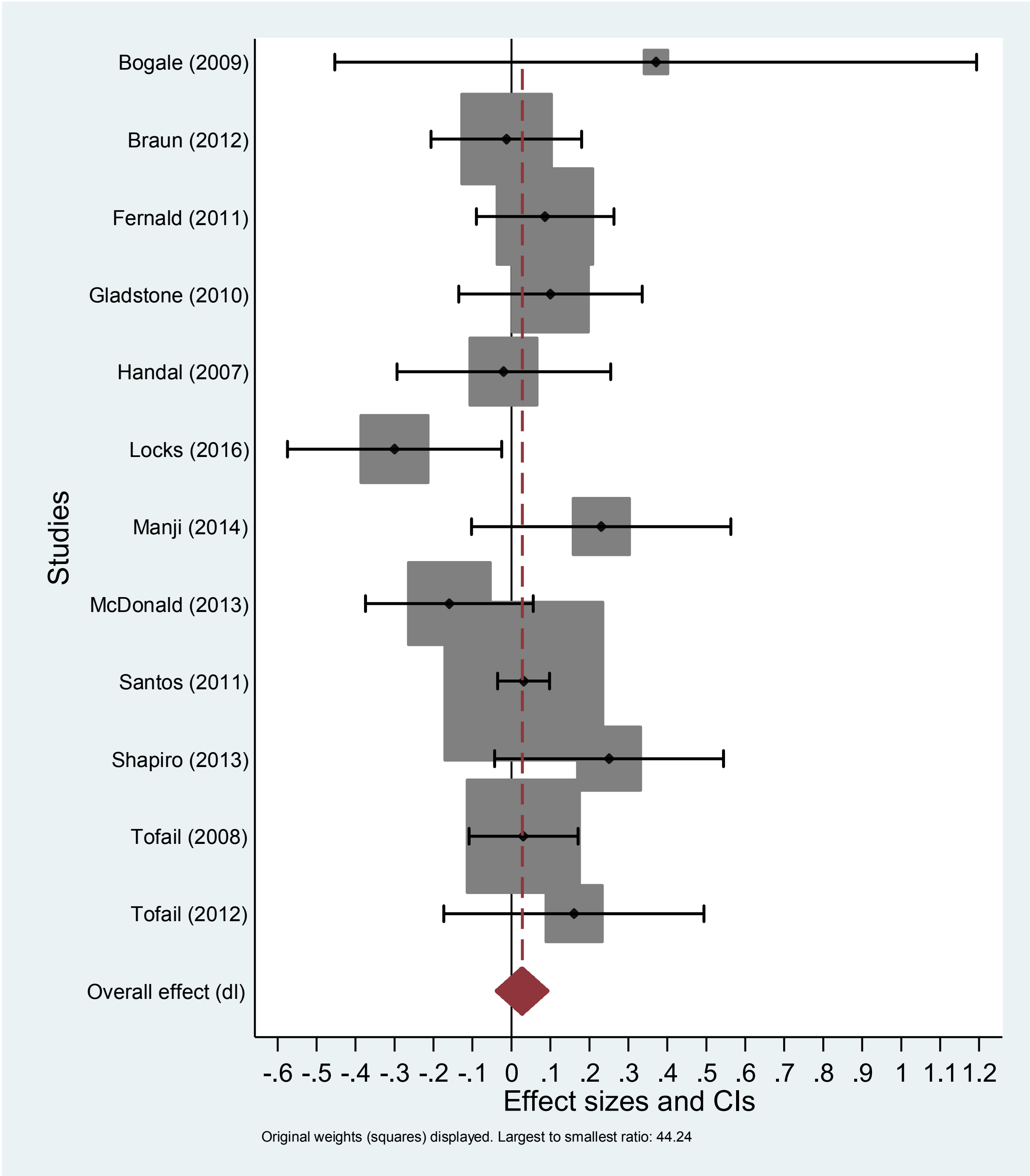

Figure 53: Association between maternal BMI 25-30 kg/m^2 (reference: 18.5-25) and cognitive development.

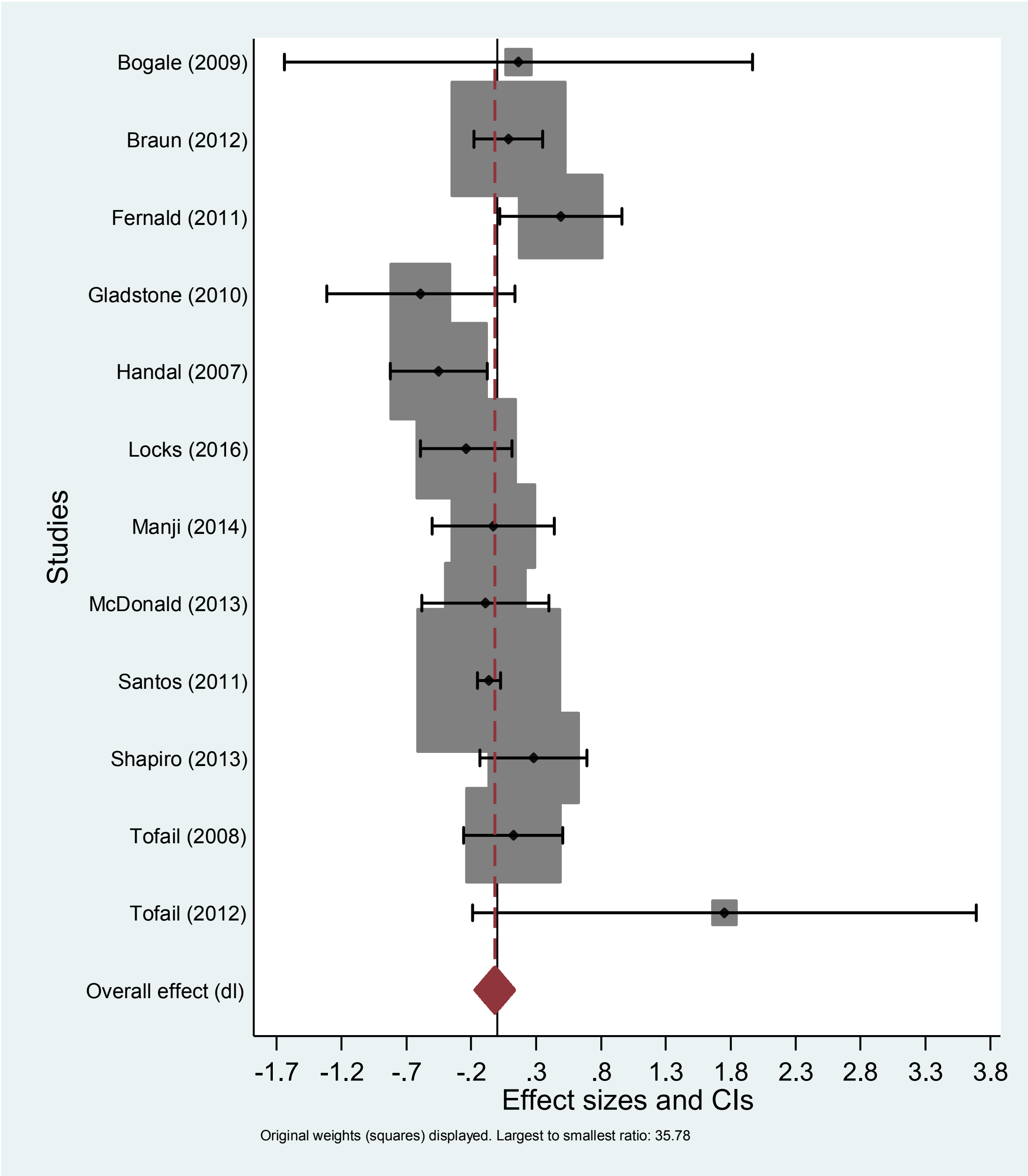

Figure 54: Association between maternal BMI >30 kg/m^2 (reference: 18.5-25) and cognitive development.

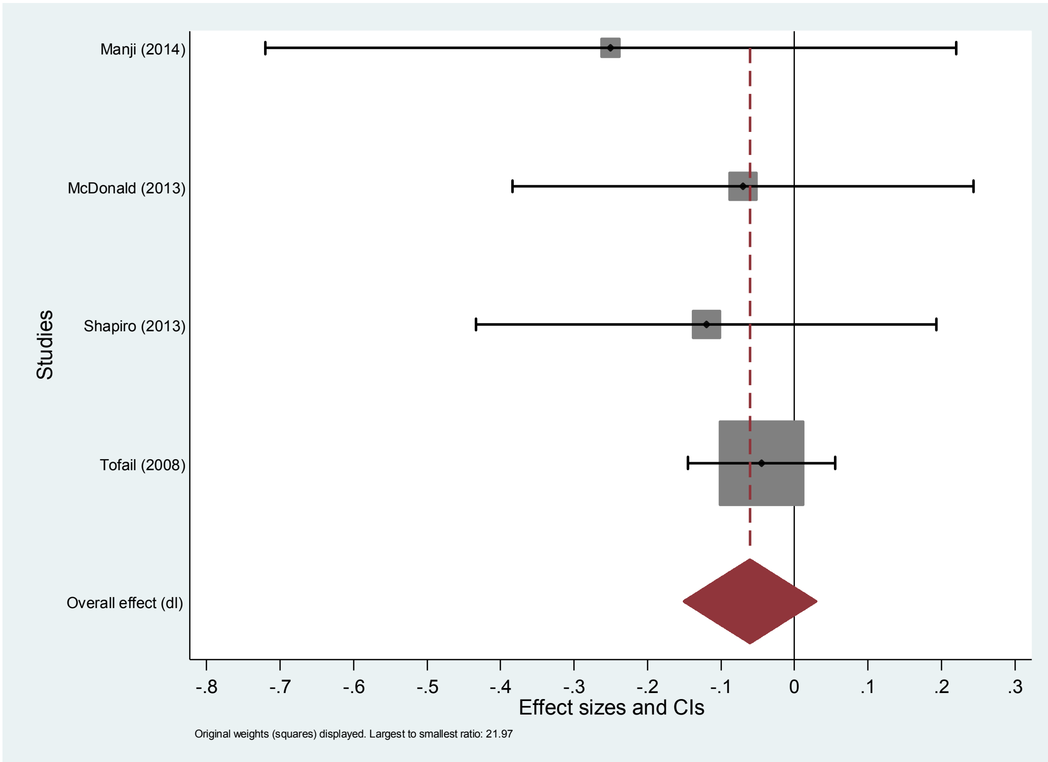

Figure 55: Association between mild anemia in pregnancy (reference: no anemia) and cognitive development.

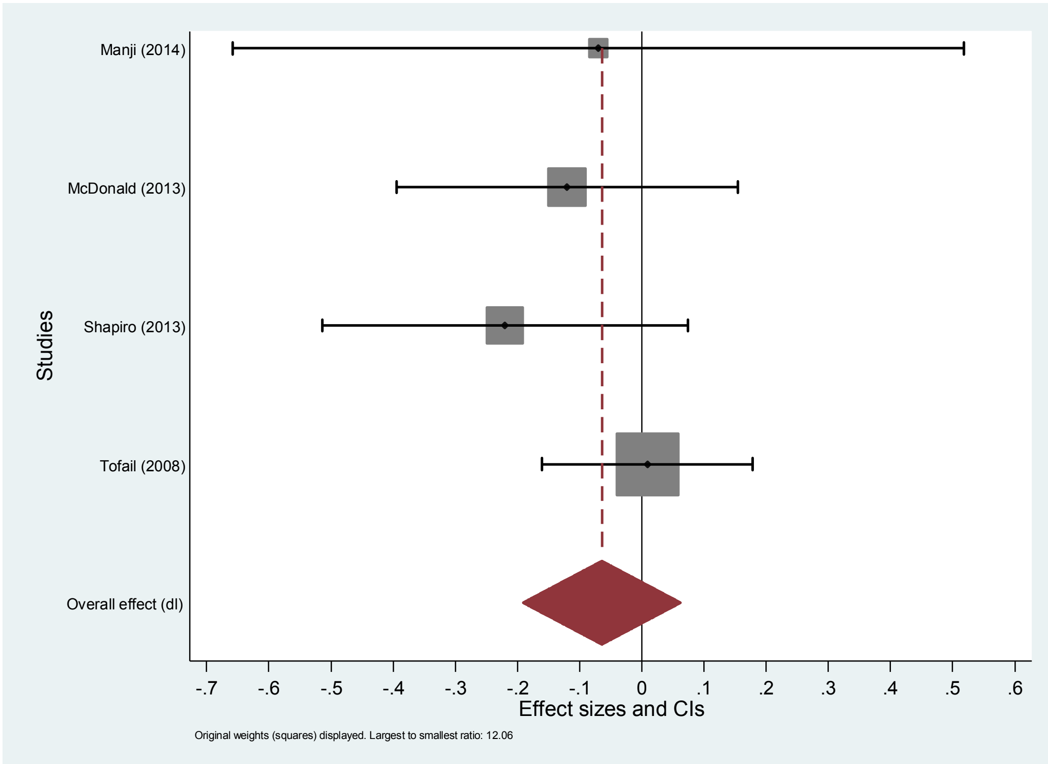

Figure 56: Association between maternal moderate anemia (reference: no anemia) and cognitive development.

5. Parental Risk Factors on Child's Motor Development

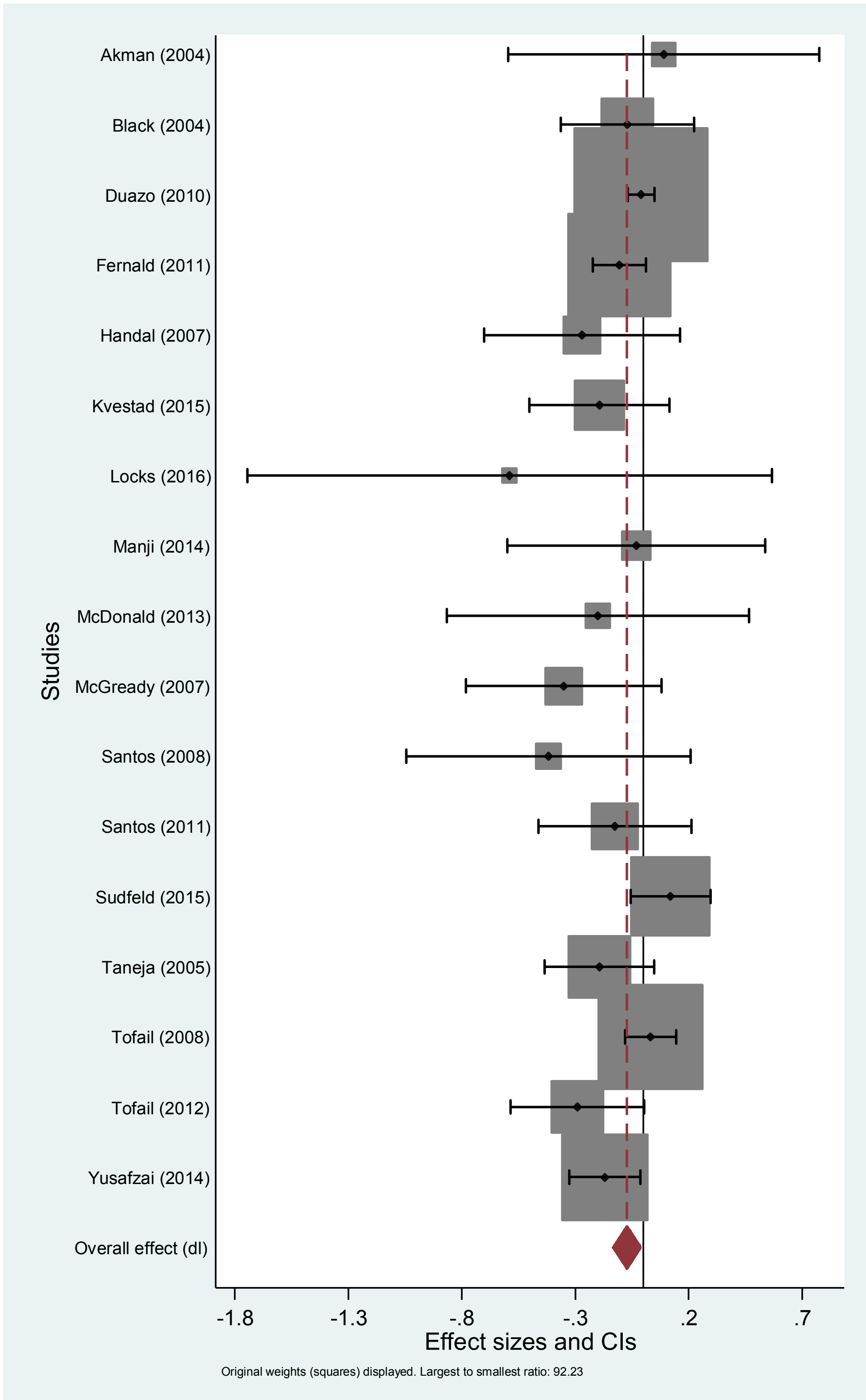

Figure 57: Association between no maternal education (reference: primary education) and motor development.

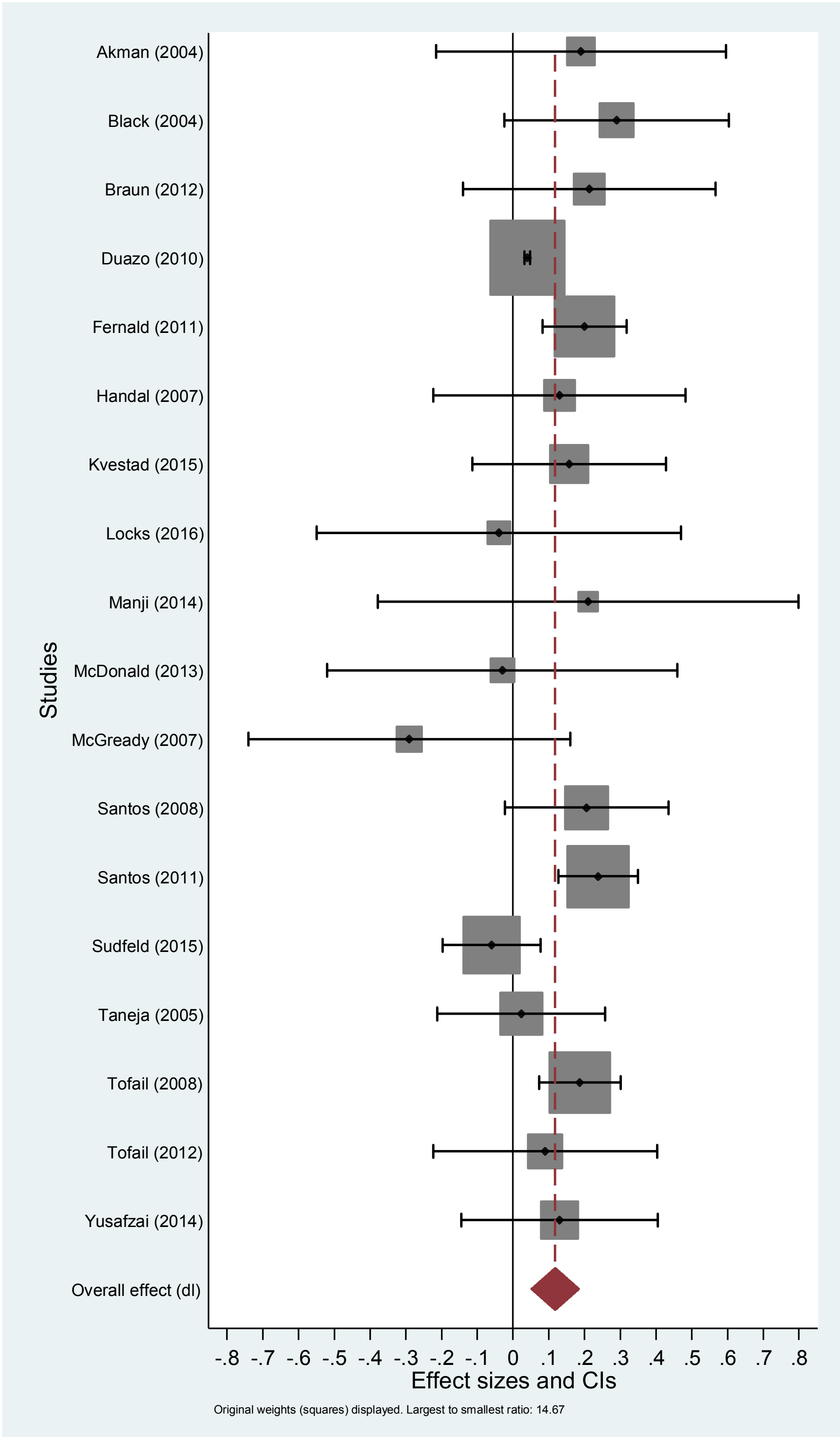

Figure 58: Association between maternal secondary education (reference: primary education) and motor development.

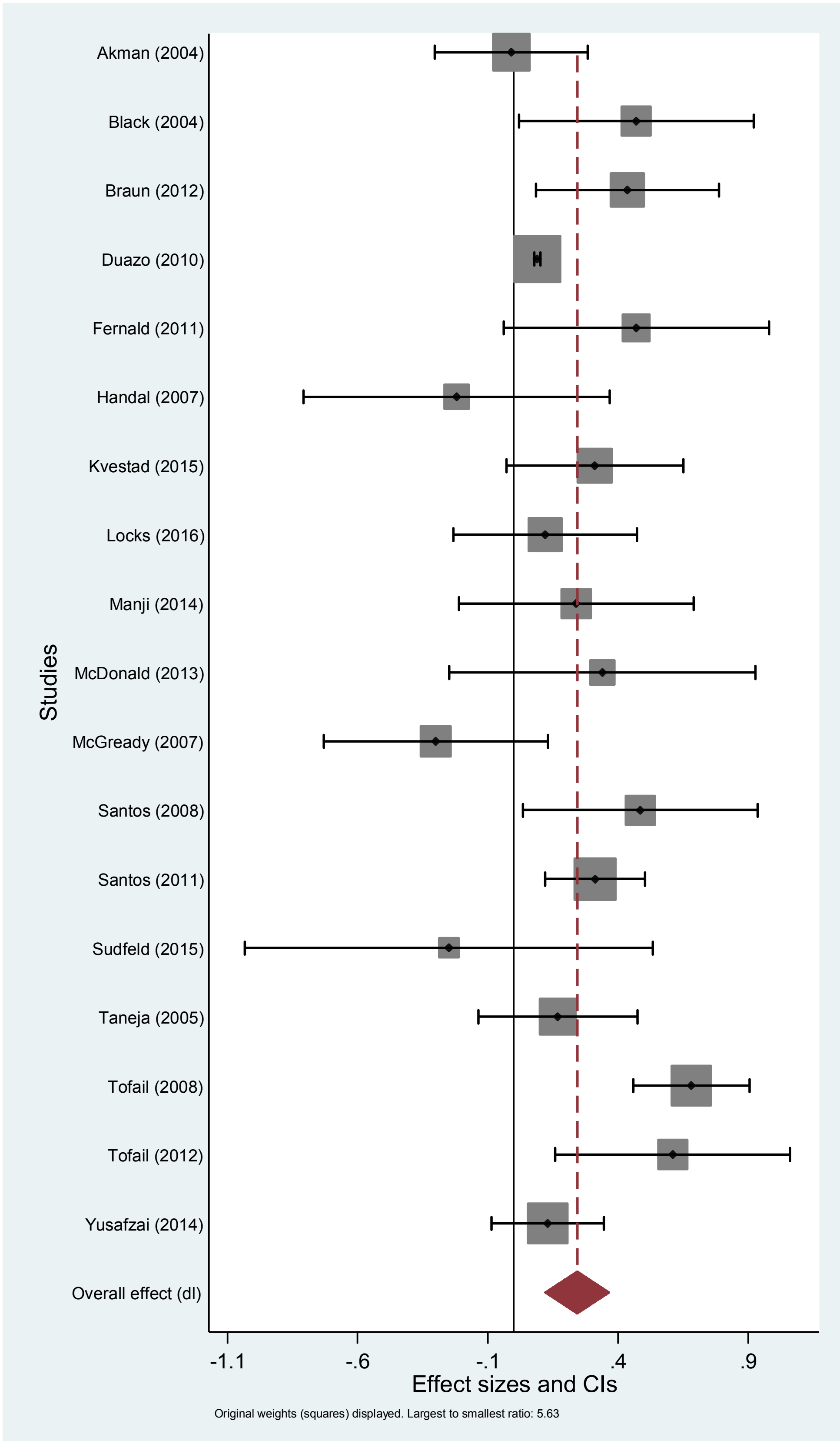

Figure 59: Association between maternal higher education (reference: primary education) and motor development.

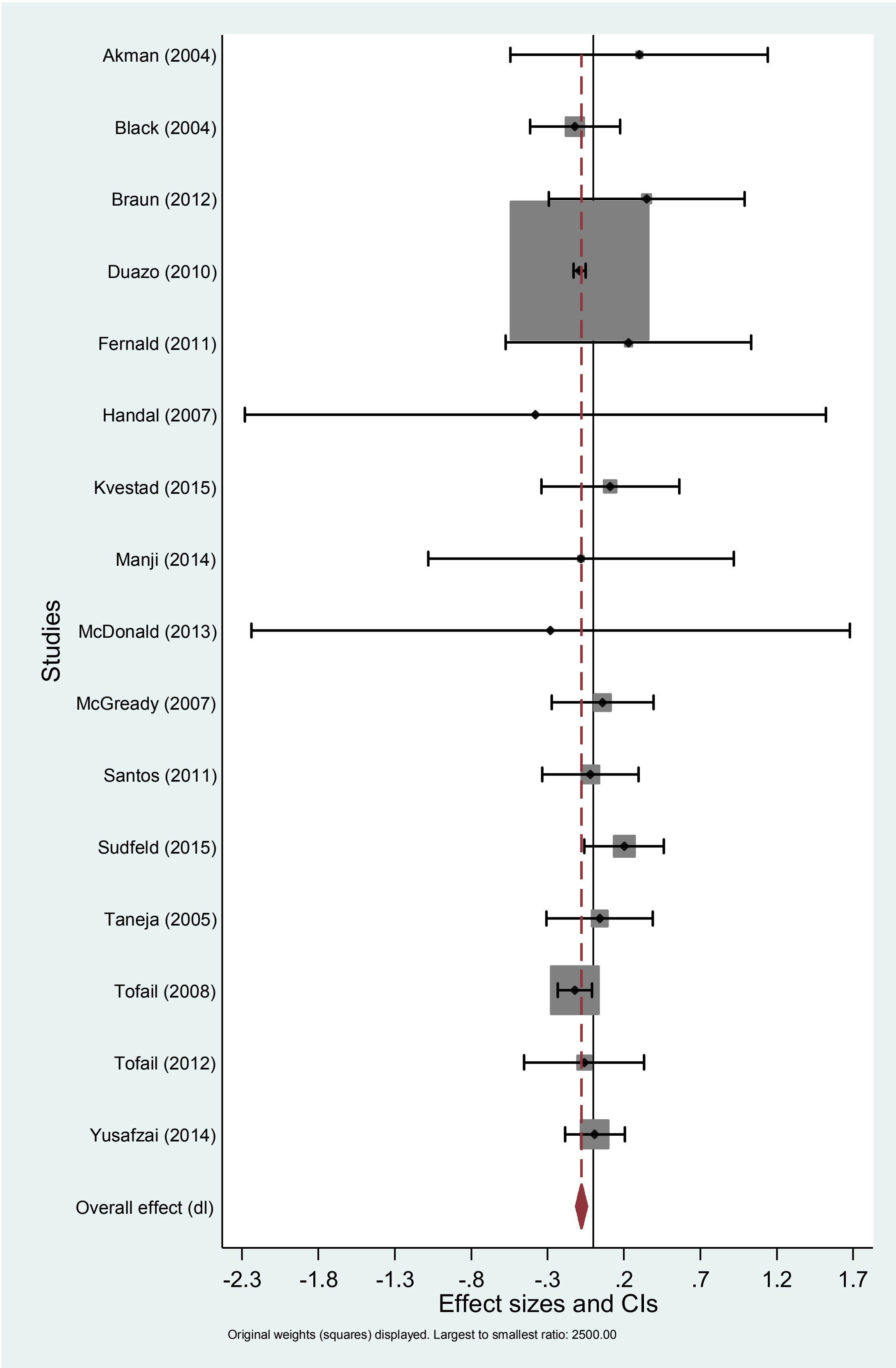

Figure 60: Association between no paternal education (reference: primary education) and motor development.

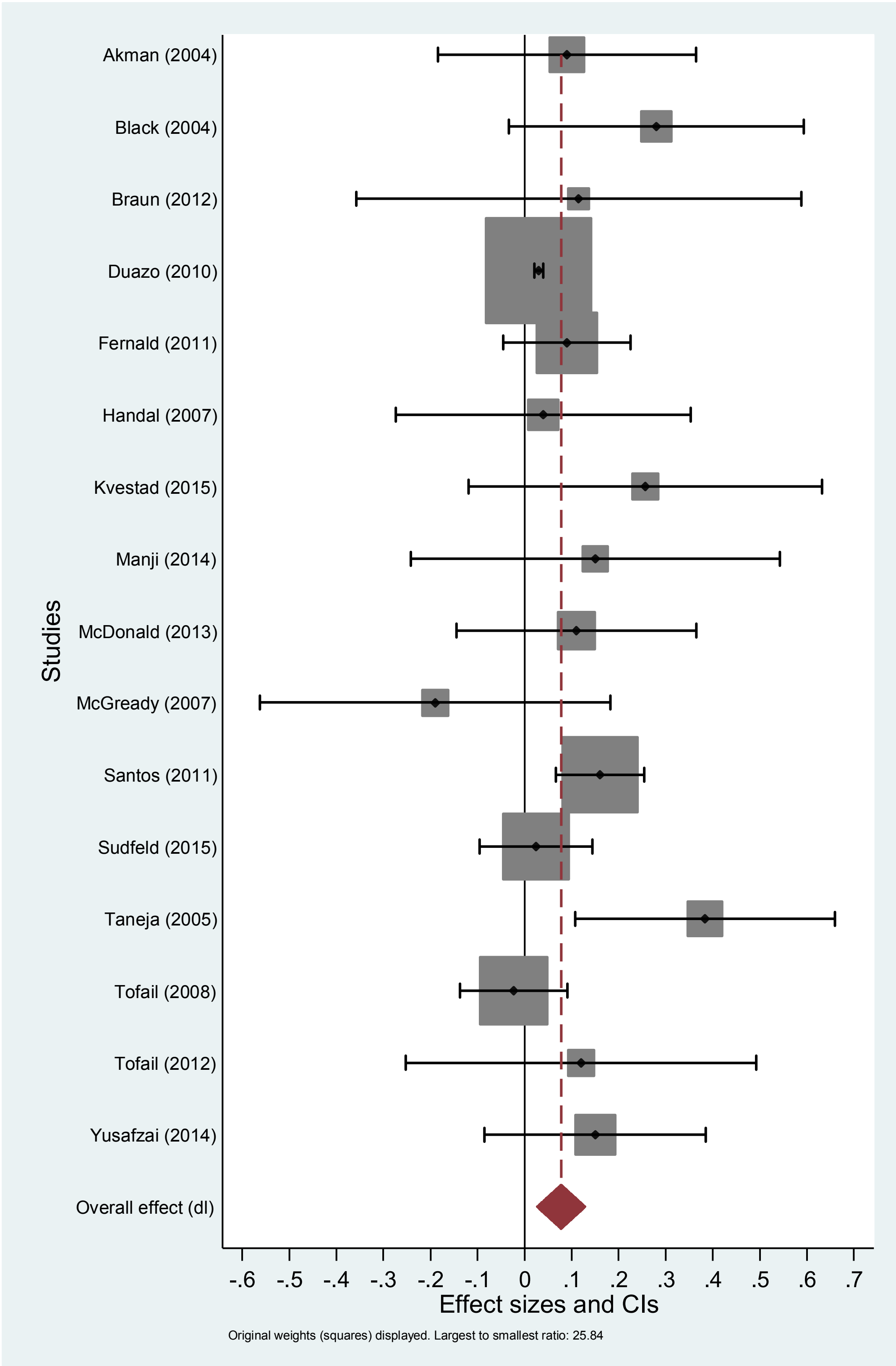

Figure 61: Association between paternal secondary education (reference: primary education) and motor development.

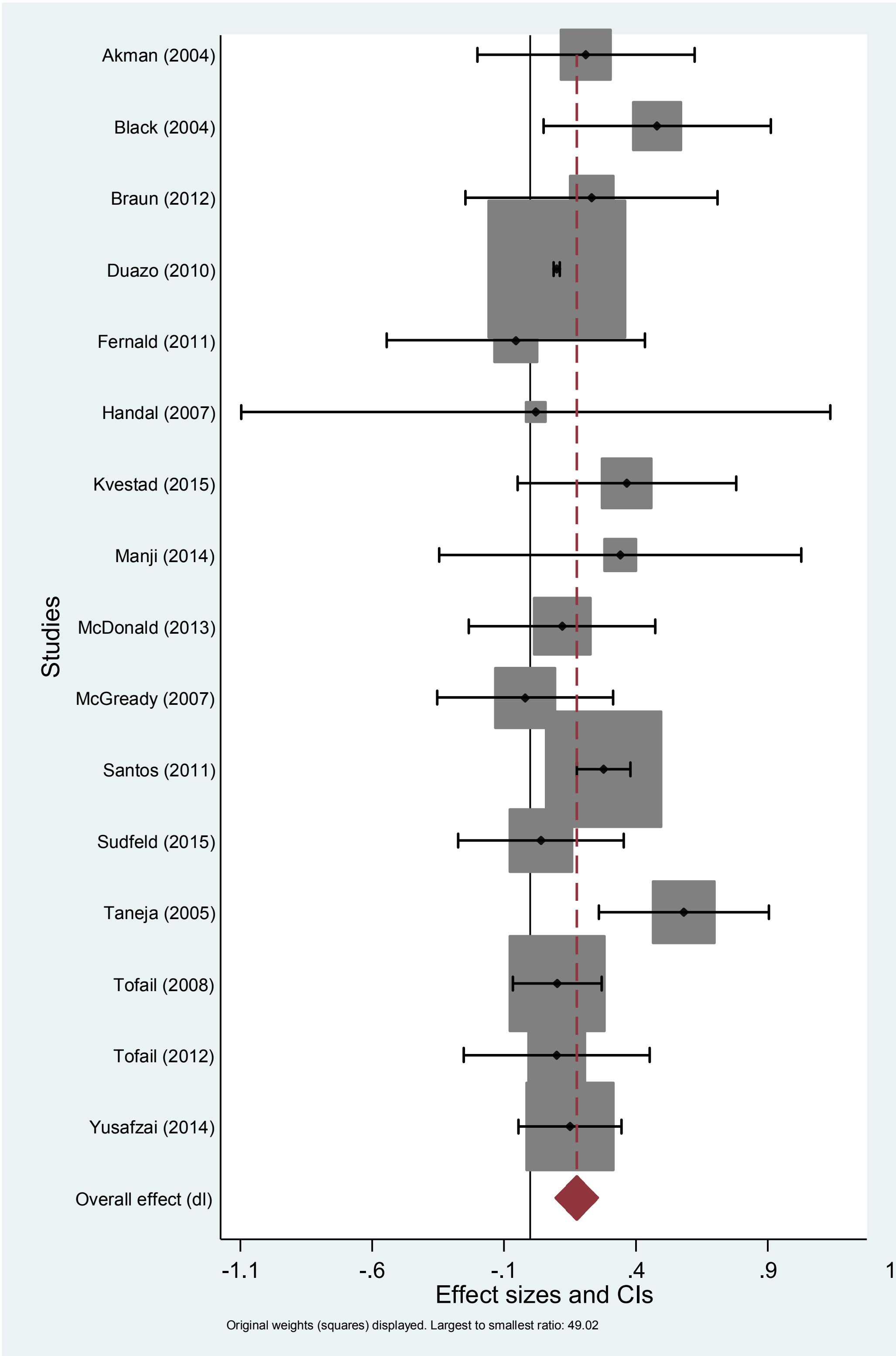

Figure 62: Association between paternal higher education (reference: primary education) and motor development.

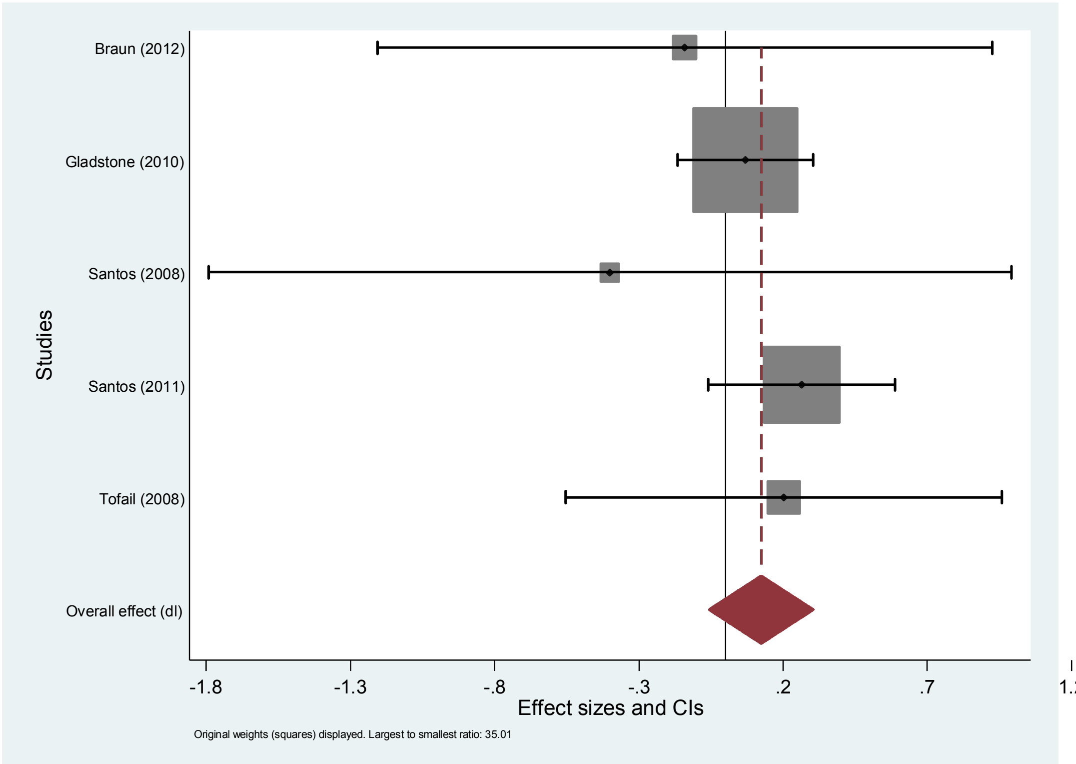

Figure 63: Association between maternal ages < 15 (reference: ages 20-34) and motor development.

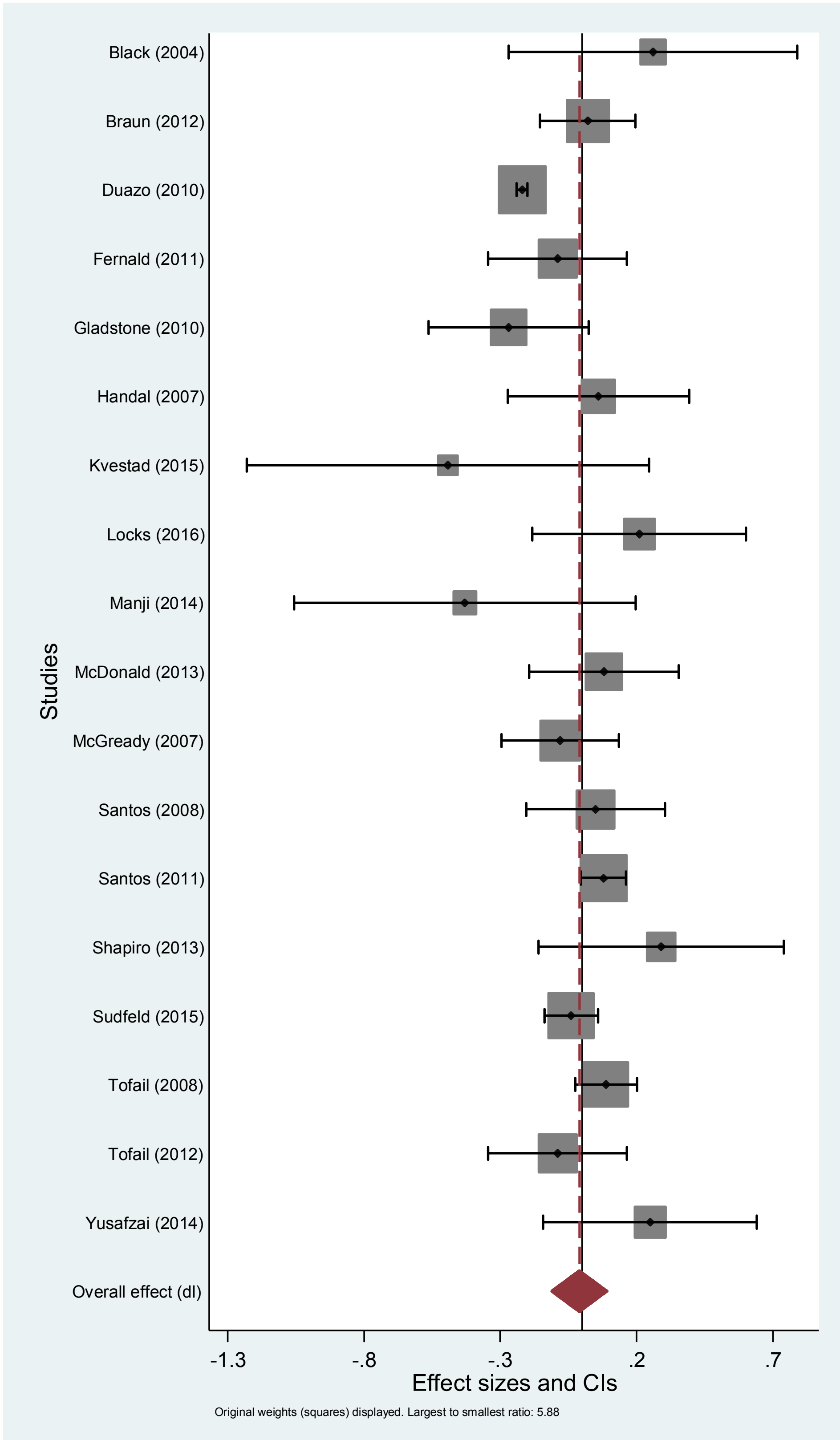

Figure 64: Association between maternal ages 15-20 (reference: ages 20-34) and motor development.

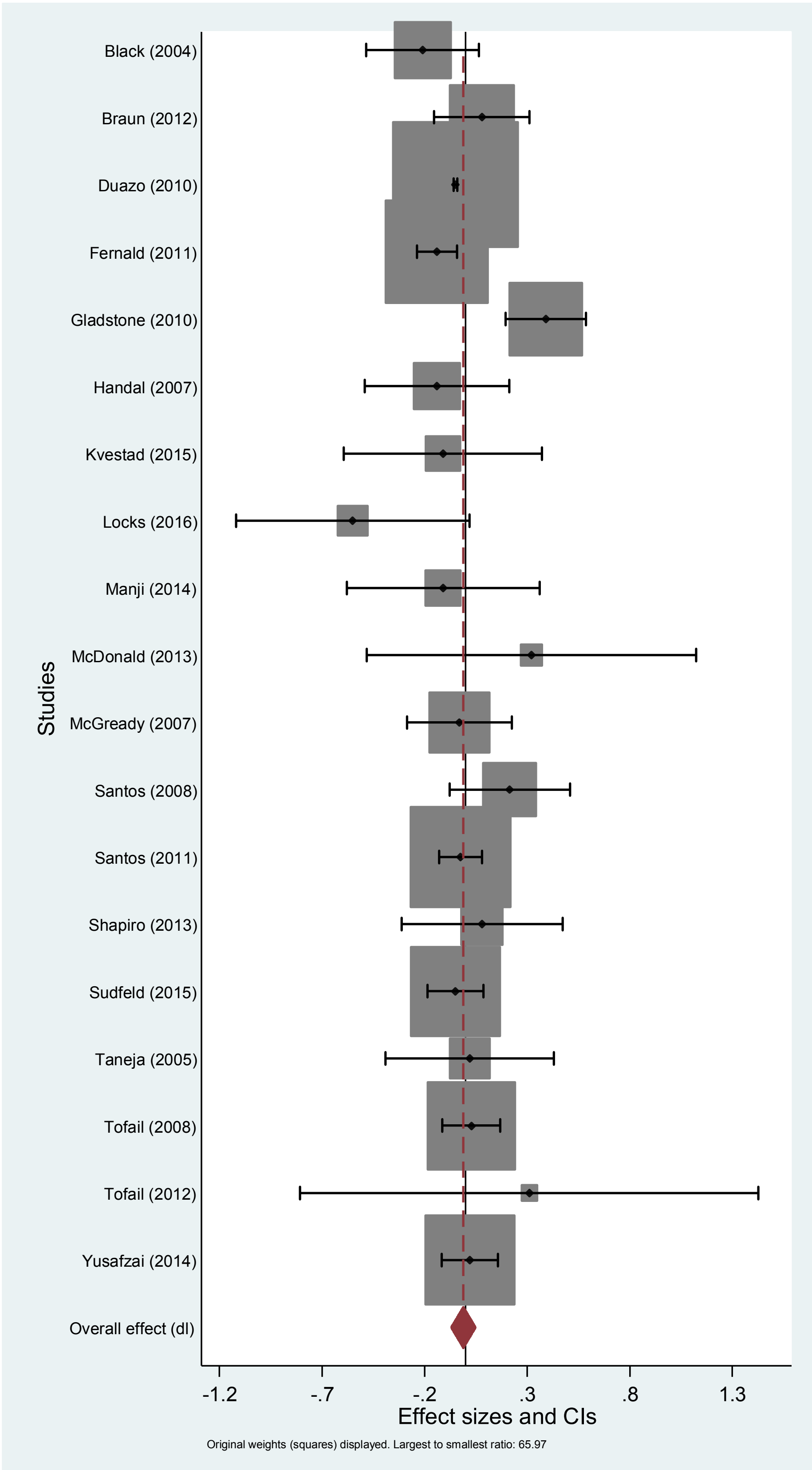

Figure 65: Association between maternal ages >35 (reference: ages 20-34) and motor development.

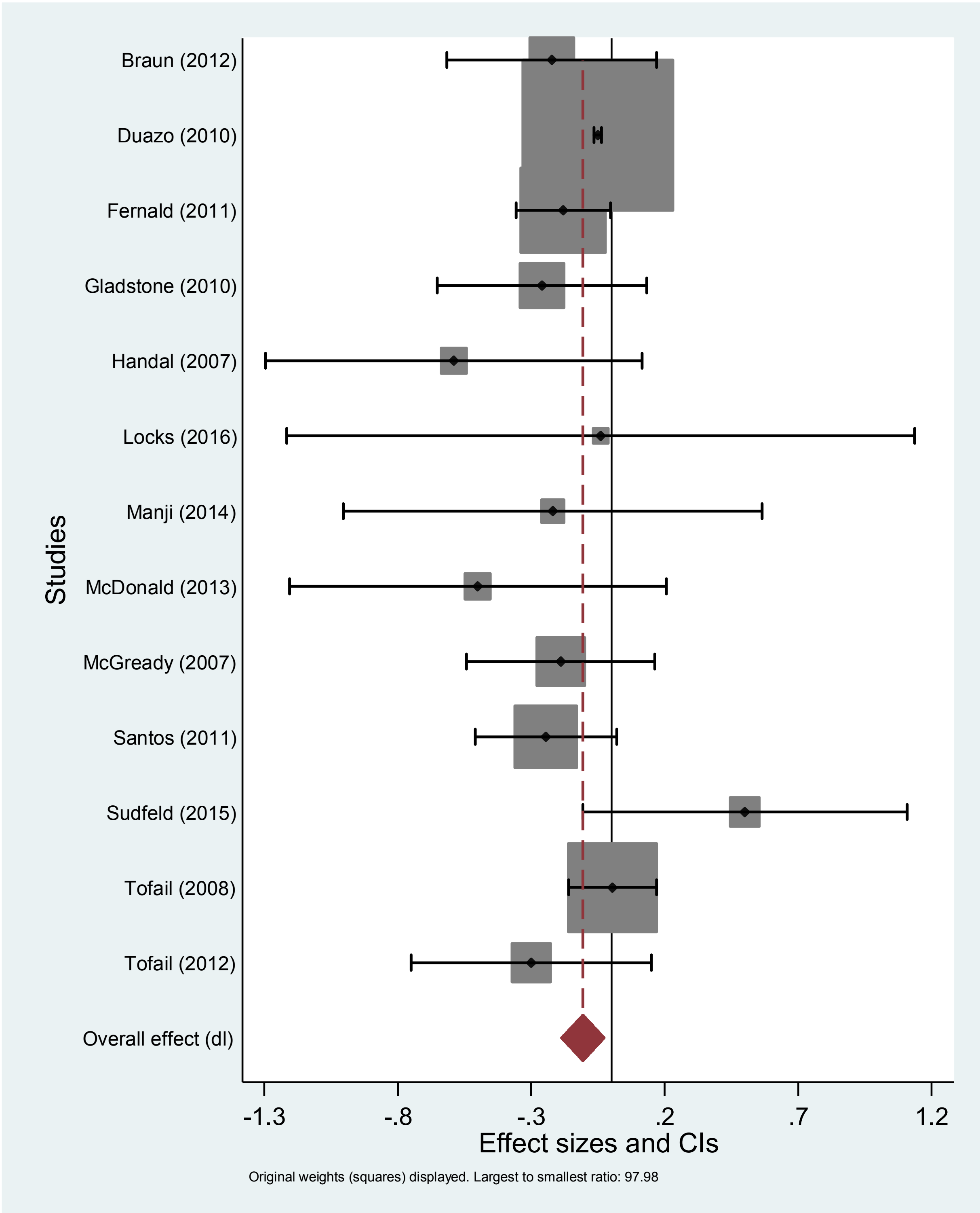

Figure 66: Association between maternal height <145 (reference: >155 cm) and motor development.

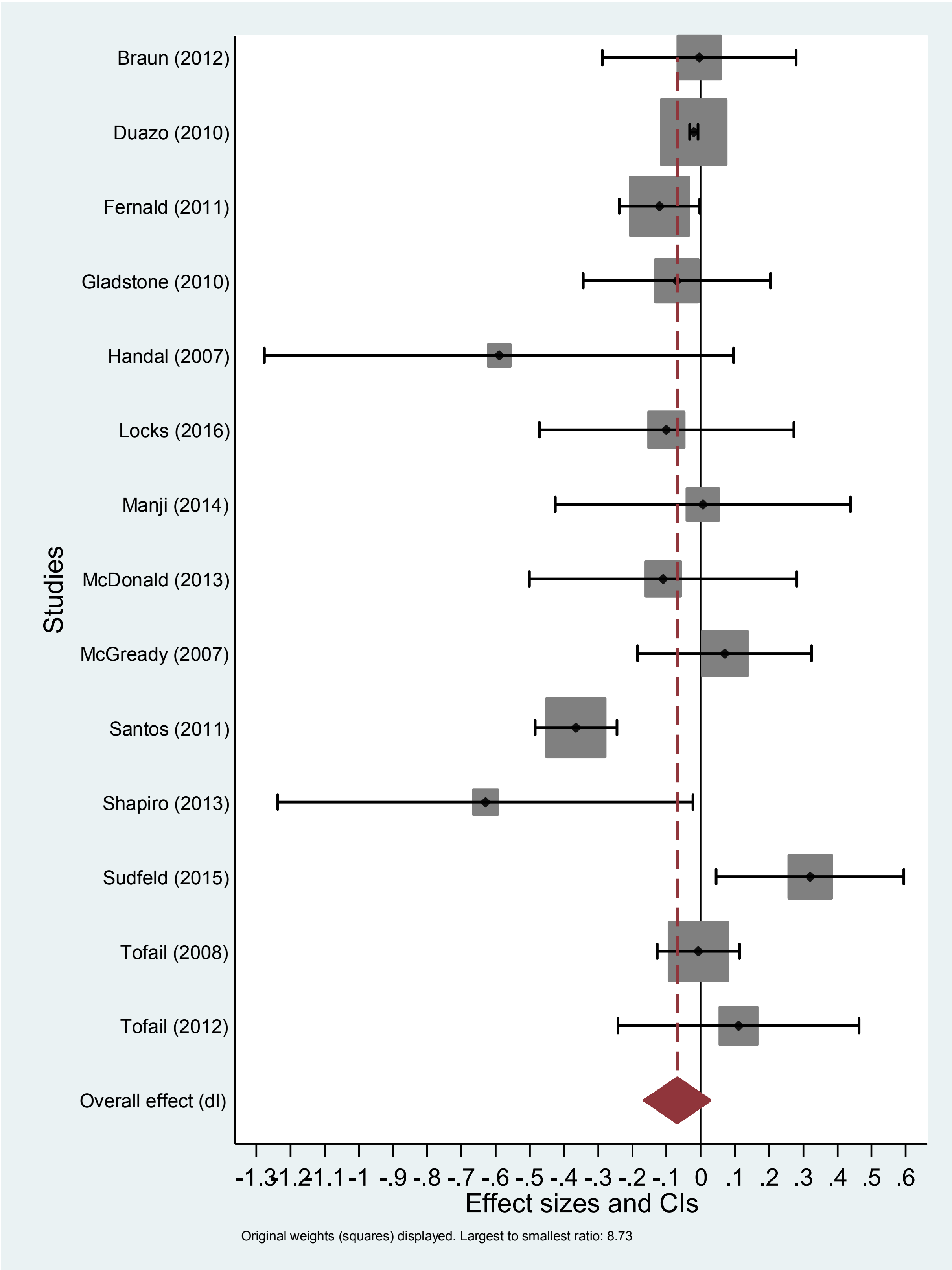

Figure 67: Association between maternal height 145-150 (reference: >155 cm) and motor development.

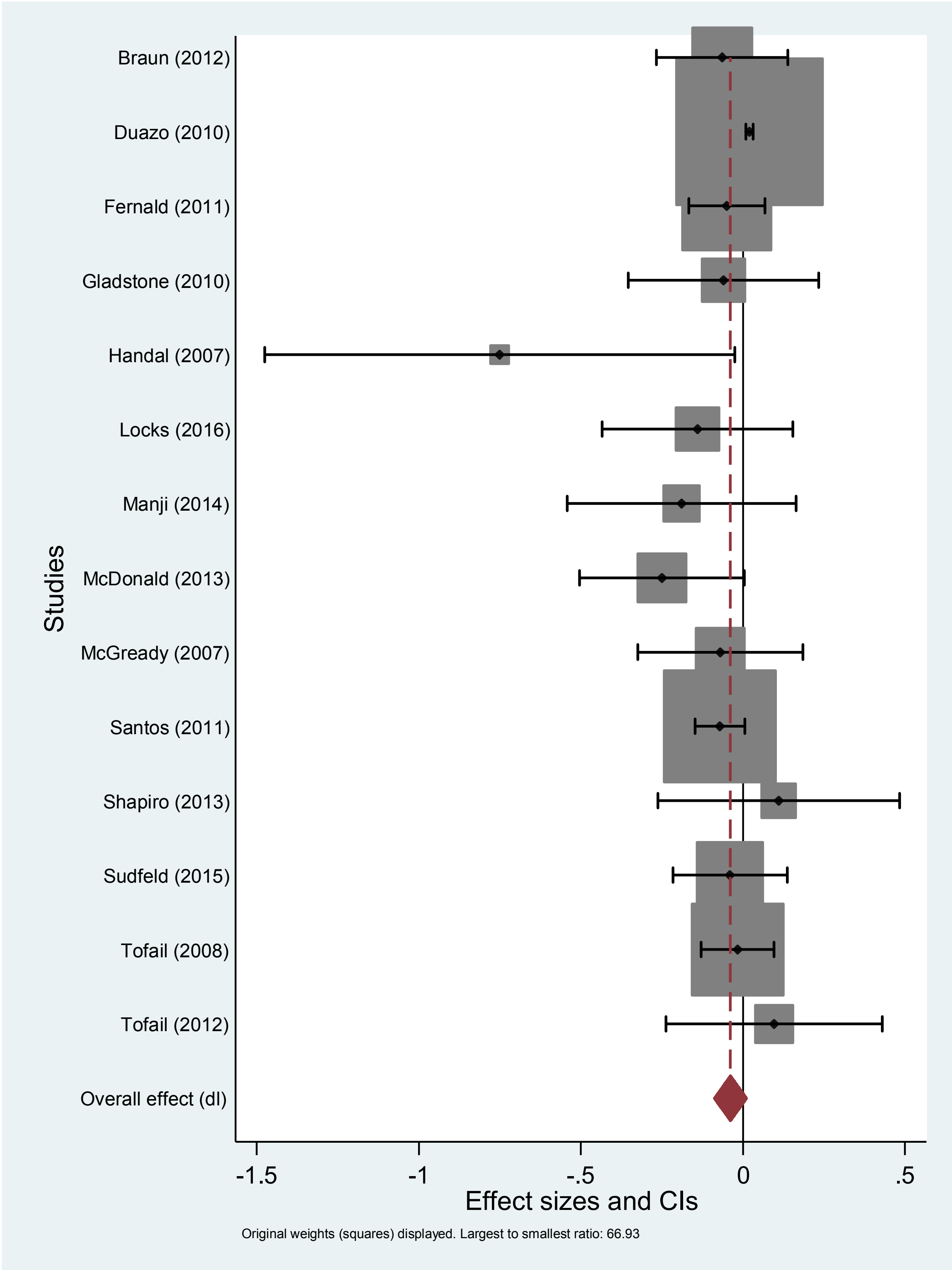

Figure 68: Association between maternal height 150-155 (reference: >155 cm) and motor development.

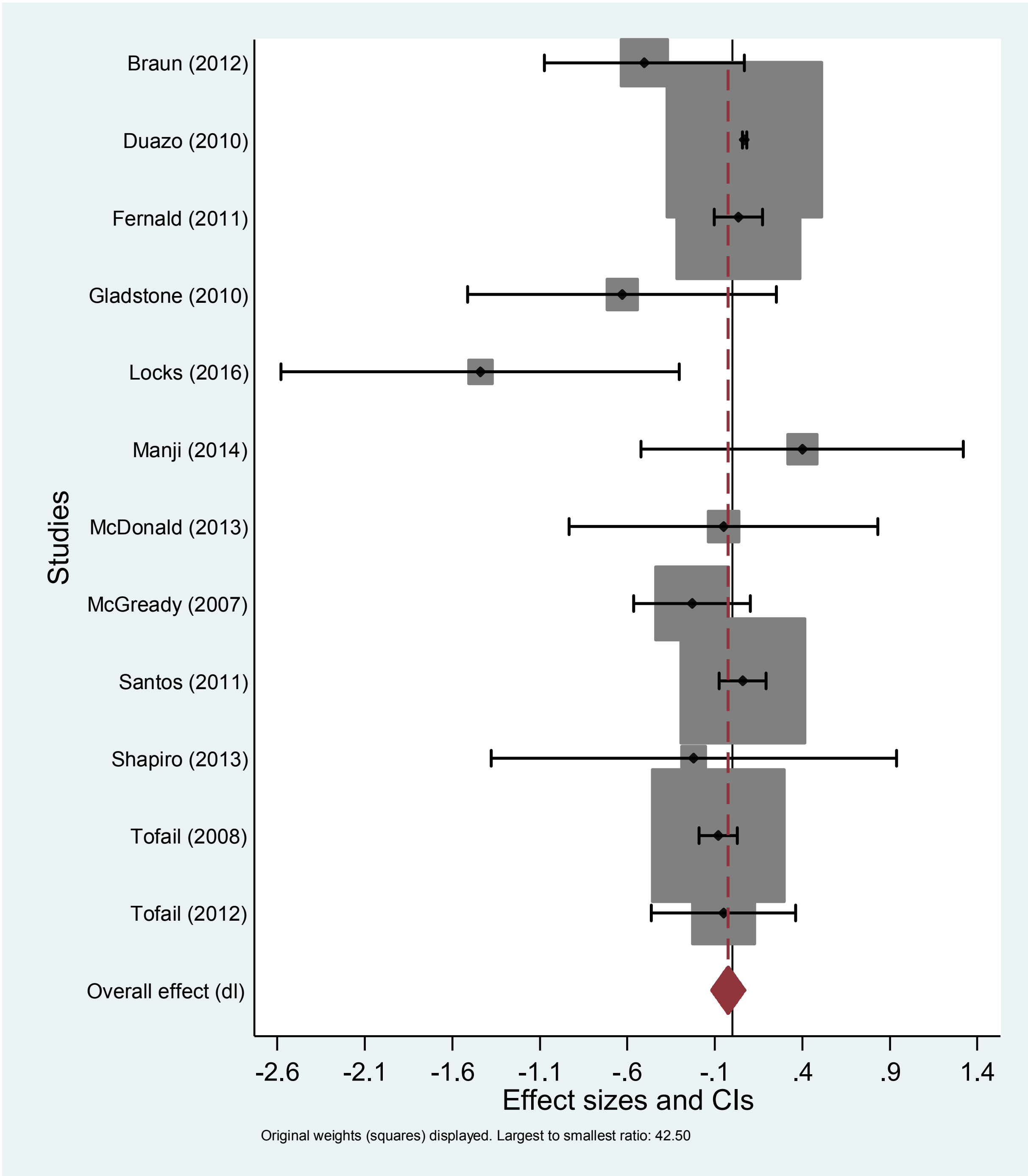

Figure 69: Association between maternal BMI <18.5 kg/m^2 (reference: 18.5-25) and motor development.

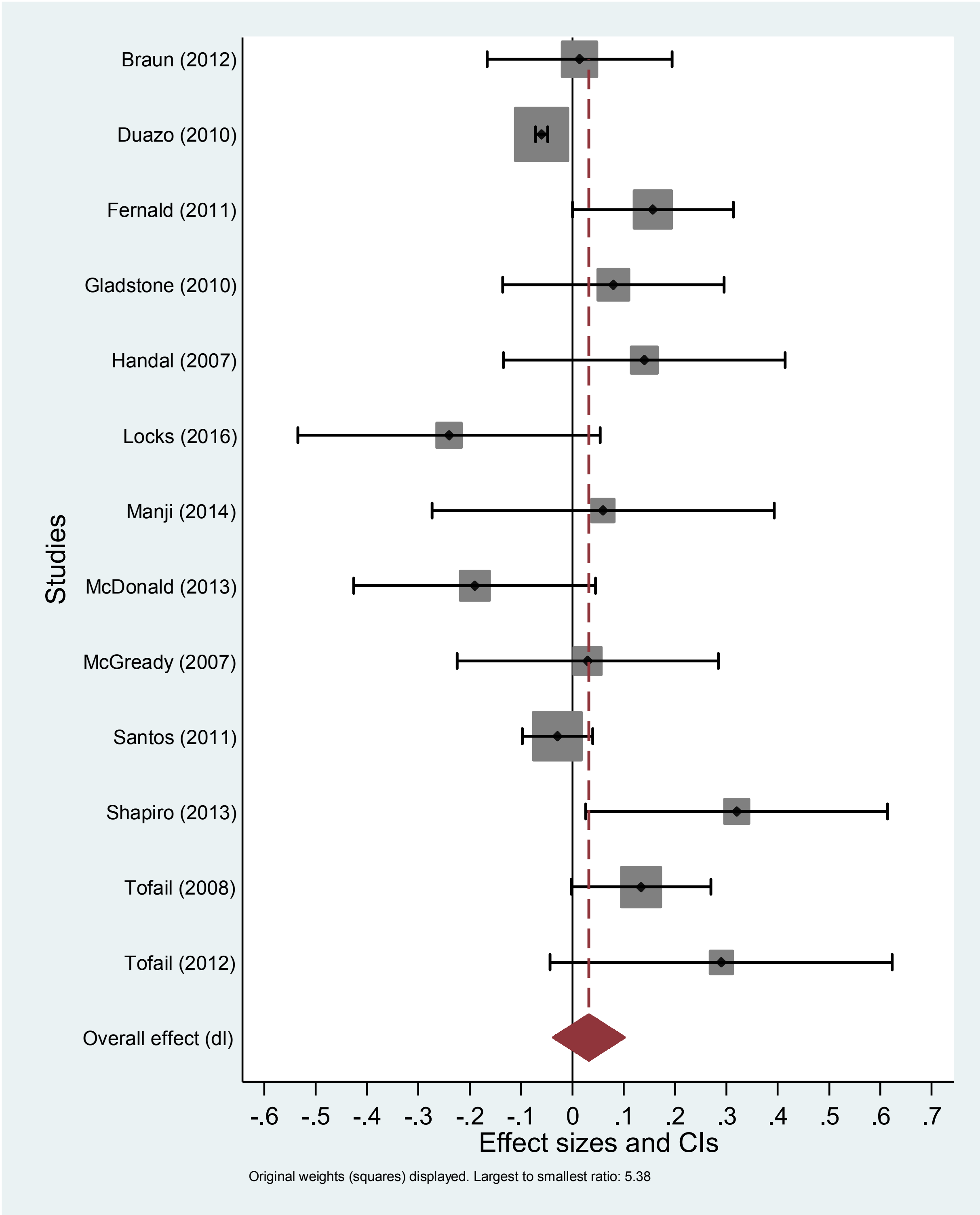

Figure 70: Association between maternal BMI <25-30 kg/m^2 (reference: 18.5-25) and motor development.

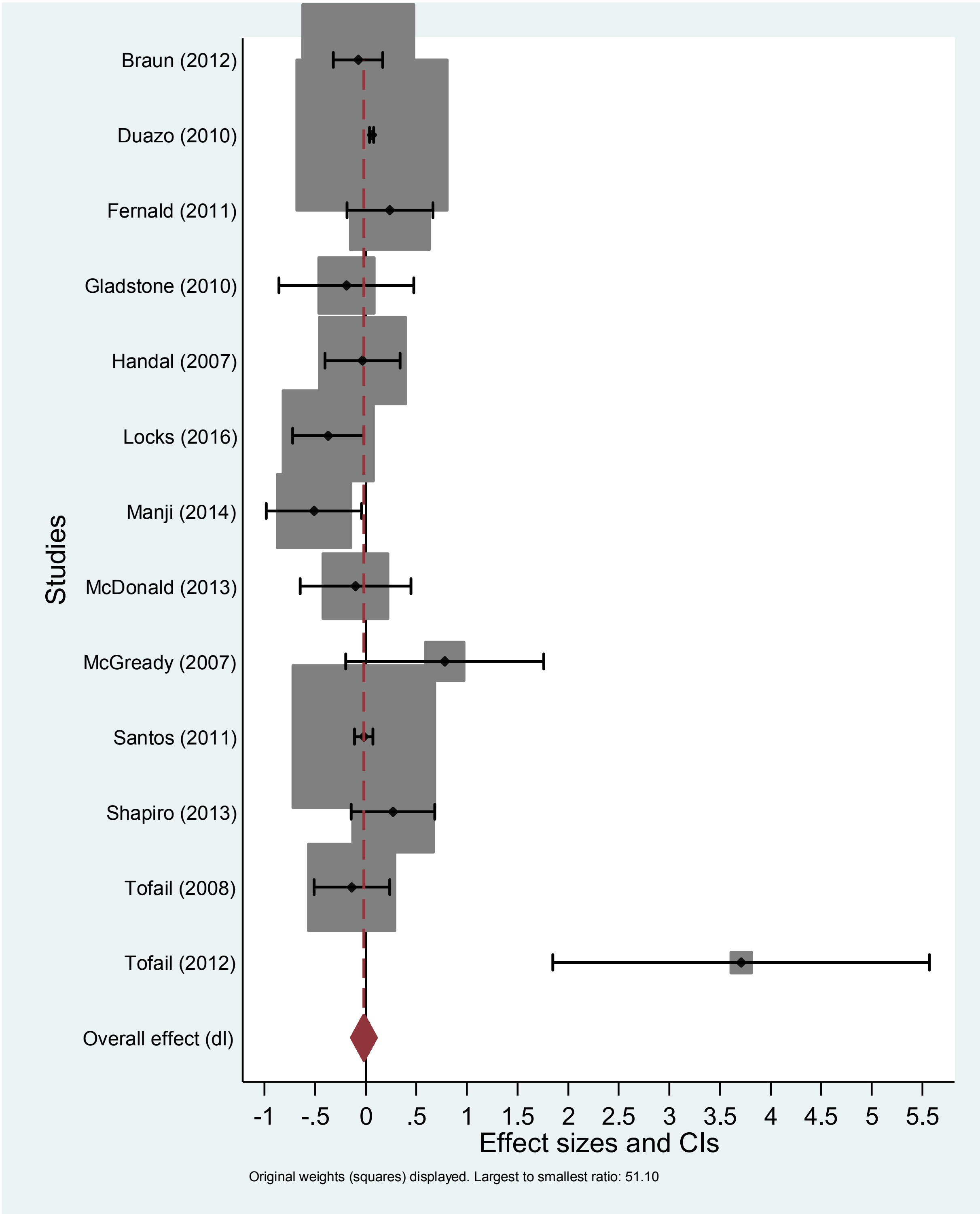

Figure 71: Association between maternal BMI >30 kg/m² (reference: 18.5-25) and motor development.

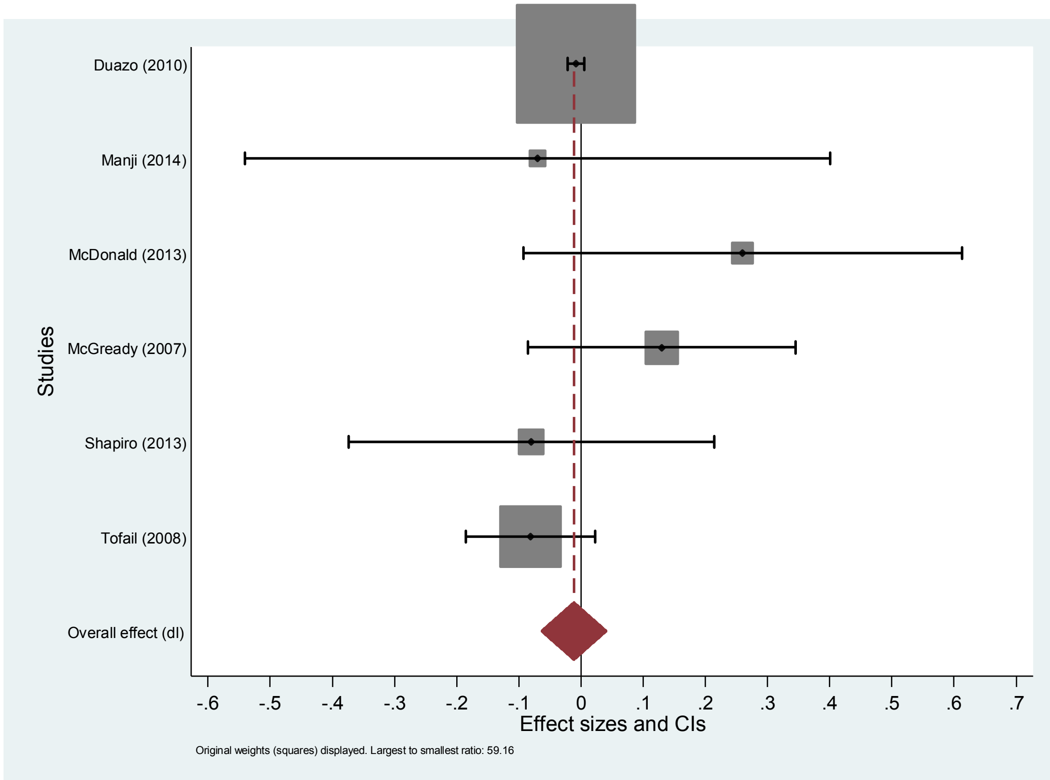

Figure 72: Association between maternal mild anemia (reference: no anemia) and motor development.

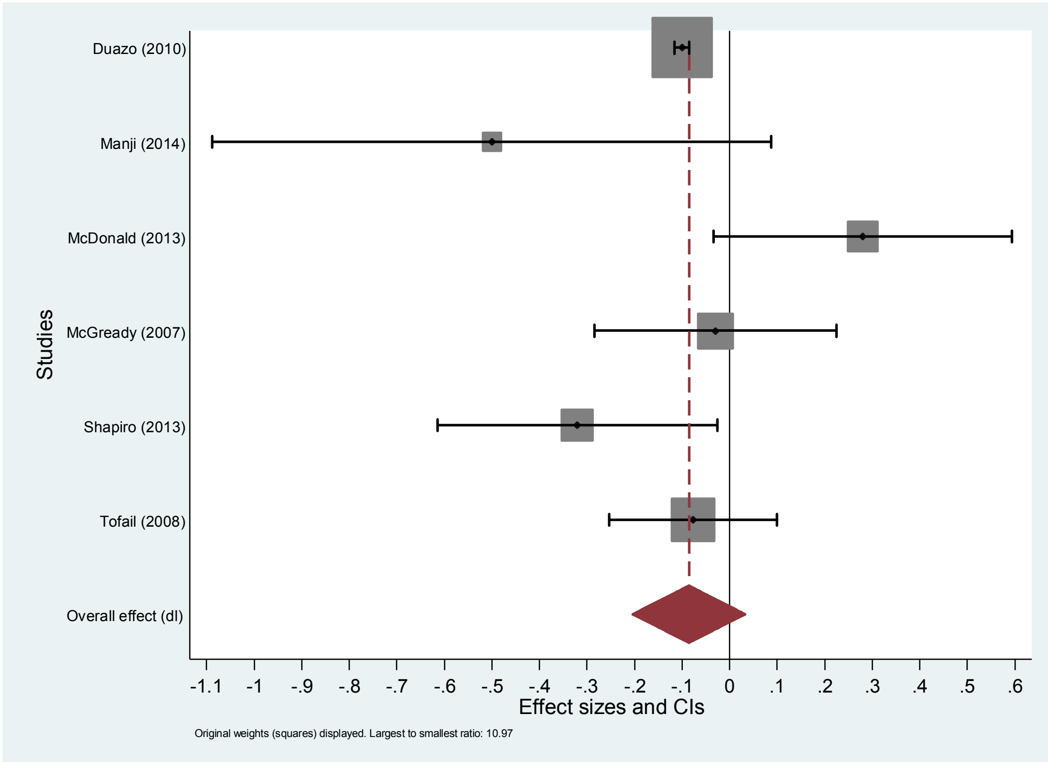

Figure 73: Association between maternal moderate anemia (reference: no anemia) and motor development.

6. Parental Risk Factors on Child's Language Development

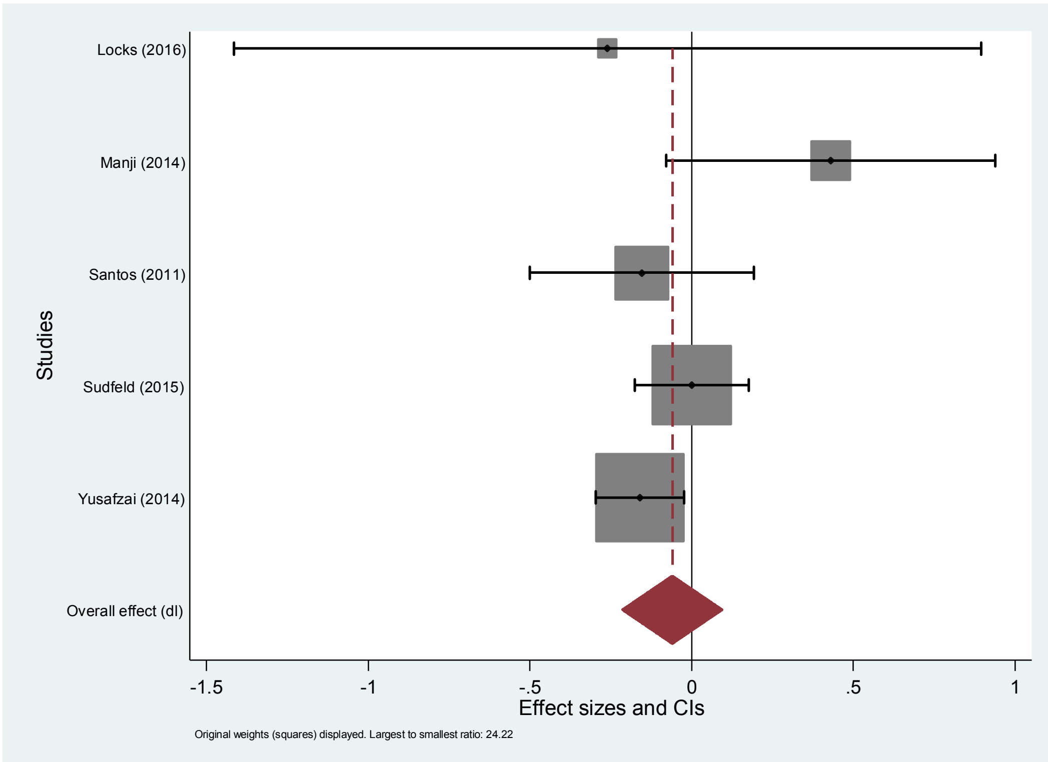

Figure 74: Association between no maternal education (reference: primary education) and language development.

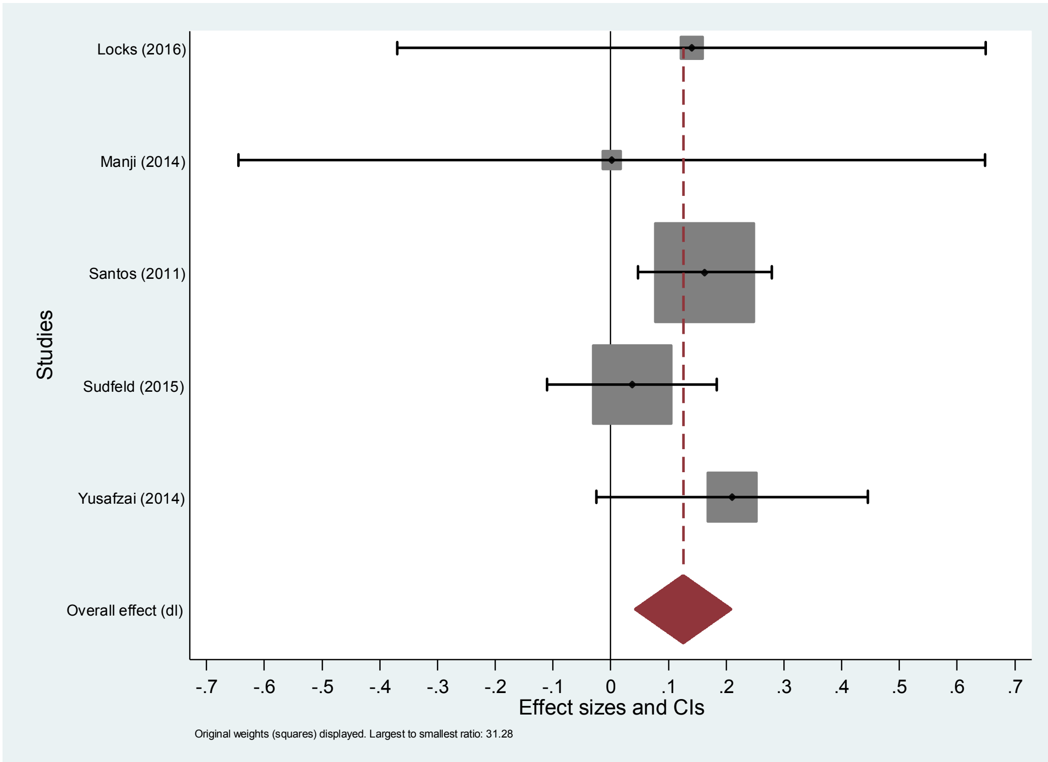

Figure 75: Association between maternal secondary education (reference: primary education) and language development.

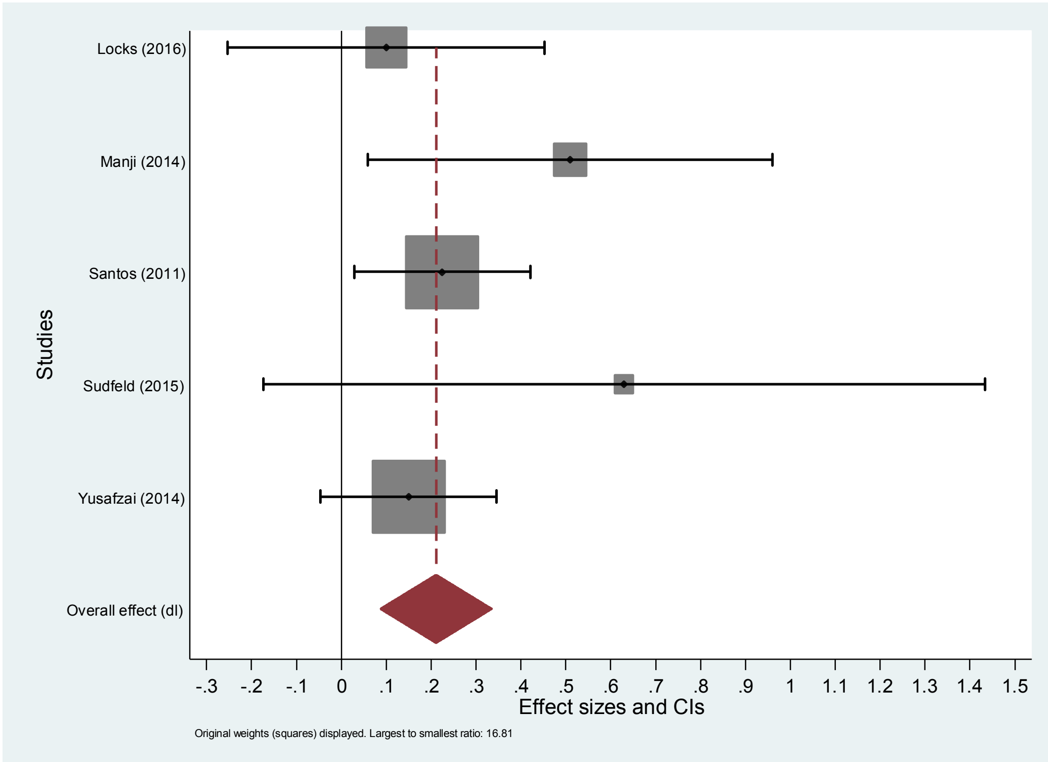

Figure 76: Association between maternal higher education (reference: primary education) and language development.

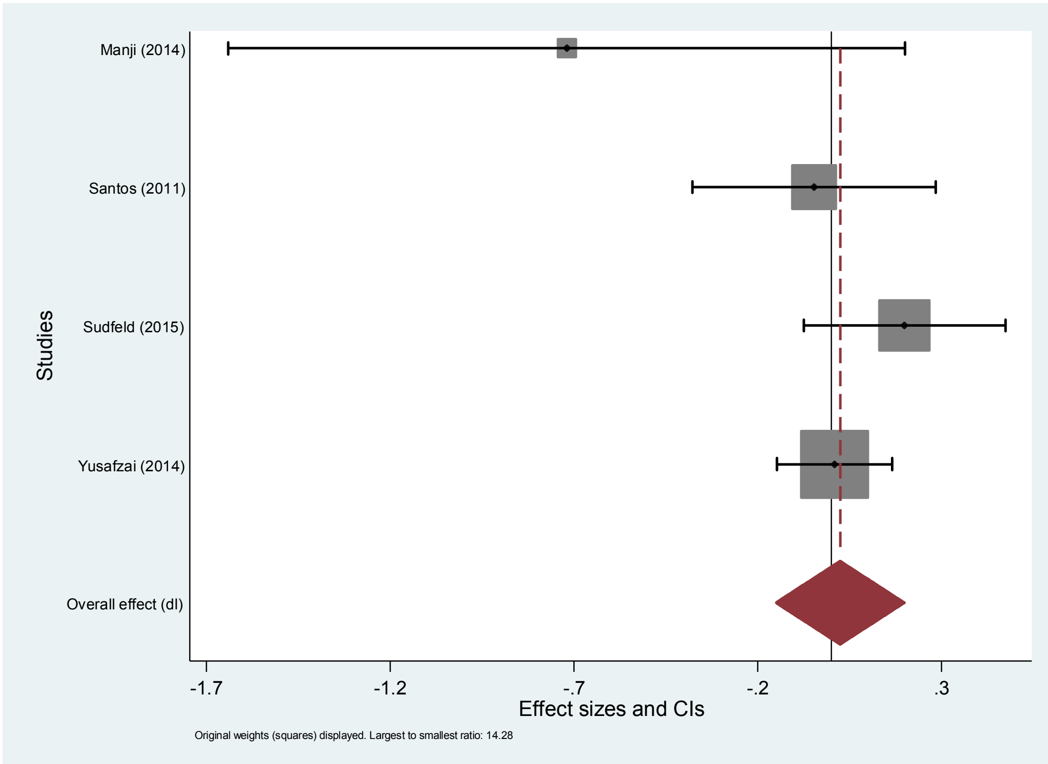

Figure 77: Association between no paternal education (reference: primary education) and language development.

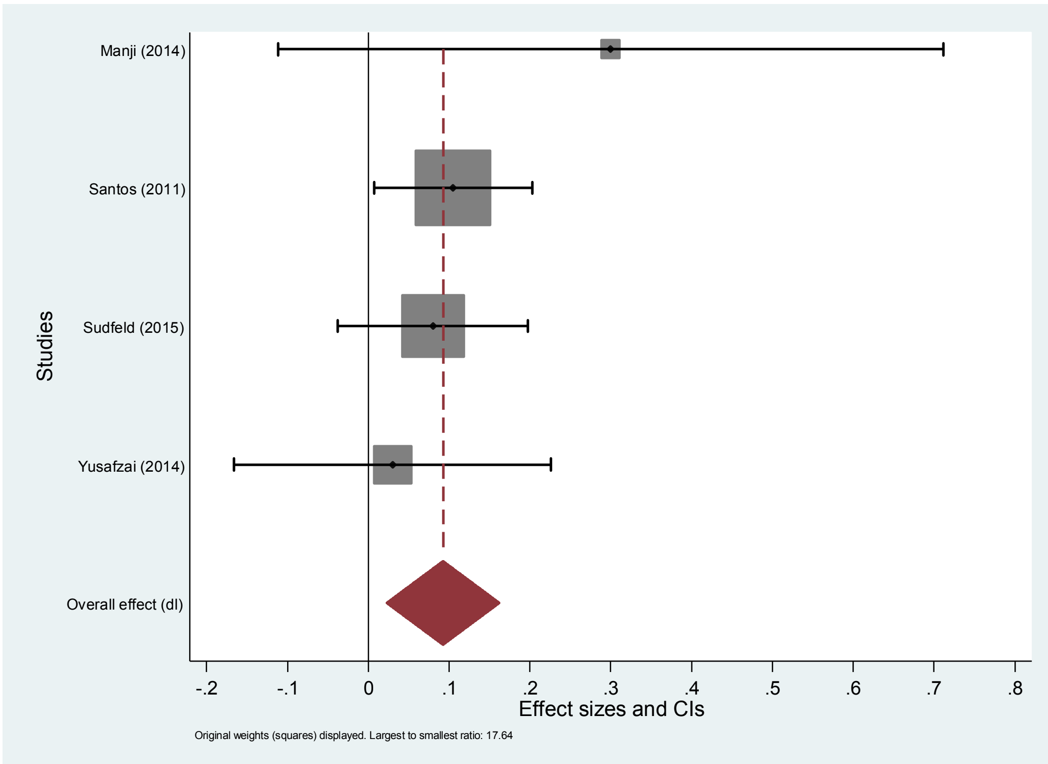

Figure 78: Association between paternal secondary education (reference: primary education) and language development.

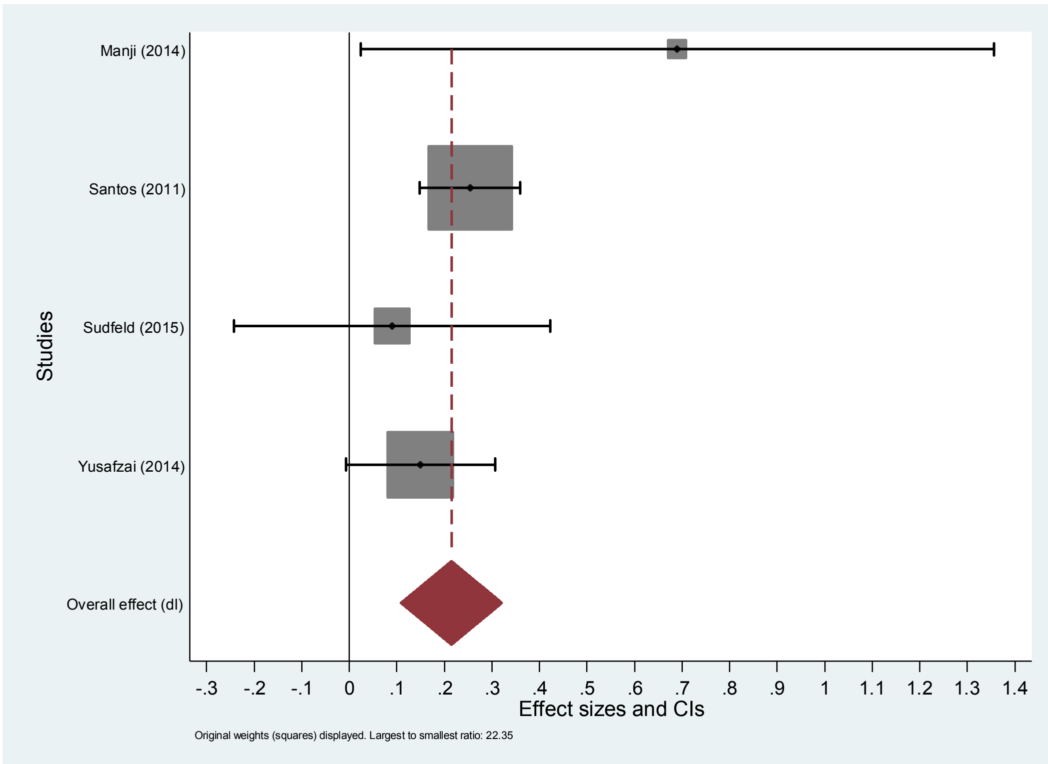

Figure 79: Association between paternal higher education (reference: primary education) and language development.

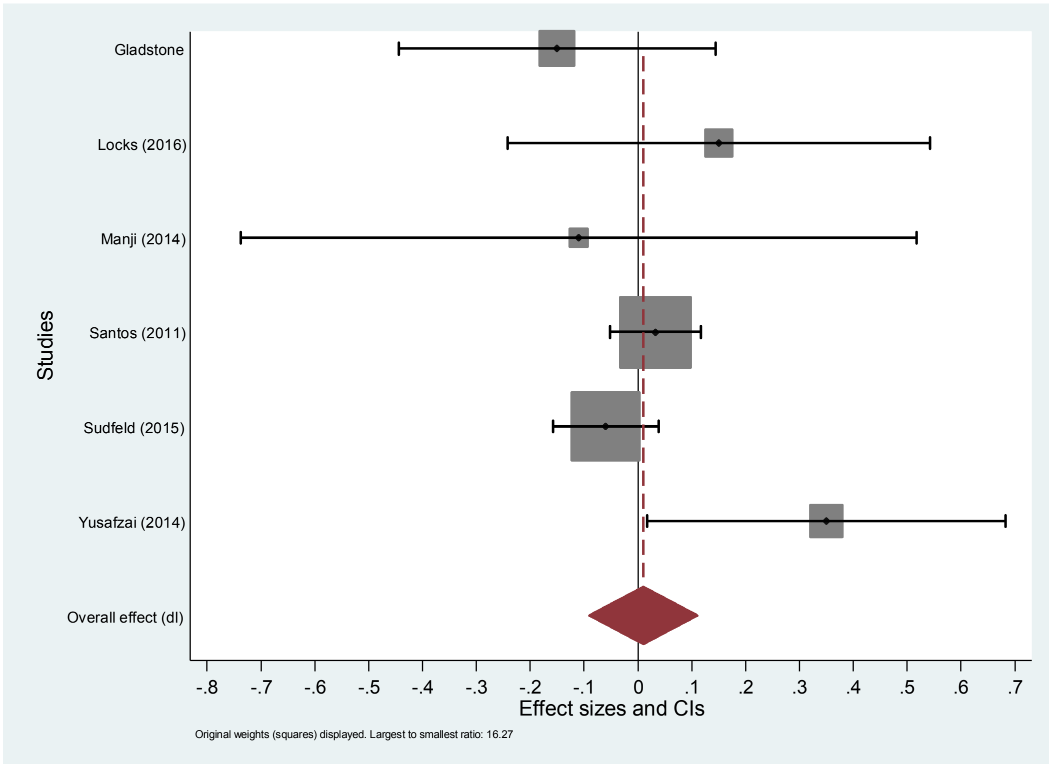

Figure 80: Association between maternal ages 15-20 (reference: ages 20-34) and language development.

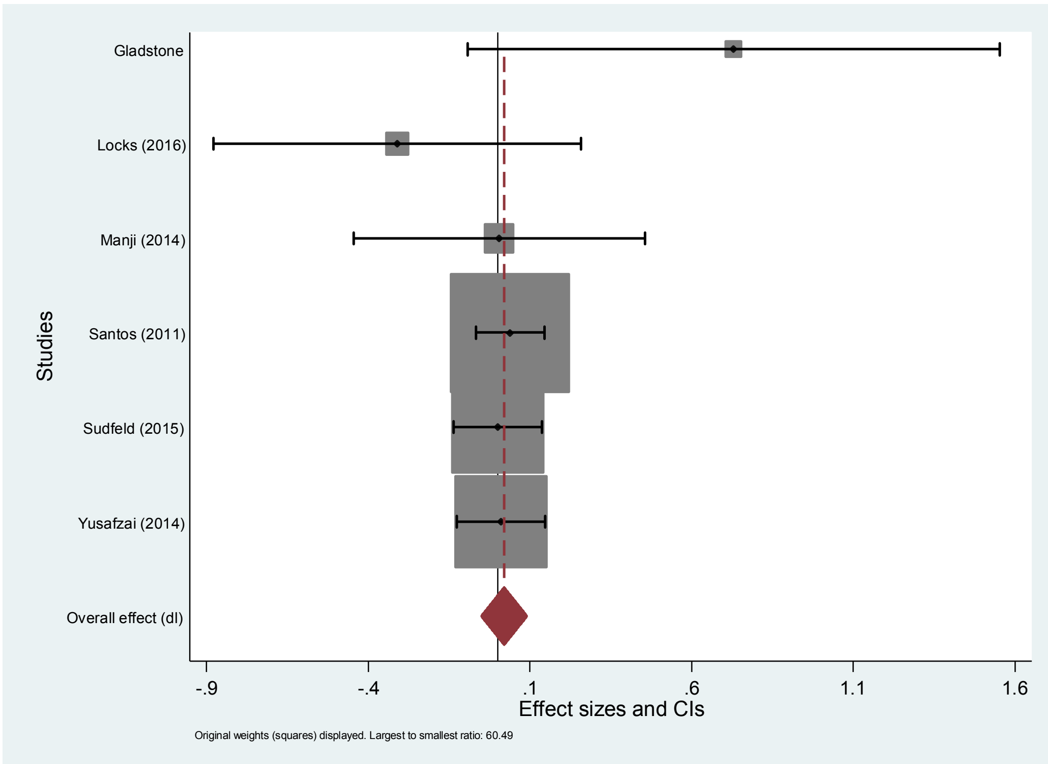

Figure 81: Association between maternal ages >35 (reference: ages 20-34) and language development.

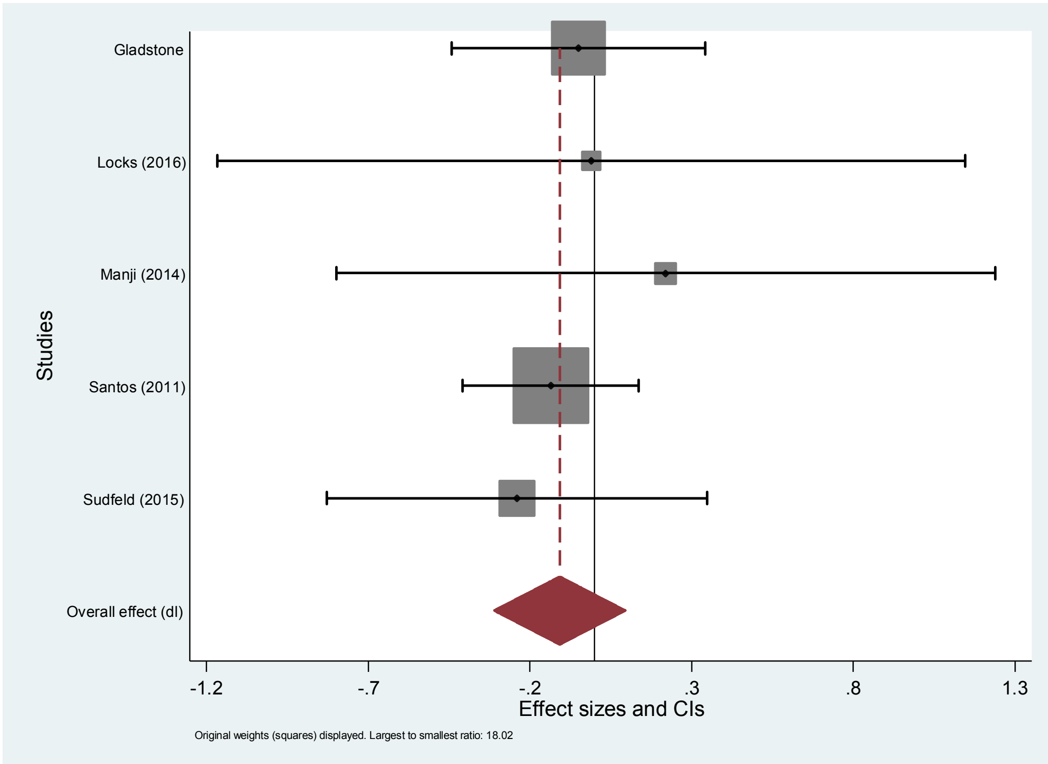

Figure 82: Association between maternal height <145 cm (reference: >155 cm) and language development.

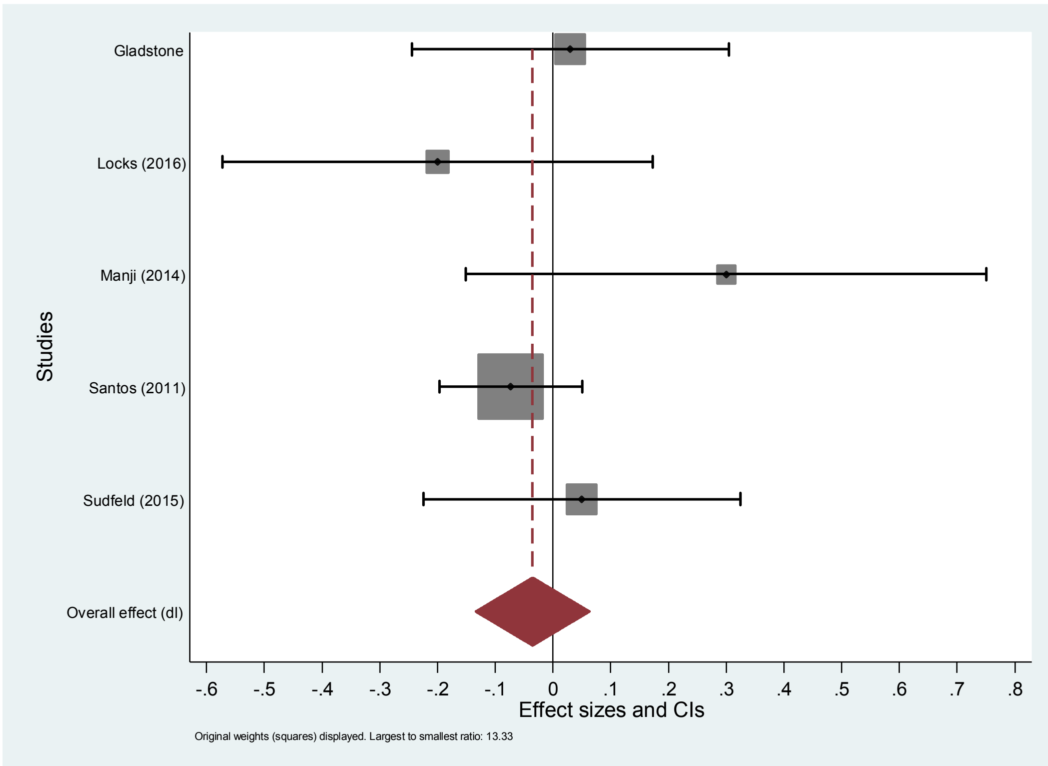

Figure 83: Association between maternal height 145-150cm (reference: >155 cm) and language development.

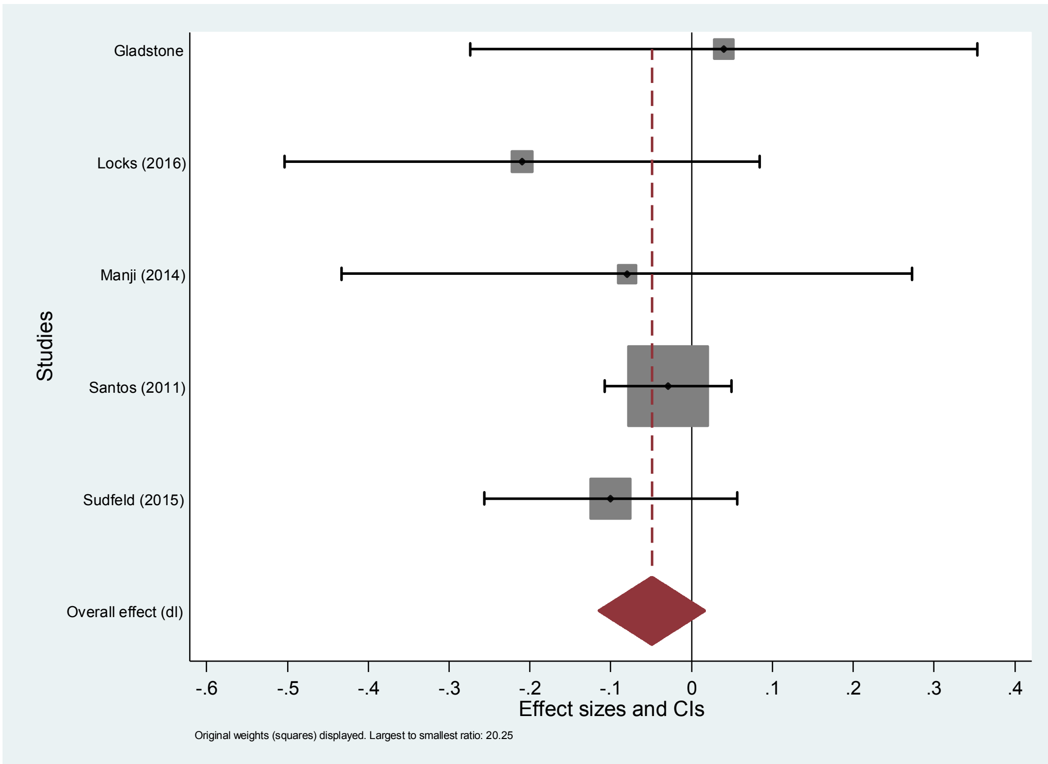

Figure 84: Association between maternal height 150-155 cm (reference: >155 cm) and language development.

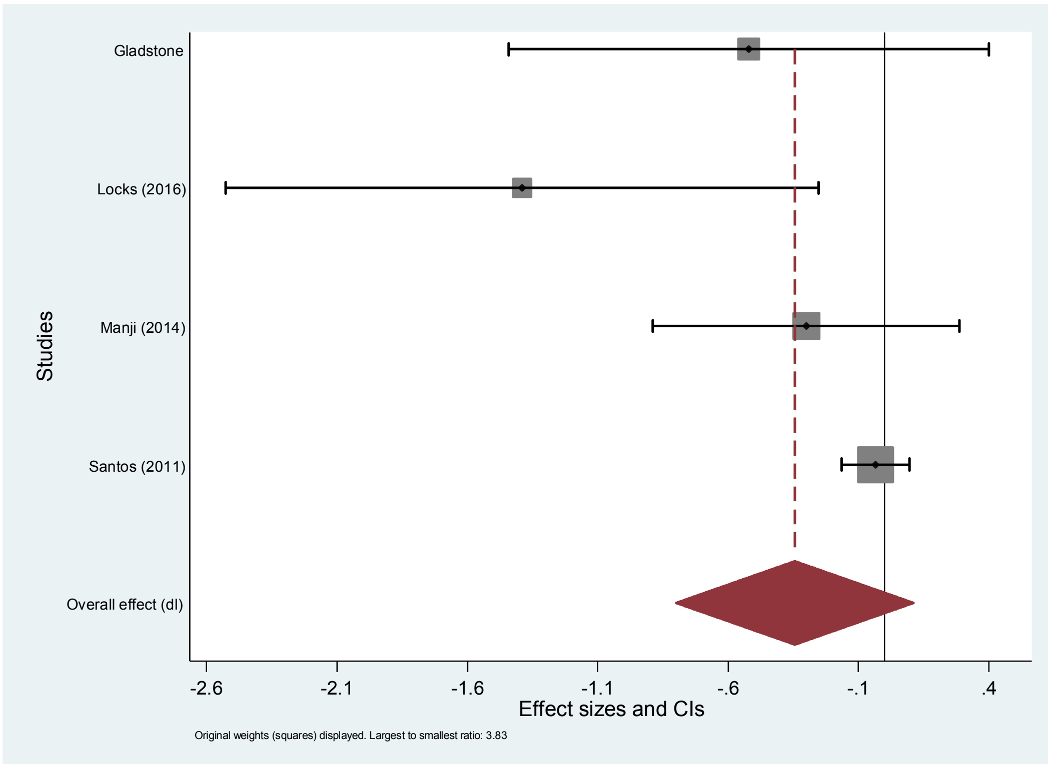

Figure 85: Association between maternal BMI 25-30 kg/m^2 (reference: 18.5-25) and language development.

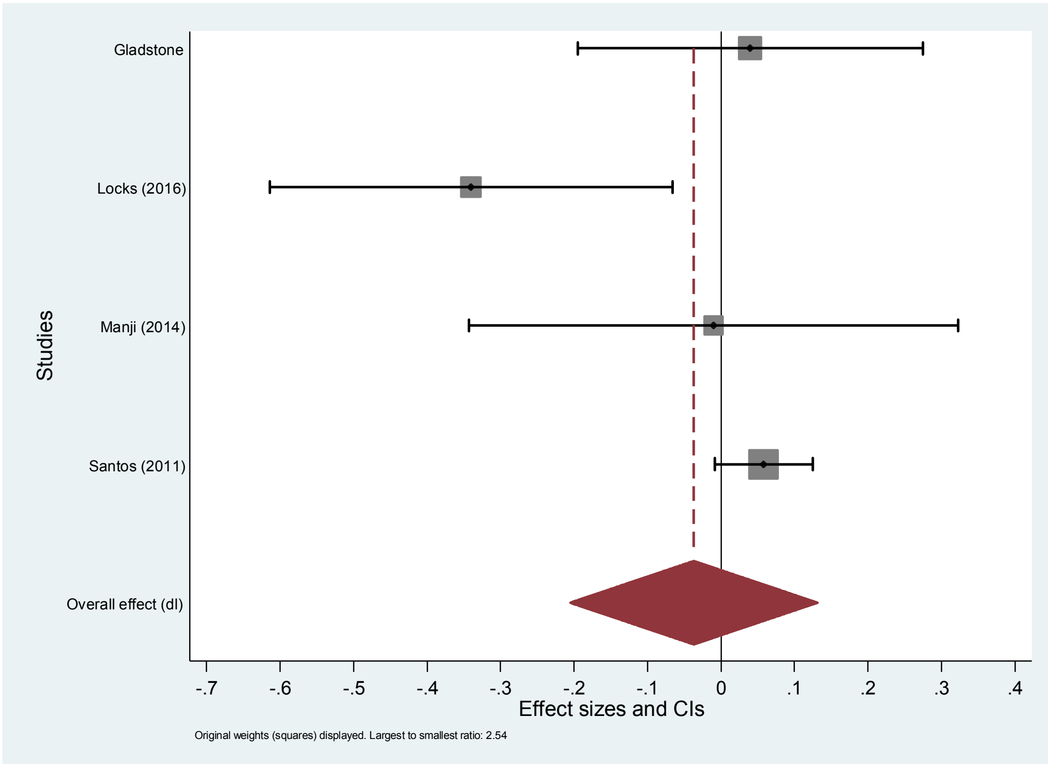

Figure 86: Association between maternal BMI >30 kg/m² (reference: 18.5-25) and language development.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	No
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6-7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration numbers.	yes
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8 & 10
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	N/A[a]
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A[b]
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A[b]
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Appendix 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Tables 2 and 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A[b]
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11-13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18 &19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	3

a. Same analyses were conducted in all individual studies by the authors and then estimates from individual studies were combined in pooled estimates. Therefore, assessment of quality of individual studies were not done.
b. Selection of studies were not based on published literature only, a large number of the studies were unpublished

PRISMA 2009 Checklist

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Early life risk factors of motor, cognitive, and language development: a pooled analysis of studies from low-and middle-income countries

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Early life risk factors of motor, cognitive, and language development: a pooled analysis of studies from low-and middle-income countries

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Short title: Risk factors of child development in LMIC

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Potential Conflicts of Interest: The authors have no conflicts of interest relevant to this article to disclose

Ethics committee approval: The pooled study was approved by the Harvard T.H. Chan School of Public Health (IRB16-0256).

Abbreviations:
AGA= Appropriate for gestational age
BSID=Bayley Scales of Infant and Toddler Development
IUGR= intra-uterine growth restriction
LBW= Low birth weight, <2500 grams
LMIC= Low-and-middle income countries
LMP= last menstrual period
ECD=Early childhood development
SDGs=Sustainable Development Goals
SMDs=standardized mean differences
SGA=Small-for-gestational age

Data availability:

Data included in the study may be available upon request. This study contains deidentified data from 21 studies. Of them, 14 investigators have shared their data with researchers at Harvard School of Public Health and seven shared results of analyses. Therefore, permission from investigators of individual studies needs to be obtained before data sharing.
All forest plots of the metanalyses of each risk factors have been uploaded as supplementary document and will be publicly available.

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Authors' contributions:

Ayesha Sania conceptualized the study, conducted the literature review, data analysis and drafted the manuscript. Christopher Sudfeld, and Wafaie Fawzi conceptualized the study and drafted the manuscript. Goodarz Danaei, Günther Fink, Dana Charles McCoy, Mary C. Smith Fawzi and Majid Ezzati provided critical input in the study design, interpretation of results and reviewed the manuscript. Zhaozhong Zhu participated in literature review and data analysis for the study. Mehmet Akman, Shams Arifeen, Aluísio J. D. Barros, David Bellinger, Maureen Black, Alemtsehay Bogale, Joseph Braun, Nynke van den Broek, Verena Ilona Carrara, Paulita Duazo, Christopher P. Duggan, Lia Fernald, Melissa Gladstone, Jena Hamadani, Alexis J. Handal, Siobán Harlow, Melissa Hidrobo, Christopher W. Kuzawa, Ingrid Kvestad, Lindsey Locks, Karim Manji, Honorati Masanja, Alicia Matijasevich, Christine McDonald, Rose McGready, Arjumand Rizvi, Darci Santos, Leticia Santos, Dilsad Save, Roger Shapiro, Barbara J. Stoecker, Tor A. Strand, Sunita Taneja, Martha-Maria Tellez-Rojo, Fahmida Tofail, and Aisha K.Yousafzai contributed data to the study, analyzed data and reviewed the manuscript. All authors had full access to their respective study data and to all statistical reports and tables of the pooled analyses and can take responsibility for the integrity of the data and accuracy of data analyses. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Abstract:

Objective: To determine the magnitude of relationships of early life factors with child development in LMICs.

Design: Meta-analyses of standardized mean differences (SMD) estimated from published and unpublished data.

Data sources: We searched Medline, bibliographies of key articles and reviews, and grey literature to identify studies from LMICs that collected data on early life exposures and child development. The most recent search was done on November 4, 2014. We then invited the first authors of the publications and investigators of unpublished studies to participate in the study.

Eligibility criteria for selecting studies: Studies that assessed at least one domain of child development in at least 100 children under 7 years of age and collected at least one early life factor of interest were included in the study.

Analyses: Linear regression models were used to assess SMDs in child development by parental and child factors within each study. We then produced pooled estimates across studies using random effects meta-analyses.

Results: We retrieved data from 21 studies including 20,882 children across 13 LMICs, to assess the associations of exposure to 14 major risk factors with child development. Children of mothers with secondary schooling had 0.14 SD (95% Confidence Interval, CI: 0.05, 0.25) higher cognitive scores compared to children whose mothers had primary education. Preterm birth was associated with 0.14 SD (-0.24, -0.05) and 0.23 SD (-0.42, -0.03) reductions in cognitive and motor scores, respectively. Maternal short stature, anemia in infancy, and lack of access to clean water and sanitation had significant negative associations with cognitive and motor development with effects ranging from -0.18 to -0.10 SDs.

Conclusions: Differential parental, environmental, and nutritional factors contribute to disparities in child development across LMICs. Targeting these factors from pre-pregnancy through childhood may improve health and development of children.

Funding: Grand Challenges Canada under the Saving Brains program (grant # 0073-03), National Institute of Health (grant # T32AI114398).

Strengths and Limitations of this study:

- Pooling data from 21 studies, this study provides the most comprehensive analysis of early life risk factors of child development in low-and middle-income countries
- The study cohorts were selected from 13 countries across the globe
- Uniform classifications of early life exposures and statistical analyses applied across studies
- 14 major risk factors, - parental, environmental and nutritional factors are included
- Data on important risk factors such as exposure to environmental neurotoxicants, responsive parenting behaviors, and child stimulation were not available

Introduction:

More than 250 million children under age 5 years in low-and middle-income countries (LMICs) are at risk of not attaining their full development potential.[1-3] The first 1000 days (from conception through 24 months of age) is critical for children's development, as the plasticity of the rapidly developing brain makes it vulnerable to harmful exposures as well as receptive to positive stimuli during this period.[4 5] Suboptimal development in early childhood may have long-term detrimental effects on education[6] and income attainment,[7] which in turn contribute to poverty and inequality across the lifecycle, and possibly also across generations.[8] Disadvantaged children with developmental deficits lose an estimated 19.8% of adult income yearly,[9] with an estimated global cost of US$ 177 billion for physical growth delays alone.[10] In recognition of the high burden and cost associated with early life disadvantage, the 2030 Sustainable Development Goals (SDGs) directly target early childhood development under SDG 4,[11] which calls for ensuring access to quality early childhood development care and pre-primary education for all children.

The relative importance of exposures to nutritional, socioeconomic and environmental risk factors in early life on different domains of child development in LMICs is poorly understood. Studies systematically reviewing the evidence linking early life risk factors to child outcomes primarily focused on growth (e.g., stunting),[9 12] identifying iodine deficiency, iron deficiency anemia, intrauterine growth restriction, maternal depression, exposure to violence, HIV infection as risk factors, and cognitive stimulation, maternal education, breastfeeding as protective factors.[13 14] However, the independent pathways from these risks to cognitive, motor and language development are not fully elucidated yet.[15 16] Consequently, priority risk factors and

interventions for improving cognitive, language, and motor development may differ from those designed to improve physical development in LMICs.

To determine the magnitude of the relationships linking early life exposures with child development in LMICs, we pooled data from 21 studies conducted in LMICs. We then examined the associations of early life risk factors on cognitive, motor and language development among children aged less than 7 years across studies. These pooled observational estimates are intended to inform the design of individual and packaged intervention studies to promote early child development in LMICs.

Methods

Study identification:

We searched Medline, bibliographies of key articles and reviews, and grey literature to identify datasets from low-income and middle-income countries (LMICs) that collected data on early life exposures and child development. Search terms included a list of risk factors, terms related to motor, cognitive, language and socioemotional development, and a list of low and middle income countries (list of search terms, appendix 1). The most recent search was done on November 4, 2014. We also identified additional datasets via communication with researchers of published studies that were not retrieved in our search. The primary criterion for inclusion of the datasets was the assessment of at least one domain of child development (cognitive, motor, language and socioemotional) using a standard child development assessment instrument in at least 100 children before 7 years of age, as well as the collection of at least one early life factor of interest as part of the study.

Following identification of the potential datasets, we contacted 50 first authors of the publications and investigators of unpublished studies, of whom 33 (66%) responded to participate in the present study (figure 1). We asked researchers to complete a survey that included questions about child development assessment tools used, age of developmental assessment and details on the early life factors measured in their study. Following the survey, 10 investigators declined to participate, 2 studies were excluded as the eligible sample size was less than 100 and 1 study was excluded as development was assessed after age 7 years. The investigators then shared results of pre-defined analyses on their data or shared data with researchers at the Harvard T.H. Chan School of Public Health to complete the analyses of individual studies and the meta-analyses.

Early life factors

We created a list of early life risk factors based on the review of the current literature[13 14]. These risk factors are represented in the 'Good Health' and 'Adequate Nutrition' components of nurturing care framework for early childhood development proposed by the WHO[17]. We enquired about the availability of data on a list of risk factors in the preliminary survey sent to the investigators. Based on the survey responses, we then selected 14 early life factors that were available in at least four datasets to include in the pooled analyses. Following the standard definitions of categories used in published studies and the survey responses on how individual studies recorded data on each risk factors, we used uniform categorization of the risk factors applicable to all datasets. Risk factors were grouped into parental factors: father's education and mother's education (categories for each variable: none <1 year; primary 1 - <6 years; secondary 6-<10 years; higher ≥10 years), maternal age (<15 years, 15-<20 years, 20-<35 years; ≥35 years), maternal height (<145 cm, 145-<150 cm, 150-<155 cm, >155 cm) maternal body mass index (BMI; <18.5 kg/m^2, 18.5-<25 kg/m^2, 25-<30 kg/m^2, ≥30 kg/m^2), hemoglobin level during pregnancy (normal ≥110 g/L; mild anemia 100-109 g/L ; moderate anemia 70-99 g/L) and child factors: birth weight (low birth weight <2500g; moderate low 2000-2500g; very low birth weight <2000g), preterm birth (preterm<37 weeks; late preterm 34-37 weeks; early preterm <34 weeks), small-for-gestational-age (SGA; <10 percentile; moderate SGA 3-<10 percentile; severe SGA <3 percentile) as determined by Alexander and Oken standards, exclusive breastfeeding until 6 months of age, hemoglobin levels in infancy (normal ≥110 g/L; mild anemia 100-109 g/L ; moderate anemia 70-99 g/L), access to clean water (yes, no), access to sanitation (yes, no) and diarrhea preceding the 6 months before development assessment (yes, no). Details on the definition and categories of the risk factors are included in appendix 2. We also enquired about data on birth spacing, maternal HIV infection, malaria, intimate partner violence and depression, but a limited number of studies had data on these factors.

Outcomes:

We included cognitive, motor and language outcomes in the analyses, socioemotional outcomes were not measured in a sufficient number of studies. If a study measured child development on multiple occasions, we included the measurement obtained at the age closest to 24 months. Since different tools were used for development assessment across studies, all development scores were standardized (z-scored) to ensure comparability between the measurements in different studies.

Analyses of individual studies:

Within each study, linear regression models were used to assess standardized mean differences (SMDs) in cognitive, motor, and language scores for the selected risk factors. Multivariable models were adjusted for child's age and sex, maternal education and a measure of socioeconomic status (e.g. household income or wealth index). Maternal education was adjusted as a confounder in all models except for the model that estimated the effects of maternal education. If a study was a randomized trial, intervention assignment was also included in the adjusted model. In addition, estimates for preterm birth and gestation-specific birth weight category (SGA and appropriate-for-gestational-age) were adjusted for each other. The missing indicator method was used for covariates when <10% of the data were missing; if more than 10% were missing the covariate was excluded from the analyses.

Meta-analysis:

Meta-analysis for a given risk factor was conducted if estimates from at least four studies were available. To account for the variation in tools used for measuring development we only pooled the means and standard errors of the standardized outcomes scores. As multivariable adjustment substantially changed the effect estimates, we used the adjusted effect estimates for meta-analysis. Given that heterogeneous effects seemed likely across the large variety of contexts studied, random effects meta-analysis was conducted using the DerSimonian and Larid method.[18] Heterogeneity was assessed using I^2 statistics. All analyses were conducted using the metaan commands in Stata 12.0 (StataCorp, College Station, TX)

Ethical consideration:

The pooled study was approved by the Harvard T.H. Chan School of Public Health (IRB16-0256).

Patient and Public Involvement:

Patients and or public were not involved**.**

Results:

Table 1 shows the characteristics of the studies included in the analyses. We included 21 data sets with developmental measurements on 20,882 children of which 8 were from Asia,[19-26] 7 were from sub-Saharan Africa,[27-33] 5 were from Latin America and 1 from Europe.[34-39] The majority of studies (n=18), including 12 randomized trials,[19-23 26 27 30-33 39] followed up the participants prospectively. The Bayley Scales of Infant and Toddler Development (BSID) was used to assess child development in most of the studies with, BSID-III administered in 5 studies,[24 27 31-33] BSID-II in 5 studies,[19-22 30] and BSID I in 1 study.[39] The Ages and Stages questionnaire was used in 2 studies,[23 37] and a few studies used local adaptations of standard tools.[29 36] The majority of the studies had data on both motor and cognitive development,[19-25 27-39] 1 study had data on motor development only[26] and 6 studies provided data on language development.[29 31-34] Development was assessed before age 2 years in most studies,[19-27 29-35 38 39] except for 3 studies that assessed development at ages between 3-6 years. [28 36 37]

Parental factors:

Pooled estimates for the association of parental factors with child cognitive, motor, and language development are presented in Table 2. Higher attained maternal education was associated with improved cognitive, motor, and language development scores. Children whose mothers attended or completed secondary school had 0.14 SD (95% CI: 0.05, 0.25), 0.12 SD (95% CI: 0.06, 0.18), and 0.13 SD (95% CI: 0.04, 0.21) higher cognitive, motor and language scores, respectively, as compared to children whose mothers only had primary school education. Compared to children of mothers with primary education, children of mothers with ≥ ten years of education scored 0.36 SD (95% CI: 0.19, 0.48), 0.26 SD (95% CI: 0.14, 0.38) and 0.21 SD (95% CI 0.09, 0.33) higher

in cognitive, motor and language scores, respectively. Children of mothers with no formal schooling scored lowest in cognitive, motor and language scores. There was a significant positive association between father's education and cognitive and motor development after adjusting for maternal education, although the magnitude of the effect sizes was smaller than for those of maternal education. We found no significant relationships between maternal age at birth and cognitive, motor, or language development.

Children of mothers with short stature (height <155 cm) tended to have lower cognitive, motor, and language scores as compared with a maternal height >155cm. Children whose mothers were <145cm scored 0.10 SD (95% CI -0.20, -0.004), 0.11 SD (95% CI: -0.19, -0.03), and 0.11 SD (95% CI: -0.31, 0.09) lower on cognitive, motor, and language development, respectively. Low maternal BMI (<18.5 kg/m^2) was significantly associated with lower cognitive development scores (SD: -0.10; 95% CI -0.19, -0.02), but not motor or language development. There was no significant association of maternal hemoglobin with child cognition.

Child factors:

Pooled estimates for the association of child factors with development are presented in Table 3. Compared to children born with normal birth weight, children born with low birth weight (<2500g) had significantly poorer cognitive and motor scores. Children with birthweights <2000g had on average 0.27 SD (95% CI: -0.49, -0.07) lower cognitive, 0.26 SD (95% CI: -0.40, -0.12) lower motor and 0.28 SD (95% CI: -0.60, 0.05) lower language scores, compared with normal birthweight children (≥2500 g). Compared to term and appropriate for gestational age (AGA) infants, preterm-AGA infants had 0.14 SD (95% CI: -0.24, -0.05) and 0.23 SD (95% CI:

-0.42, -0.03) lower cognitive and motor scores, respectively. Term-SGA infants had poorer developmental scores in some studies, but the pooled effect estimates for term-SGA, adjusted for preterm birth, were not statistically significant.

Anemia in infancy was significantly and negatively associated with both motor and cognitive development scores. Combined effect sizes of moderate anemia were -0.18 SD (95% CI -0.27, -0.09) for motor and -0.11 SD (95% CI -0.12, - 0.10) for cognitive scores. Compared to children residing in households with access to clean water, children without access had 0.10 SD (95% CI: -0.12, -0.09) lower cognitive and 0.07 SD (95% CI: -0.16, 0.01) lower motor and 0.15 SD (95% CI: -0.35, -0.05) lower language scores. Children without access to clean sanitation had 0.13 SD (95% CI: -0.18, -0.07) lower cognitive and 0.10 SD (95% CI: -0.19, -0.01) lower motor scores. In the pooled analyses, exclusive breastfeeding until 6 months of age and diarrhea during the preceding 6-month of development assessment did not have significant associations with either cognitive or motor development.

Figures 2 and 3 present effect sizes of all risk factors included in the analyses. Forests plots of metanalysis of individual risk factors are included in appendix 2, Figures 1-86.

Discussion:

This pooled analysis of development assessment of 20,882 children from 21 LMIC studies determined that low maternal and paternal education, short maternal stature, low birth weight, preterm birth, anemia in infancy, and lack of access to clean water and sanitation were associated with lower child development scores among children < 7 years of age. We did not find significant associations of maternal anemia, fetal growth restriction, exclusive breastfeeding, or childhood diarrhea with development scores.

We observed a dose-response relationship between parental education and child development. While a large body of literature supports the consistent role of maternal education in promoting children's language and cognitive developments, evidence on the role of paternal education is more limited.[35 40 41] Recent reports suggest advanced language and cognitive development among children of more educated fathers that persisted after adjustment for family income and mothers' education.[42] Maternal education is associated with more warm, responsive, and stimulating home environments, which in turn are predictive of more positive developmental outcomes for children.[43] High maternal education is also linked with protective factors like good feeding and hygiene practices and frequent utilization of antenatal care and child immunization.[44 45] In addition, low maternal education is associated with known risk factors of poor child development such as malnutrition in children, and depression and stress in mothers.[46 47] Although prior work suggests that less educated mothers tend to be less receptive to early childhood development (ECD) messages, research also shows that their children may benefit more from ECD interventions.[48] Therefore, adopting a 2-generational intervention approach to empower parents and improve parenting capacity are likely to generate long-term benefits for child development.

Due to the availability of maternal education data, low maternal education can serve as a simple risk marker to target children in need of ECD intervention.[49]

We found significant negative associations of preterm birth with cognitive and motor development but not with language development. Meta-analyses of studies conducted in developed countries reported lower IQ scores and cognitive functioning, [50-52] along with deficits in motor [53], language [54], and visual-spatial abilities[55] in preterm infants. Reduction of the intrauterine period interrupts the trajectory of neurodevelopmental processes such as synapse formation and myelination, which often leads to neurocognitive deficits.[56] Although most preterm infants catch up in physical growth[57], this deficit in neurocognitive development often persists into childhood and adolescence.[58 59] Given the high incidence of preterm delivery in LMIC[60] and the increased survival of preterm infants with medical advances, the burden of the developmental deficits caused by preterm birth in LMIC may be increasing. There are currently few interventions to prevent preterm birth[61]; however, a variety of psychosocial interventions to alleviate the adverse neurodevelopmental effects of preterm birth implemented at different points in early childhood have shown modest short-term benefits.[62]

We found that fetal growth restriction, assessed via SGA, was not significantly associated with child development. This agrees with several reports from developed countries[63-65] whereas others have reported adverse effects of SGA on cognitive and motor functioning[32 66 67]. These disparate findings could be caused by different definitions of SGA and/or timing of the developmental assessment. Most studies from LMICs used LBW (as marker of SGA), which is also caused by prematurity, a major risk predictor of child development. There is some evidence that with

adequate nutrition, the developmental deficit in SGA infants is often compensated with age, although the gap in physical growth remains[68]. This finding underscores the potentially differential roles and separate causal mechanisms of effects of early life risk factors for physical and mental development. It is important to note that the effect size for SGA may be biased downwards considering the heterogeneity in outcome and the measurement error due to the use of last menstrual period (LMP) date for the estimation of gestational age in most the studies. We found significant negative associations between short maternal stature (<145 cm) and low BMI (<18.5 kg/m2)[69] on cognitive function, which may indicate the role of chronic malnutrition of mothers over their life course on pregnancy health and development of fetus. These are also known risk factors of SGA,[69] suggesting that adverse effects of fetal growth restriction on child development are possible. Further research is needed to quantify the effects of fetal growth restriction on children's development and evaluate the effects of interventions to alleviate the negative impacts of SGA on development.

We found an adverse role of anemia in infancy with motor and cognitive development. Prior studies reported significant effects of anemia on cognitive, motor and socioemotional development that persisted into middle childhood during longitudinal follow-up[70]. Worldwide, the predominant cause of anemia for infants and children is iron deficiency[71], which can interfere with myelination, synapse formation and protein expression during sensitive periods of neurodevelopment[72]. Meta-analyses of randomized trials of infant iron supplementation have not established an effect on child development; however statistical power to detect effect sizes of < 0.2 SD as our analysis predicts is limited due to few trials with large enough sample sizes.[73 74] In our pooled analyses, maternal anemia during pregnancy, an important determinant of anemia in

infancy[75], was not significantly associated with children's development. We also did not find a significant association between exclusive breastfeeding until 6 months of age and children's development. Nevertheless, few studies included in our pooled analyses had a sufficient number of infants who were exclusively breastfed until six months to allow for a well-powered analysis. Because of the multidimensional benefits of breastfeeding from infection prevention to fostering mother-infant bonding and infant attachment, significant positive effects of exclusive breastfeeding on child development are plausible. Meta-analyses of studies of effects of breastfeeding on children's development reported significant increases in intelligence and cognitive scores[76 77]; however some studies have attributed these associations entirely to the presence of confounding by socioeconomic status and stimulation at home.[78]

This study is among the first to report on the associations between lack of access to safe water and sanitation and child cognitive development. The burden of developmental deficit attributed to these risk factors is likely very high as a large proportion of the population in LMICs reside in unhygienic environments with limited access to safe water. The effects of poor sanitation and unsafe water on child cognitive development are potentially mediated through childhood anemia, inflammation and undernutrition resulting from frequent enteric infections[79]. However, in the pooled analyses, we did not find any significant adverse associations between diarrhea and development, which is different from previously published evidence[23 80 81]. One potential explanation for the lack of association found in this study may be measurement error: diarrhea is inherently complex and hard to measure; variations in the definitions of episodes as well as parental inability to correctly report diarrhea may have led to the failure to detect potential effects of diarrhea on cognitive, motor and language development in this study.

The strengths of this pooled study include the global coverage of the cohorts, the large sample size, and uniform classifications of early life exposures and statistical analyses across studies. Nevertheless, there are also several limitations, including the lack of data on exposure to environmental neurotoxicants, maternal depression, responsive parenting behaviors, and child stimulation and early education. A recent meta-analysis determined that the potential effect of responsive stimulation on cognitive development at 2 years of age was +0.42SD (95% CI: 0.36, 0.48)[82], which is larger than all risk factors examined in our analysis. Thus, comprehensive packages of environmental, nutrition, and stimulation interventions may produce larger effect sizes than interventions targeting single risks. In addition, due to the observational nature of the studies included in this analysis, we are unable to determine a causal relationship between parental and child factors with child development. Although we have adjusted for major confounders the potential for residual confounding remains. Last, there was moderate to high levels of heterogeneity, as indicated by the I^2 values, in some of our pooled estimates. The magnitude of the relationship for maternal education, prematurity, birthweight, SGA, and access to water and sanitation appeared to vary by study cohort. As a result, cultural and other contextual factors may be important in determining the strength of the relationship between health and nutrition exposures with child development outcomes. Accordingly, future intervention studies should be conducted among diverse study populations as their effect may importantly differ by setting.

In summary, in a pooled study of 21 studies in LMICs, we determined that multiple risk factors classically associated with child morbidity and mortality also appear to have negative associations with cognitive, motor, and language development. As a result, our study suggests that interventions that span pre-pregnancy through early and middle childhood may be necessary to provide optimal child development in LMICs. Future research should focus on determining the effectiveness of, and delivery strategies for comprehensive intervention packages to promote child development.

Key Words:

Motor development
cognitive development
Language development
Early life risk factors
Preterm
SGA
Maternal education
Paternal education
Maternal short stature
Maternal anemia
anemia in infancy,
Access to clean water
Access to sanitation
Breastfeeding
Diarrhea

Figure Legends

Figure 1: Flow chart of study selection

Figure 2: Pooled estimates of association between maternal factors and development

Figure 3: Pooled estimates of association between child factors and development

Table 1: Characteristics of the included studies

	Study	Setting	Primary study design	Study population	N (data on child development)	Child development tool used	Child age in years at assessment (mean±SD)
Asia							
1	Black (2004)[19]	Bangladesh	randomized controlled trial	birth cohort	221	Bayley Scales of Infant and Toddler Development, 2nd edition (BSID-II) and the Home Observation for Measurement of the Environment (HOME) Inventory	1.06±0.03
2	Tofail (2008)[20]	Bangladesh	randomized controlled trial	birth cohort	2853 total (2116 tested)	2 problem-solving tests, motor index of Bayley Scales of Infant and Toddler Development, 2nd edition (BSID-II) and Wolke's behavior ratings	0.61±0.02
3	Tofail (2012)[21]	Bangladesh	randomized controlled trial	prospective, community-based cohort	249	Bayley Scales of Infant and Toddler Development, 2nd edition (BSID-II)	0.84±0.01
4	Taneja (2005)[22]	India	randomized placebo-controlled trial	Prospective, community-based cohort	571	Bayley Scales of Infant and Toddler Development, 2nd edition (BSID-II)	1.25±0.16
5	Kvestad (2015)[23]	India	randomized placebo-controlled trial	prospective, community-based cohort	422	Ages and Stages Questionnaire, 3rd edition (ASQ-3)	1.37±0.60
6	Yousafzai (2014)[24]	Pakistan	community-based cluster-randomized effectiveness trial	prospective, community-based cohort	1357	Bayley Scales of Infant and Toddler Development, 3rd edition (BSID-III)	11.6 ±0.83
7	Duazo (2010)[25]	Philippines	longitudinal program evaluation	birth cohort	4904	Philippines Revised Early Childhood Development Checklist (REC)	1.62±0.88
8	McGready (2007)[26]	Thailand	randomized controlled trial	prospective, facility-based cohort	503	Shoklo Developmental Test	1.62±0.02
Sub-Saharan Africa							
9	Shapiro (2013)[27]	Botswana	randomized controlled trial	prospective, community-based cohort	224	Bayley Scales of Infant and Toddler Development, 3rd edition (BSID-III)	2.03±0.08
10	Alemtsehay (2009)[28]	Ethiopia	cross-sectional study	cross-sectional, community-based cohort	100	Raven's Colored Progressive Matrices (CPM) and Kaufman Assessment Battery for Children-II (KABC-II)	5.11±0.24
11	Gladstone (2011)[29]	Malawi	cross-sectional community-based cohort study	community-based cohort	840	Ten Question Questionnaire [TQQ] and Malawi Developmental Assessment Tool [MDAT]	1.74±0.33
12	McDonald (2013)[30]	Tanzania	randomized placebo-controlled trial	birth cohort	305	Bayley Scales of Infant and Toddler Development, 2nd edition (BSID-II)	1.28±0.04
13	Manji (2014)[31]	Tanzania	randomized placebo-controlled trial	birth cohort	206	Bayley Scales of Infant and Toddler Development, 3rd edition (BSID-III)	1.28±0.04
14	Sudfeld (2015)[32]	Tanzania	randomized placebo-controlled trial	birth cohort	958	Bayley Scales of Infant and Toddler Development, 3rd edition (BSID-III)	2.25±0.52

	Study	Setting	Primary study design	Study population	N (data on child development)	Child development tool used	Child age in years at assessment (mean±SD)
15	Locks (2016)[33]	Tanzania	randomized placebo-controlled trial	birth cohort	248	Bayley Scales of Infant and Toddler Development, 3rd edition (BSID-III)	1.21±0.03
Latin America							
16	Santos IS (2011)[34]	Brazil	longitudinal birth cohort survey	2004 Pelotas birth cohort	3868	Battelle Screening Developmental Inventory (BSDI)	1.99 ± 0.05
17	Santos (2008)[35]	Brazil	longitudinal birth cohort survey	Longitudinal, community-based cohort	365	Wechsler Pre-School and Primary Scale of Intelligence-Revised (WPPSI-R)	5.80±3.02
18	Fernald (2011)[36]	Ecuador	randomized effectiveness trial	Prospective, community-based cohort	1265	MacArthur-Bates Communicative Development Inventory, short form, Spanish version	4.59±0.87
19	Handal (2008)[37]	Ecuador	cross-sectional	Community based, selected using door-to-door survey	283	Ages and Stages Questionnaire (ASQ)	2.46±1.46
20	Braun (2012)[38]	Mexico	prospective cohort study	prospective, facility-based cohort	1032	Bayley Scales of Infant and Toddler Development, 2nd edition (BSID-II) McCarthy Scales of Children's Abilities (MSCA)	2.02±0.03
Europe							
21	Akman (2004)[39]	Europe-Turkey	randomized clinical trial	facility-based hospital	108	Bayley Scales of Infant and Toddler Development, 1st edition (BSID-I)	1.42±0.59

Table 2: Summary results of meta-analysis of associations of parental factors and cognitive, motor and language developments

Risk Factor	Cognitive				Motor				Language			
	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)
Mother's education												
No education (<1 years)	15	-0.12 (-0.24, -0.008)	0.05	50.8	18	-0.07 (-0.13, -0.01)	0.03	18.2	5	-0.06 (-0.21, -0.09)	0.49	35.5
Primary (1- <6 years)		Reference				Reference				Reference		
Secondary (6- <10 years)	17	0.14 (0.05, 0.24)	< 0.01	59.7	19	0.12 (0.06, 0.18)	< 0.01	51.8	5	0.13 (0.04, 0.21)	0.04	0.0
Higher (≥10 years)	17	0.36 (0.19, 0.48)	< 0.01	65.8	19	0.26 (0.14, 0.38)	< 0.01	70.6	5	0.21 (0.09, 0.33)	0.03	0.0
Father's education												
No education (<1 years)	13	-0.005 (-0.08, 0.07)	0.91	0.0	17	-0.08 (-0.11, -0.04)	< 0.01	0.0	4	0.02 (-0.15, 0.20)	0.80	30.0
Primary (1- <6 years)		Reference				Reference				Reference		
Secondary (6- <10 years)	15	0.06 (0.015, 0.11)	0.02	0.0	17	0.08 (0.03, 0.13)	< 0.01	30.3	4	0.09 (0.02, 0.16)	0.08	0.0
Higher (≥10 years)	15	0.15 (0.08, 0.21)	< 0.01	0.0	17	0.18 (0.10, 0.26)	< 0.01	42.3	4	0.22 (0.11, 0.32)	0.03	17.9
Mother's age												
<15 years	5	-0.06 (-0.13, 0.25)	0.57	0.0	5	0.12 (-0.06, 0.30)	0.25	0.0	2	n/a	n/a	n/a
15-<20 years	18	-0.007 (-0.06, 0.05)	0.80	10.7	20	-0.02 (-0.11, 0.08)	0.75	83.6	6	0.01 (-0.09, 0.11)	0.85	37.0
20-34 years		Reference				Reference				Reference		
≥35 years	18	-0.01 (-0.06, 0.04)	0.58	0.0	20	-0.006 (-0.07, 0.05)	0.85	50.1	6	0.02 (-0.05, 0.09)	0.59	0.0
Mother's height												
<145 cm	11	-0.10 (-0.20, -0.004)	0.07	0.0	13	-0.11 (-0.19, -0.03)	0.02	21.5	5	-0.11 (-0.31, 0.09)	0.35	0.0
145 -<150 cm	13	-0.11 (-0.19, -0.02)	0.03	27.1	15	-0.07 (-0.16, 0.03)	0.17	71.1	5	-0.06 (-0.13, 0.06)	0.52	0.0
150- <155 cm	13	-0.09 (-0.14, -0.04)	< 0.01	3.3	15	-0.04 (-0.09, 0.009)	0.14	31.5	5	-0.05 (-0.12, 0.02)	0.22	0.0
>155 cm		Reference				Reference				Reference		
Mother's BMI (kg/m^2)												

Risk Factor	Cognitive				Motor				Language			
	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)
<18.5	11	-0.11 (-0.20, -0.02)	0.03	12.7	13	-0.02 (-0.11, 0.07)	0.69	51.4	3	n/a	n/a	n/a
18.5 -<25		Reference				Reference				Reference		
25-<30	12	0.03 (-0.04, 0.09)	0.44	23.3	14	0.04 (-0.03, 0.11)	0.31	64.6	4	-0.04 (-0.21, 0.13)	0.70	61.0
≥30	12	-0.02 (-0.17, 0.14)	0.82	46.3	14	-0.02 (-0.14, 0.10)	0.77	63.6	4	-0.14 (-0.34, 0.06)	0.26	35.9
Mother's hemoglobin level (g/L)												
Normal (≥110 g/L))		Reference				Reference				Reference		
Mild anemia (100-109 g/L)	4	-0.06 (-0.15, 0.03)	0.28	0.0	11	0.06 (0.008, 0.11)	0.04	29.7	1	n/a	n/a	n/a
Moderate anemia (70-99 g/L)	4	-0.06 (-0.19, 0.06)	0.39	0.0	6	-0.01 (-0.06, 0.04)	0.68	16.3	1	n/a	n/a	n/a

[1]Adjusted for child's gender and age, mother's education and household wealth

Table 3: Summary results of meta-analysis of associations of child factors and cognitive, motor and language developments, standardized scores

Risk Factor	Cognitive				Motor				Language			
	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)
Birth weight (g)												
Normal (≥2500 g)		Reference				Reference				Reference		
Low (<2500 g)	14	-0.13 (-0.20, -0.07)	< 0.01	51.0	15	-0.14 (-0.23, -0.06)	< 0.01	66.5	5	-0.11 (-0.22, 0.00)	0.12	74.6
Moderate low (2000-2500 g)	14	-0.07 (-0.12, -0.03)	< 0.01	17.2	15	-0.11 (-0.20, -0.02)	0.03	64.0	5	-0.05 (-0.10, 0.01)	0.20	29.6
Very low (<2000 g)	14	-0.27 (-0.49, -0.07)	0.02	74.0	13	-0.26 (-0.40, -0.12)	< 0.01	74.9	5	-0.28 (-0.60, 0.05)	0.17	81.1
Gestational age (g)[2]												
Term (≥37 weeks)		Reference				Reference				Reference		
Late preterm (34-37 weeks)	8	-0.21 (-0.39, -0.04)	0.04	69.8	8	-0.14 (-0.33, 0.04)	0.17	74.5	5	-0.05 (-0.23, 0.13)	0.64	72.1
Early preterm (<34 weeks)	8	-0.16 (-0.34, 0.31)	0.15	53.5	7	-0.26 (-0.53, 0.006)	0.10	65.0	4	-0.20 (-0.55, 0.15)	0.35	75.4
Size for gestational age[3]												
AGA (≥10 percentile)		Reference				Reference				Reference		
Moderate SGA (3-<10 percentile)	8	-0.05 (-0.11, 0.12)	0.16	0.0	9	-0.01 (-0.10, 0.07)	0.77	36.6	4	-0.06 (-0.18, 0.06)	0.40	29.4
Severe SGA (<3 percentile)	8	-0.09 (-0.24, 0.07)	0.30	72.0	9	0.02 (-0.09, 0.12)	0.78	37.4	4	0.03 (-0.13, 0.19)	0.73	37.7
Gestational age and Size-for-gestational age												
Term-AGA		Reference				Reference				Reference		
Preterm-AGA	8	-0.14 (-0.24, -0.05)	0.02	17.0	9	-0.23 (-0.42, -0.03)	0.05	76.5	4	-0.02 (-0.23, 0.19)	0.87	78.0
Term-SGA	8	-0.02 (-0.10, 0.06)	0.66	44.6	9	-0.007 (-0.08, 0.06)	0.84	31.4	4	-0.03 (-0.12, 0.06)	0.55	9.3
Preterm-SGA	5	-0.17 (-0.29, -0.05)	0.05	0.0	5	-0.15 (-0.40, 0.09)	0.29	53.1	3	n/a	n/a	n/a
Exclusive breastfeeding												
Yes		Reference				Reference				Reference		
No	4	-0.02 (-0.08, 0.04)	0.60	0.0	4	-0.05 (-0.13, 0.04)	0.36	16.4	3	n/a	n/a	n/a

Risk Factor	Cognitive				Motor				Language			
	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)
Child hemoglobin level (g/L)												
Normal (≥110 g/L)		Reference				Reference				Reference		
Mild anemia (100-109 g/L)	9	-0.06 (-0.13, 0.01)	0.14	27.7	9	-0.03 (-0.13, 0.07)	0.54	51.2	3	n/a	n/a	n/a
Moderate anemia (70-99 g/L)	9	-0.11 (-0.12, -0.10)	< 0.01	0.0	9	-0.18 (-0.28, -0.09)	< 0.01	49.0	3	n/a	n/a	n/a
Access to clean water												
Yes		Reference				Reference				Reference		
No	8	-0.10 (-0.12, -0.09)	< 0.01	0.0	8	-0.07 (-0.16, 0.01)	0.14	71.0	4	-0.15 (-0.35, 0.05)	0.23	82.5
Access to sanitation												
Yes		Reference				Reference				Reference		
No	8	-0.13 (-0.18, -0.07)	< 0.01	47.5	8	-0.10 (-0.19, -0.01)	0.05	82.8	4	-0.12 (-0.27, 0.03)	0.21	92.4
Diarrhoea												
Yes	5	-0.02 (-0.16, 0.13)	0.84	66.8	5	-0.02 (-0.14, 0.09)	0.71	62.8	2	n/a	n/a	n/a
No		Reference				Reference				Reference		

[1]Adjusted for child's gender and age, mother's education and household wealth
[2]Adjusted for small for gestational age
[3]Adjusted for gestational age

AGA: Appropriate for Gestational Age
SGA: Small for Gestational Age

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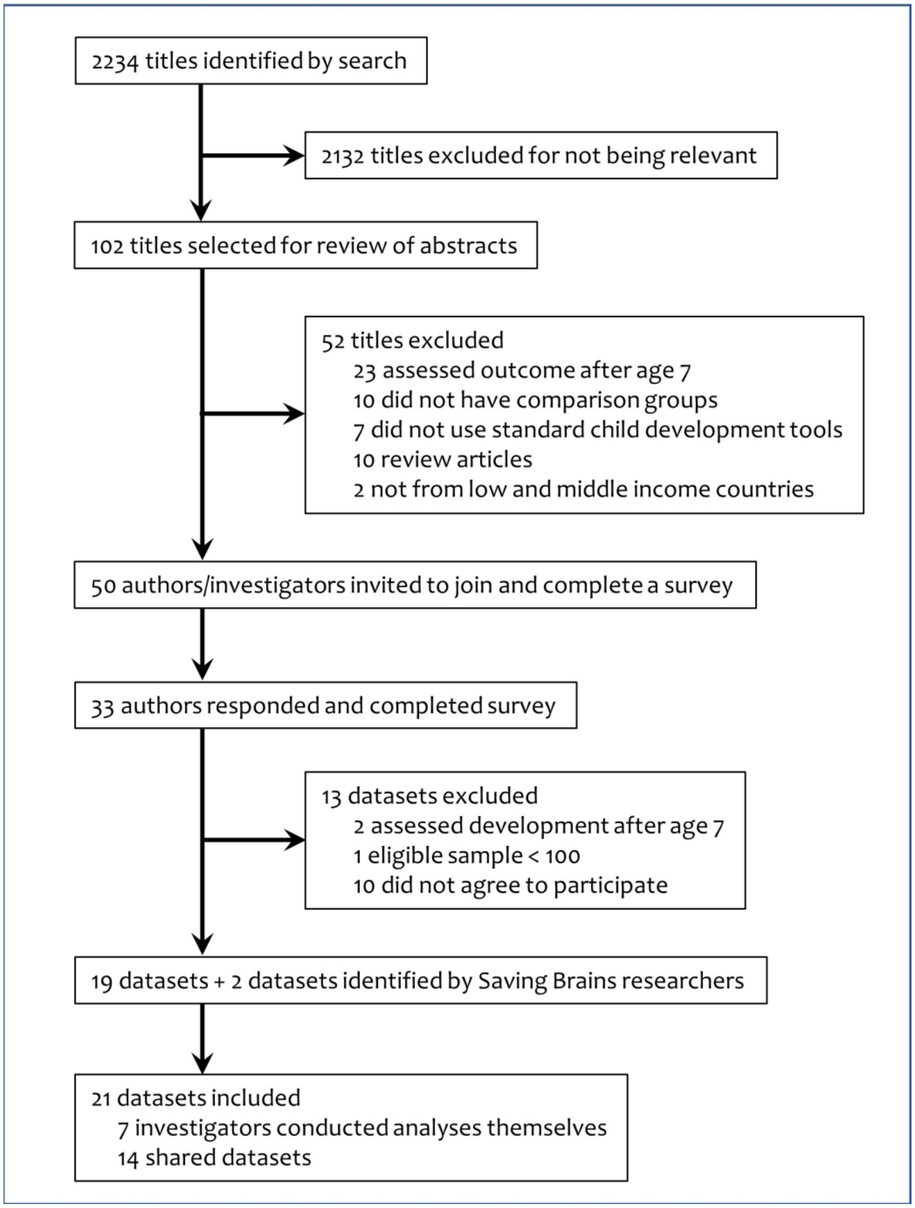

Figure 1: flow chart of study selection

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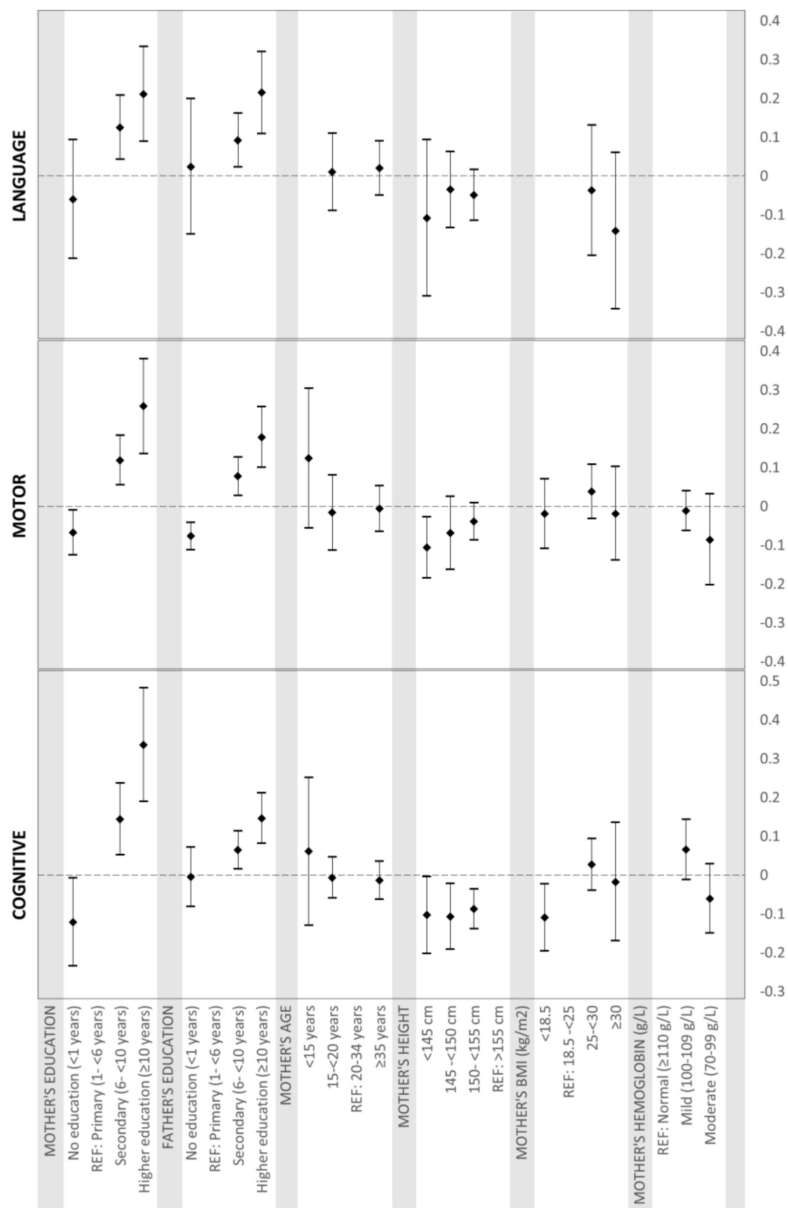

Figure 2: Pooled estimates of association between maternal factors and development

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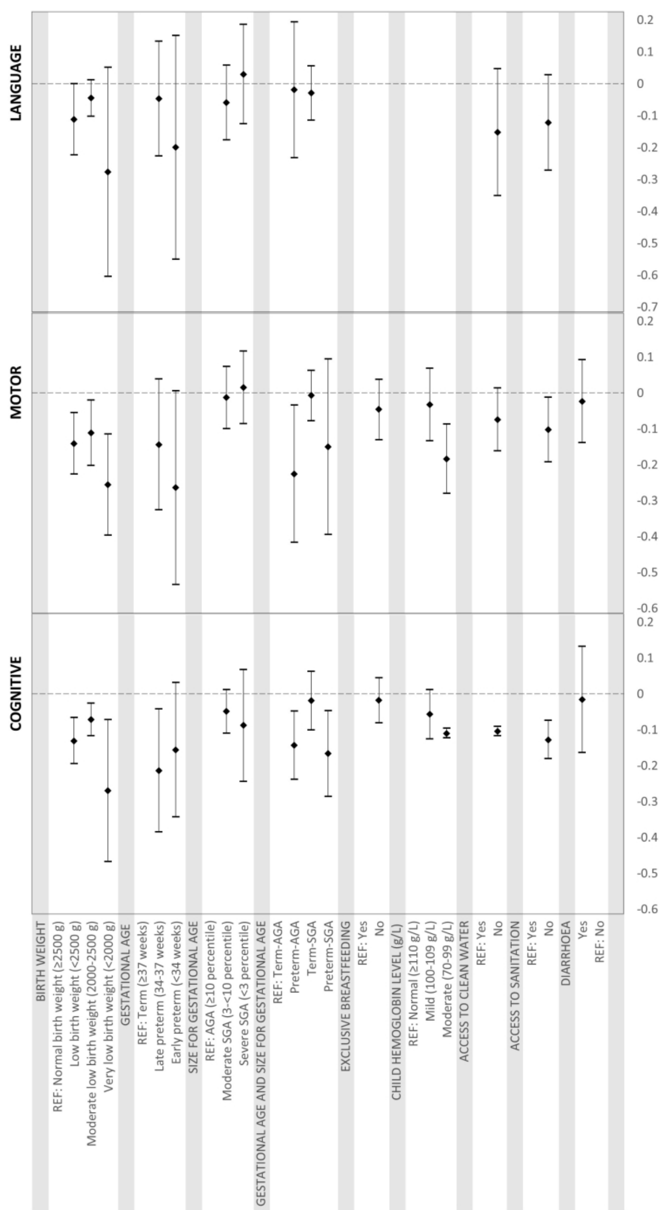

Figure 3: Pooled estimates of association between child factors and development.

157x284mm (300 x 300 DPI)

Appendix 1: Search terms

("child"[MeSH] OR "infant"[MeSH]) AND ("child development"[MeSH] OR "cognition"[MeSH] OR "psychomotor disorders"[MeSH] OR "psychomotor performance"[MeSH] OR "motor skills"[MeSH] OR "intelligence"[MeSH] OR "IQ"[All Fields] OR "executive function"[MeSH] OR "attention"[MeSH] OR "memory"[MeSH] OR "learning"[MeSH] OR "education"[MeSH] OR "reading"[MeSH] OR "mathematics"[MeSH] OR "learning disorders"[MeSH] OR "aptitude tests"[MeSH] OR "language tests"[MeSH] OR "mental health"[MeSH] OR "child behavior"[MeSH] OR "emotional intelligence"[MeSH] OR "emotions"[MeSH] OR "temperament"[MeSH] OR "self concept"[MeSH] OR "self efficacy"[MeSH] OR "mental competency"[MeSH] OR "aggression"[MeSH]) AND ("preterm"[All Fields] OR "low birth weight"[All Fields] OR “maternal height” OR “maternal underweight” OR “malaria” OR “birth spacing” OR “Teen pregnancy” OR “anemia” or “hemoglobin” OR “HIV” OR “iron supplement” OR “iron deficiency” OR “childhood diarrhea” OR “HIV” OR “zinc” OR “iodine” OR “sanitation” OR “clean water” OR “breastfeeding” OR “hookworms”) AND ("Armenia"[All Fields] OR "Azerbaijan"[All Fields] OR "Georgia"[All Fields] OR "Kazakhstan"[All Fields] OR "Kyrgyzstan"[All Fields] OR "Mongolia"[All Fields] OR "Tajikistan"[All Fields] OR "Turkmenistan"[All Fields] OR "Uzbekistan"[All Fields] OR "Afghanistan"[All Fields] OR "Bangladesh"[All Fields] OR "Bhutan"[All Fields] OR "India"[All Fields] OR "Nepal"[All Fields] OR "Pakistan"[All Fields] OR "Cambodia"[All Fields] OR "Indonesia"[All Fields] OR "Lao People's Democratic Republic"[All Fields] OR "Malaysia"[All Fields] OR "Maldives"[All Fields] OR "Mauritius"[All Fields] OR "Mayotte"[All Fields] OR "Myanmar"[All Fields] OR "Philippines"[All Fields] OR "Seychelles"[All Fields] OR "Sri Lanka"[All Fields] OR "Thailand"[All Fields] OR "Viet Nam"[All Fields] OR "Anguilla"[All Fields] OR "Antigua and Barbuda"[All Fields] OR "Aruba"[All Fields] OR "Bahamas"[All Fields] OR "Barbados"[All Fields] OR "Belize"[All Fields] OR "Bermuda"[All Fields] OR "British Virgin Islands"[All Fields] OR "Cayman Islands"[All Fields] OR "Cuba"[All Fields] OR "Turks and Caicos Islands"[All Fields] OR "Bolivia"[All Fields] OR "Ecuador"[All Fields] OR "Peru"[All Fields] OR "Colombia"[All Fields] OR "Costa Rica"[All Fields] OR "El Salvador"[All Fields] OR "Guatemala"[All Fields] OR "Honduras"[All Fields] OR "Mexico"[All Fields] OR "Nicaragua"[All Fields] OR "Panama"[All Fields] OR "Venezuela"[All Fields] OR "Argentina"[All Fields] OR "Chile"[All Fields] OR "Falkland Islands"[All Fields] OR "Malvinas"[All Fields] OR "Uruguay"[All Fields] OR "Brazil"[All Fields] OR "Paraguay"[All Fields] OR "Algeria"[All Fields] OR "Bahrain"[All Fields] OR "Egypt"[All Fields] OR "Iran"[All Fields] OR "Iraq"[All Fields] OR "Jordan"[All Fields] OR "Kuwait"[All Fields] OR "Lebanon"[All Fields] OR "Libyan Arab Jamahiriya"[All Fields] OR "Morocco"[All Fields] OR "Occupied Palestinian Territory"[All Fields] OR "Oman"[All Fields] OR "Qatar"[All Fields] OR "Saudi Arabia"[All Fields] OR "Syrian Arab Republic"[All Fields] OR "Tunisia"[All Fields] OR "Turkey"[All Fields] OR "United Arab Emirates"[All Fields] OR "Western Sahara"[All Fields] OR "Yemen"[All Fields] OR "American Samoa"[All Fields] OR "Cook Islands"[All Fields] OR "Fiji"[All Fields] OR "French Polynesia"[All Fields] OR "Guam"[All Fields] OR "Kiribati"[All Fields] OR "Marshall Islands"[All Fields] OR "Micronesia"[All Fields] OR "Nauru"[All Fields] OR "New Caledonia"[All Fields] OR "Niue"[All Fields] OR "Northern Mariana Islands"[All Fields] OR "Palau"[All Fields] OR "Papua New Guinea"[All Fields] OR "Pitcairn"[All Fields] OR "Samoa"[All Fields] OR "Solomon Islands"[All Fields] OR "Tokelau"[All Fields] OR "Tonga"[All Fields] OR "Tuvalu"[All Fields] OR "Vanuatu"[All Fields] OR "Wallis and Futuna Islands"[All Fields] OR "Angola"[All Fields] OR "Central African Republic"[All Fields] OR

"Congo"[All Fields] OR "Democratic Republic of the Congo"[All Fields] OR "Equatorial Guinea"[All Fields] OR "Gabon"[All Fields] OR "Burundi"[All Fields] OR "Comoros"[All Fields] OR "Djibouti"[All Fields] OR "Eritrea"[All Fields] OR "Ethiopia"[All Fields] OR "Kenya"[All Fields] OR "Madagascar"[All Fields] OR "Malawi"[All Fields] OR "Mozambique"[All Fields] OR "Rwanda"[All Fields] OR "Somalia"[All Fields] OR "Sudan"[All Fields] OR "Uganda"[All Fields] OR "United Republic of Tanzania"[All Fields] OR "Zambia"[All Fields] OR "Botswana"[All Fields] OR "Lesotho"[All Fields] OR "Namibia"[All Fields] OR "South Africa"[All Fields] OR "Swaziland"[All Fields] OR "Zimbabwe"[All Fields] OR "Benin"[All Fields] OR "Burkina Faso"[All Fields] OR "Cameroon"[All Fields] OR "Cape Verde"[All Fields] OR "Chad"[All Fields] OR "Cote d'Ivoire"[All Fields] OR "Gambia"[All Fields] OR "Ghana"[All Fields] OR "Guinea"[All Fields] OR "Guinea-Bissau"[All Fields] OR "Liberia"[All Fields] OR "Mali"[All Fields] OR "Mauritania"[All Fields] OR "Niger"[All Fields] OR "Nigeria"[All Fields] OR "Saint Helena"[All Fields] OR "Sao Tome and Principe"[All Fields] OR "Senegal"[All Fields] OR "Sierra Leone"[All Fields] OR "Togo"[All Fields])

Appendix 2: Forest plots

1. Child Risk Factors on Child's Cognitive Development

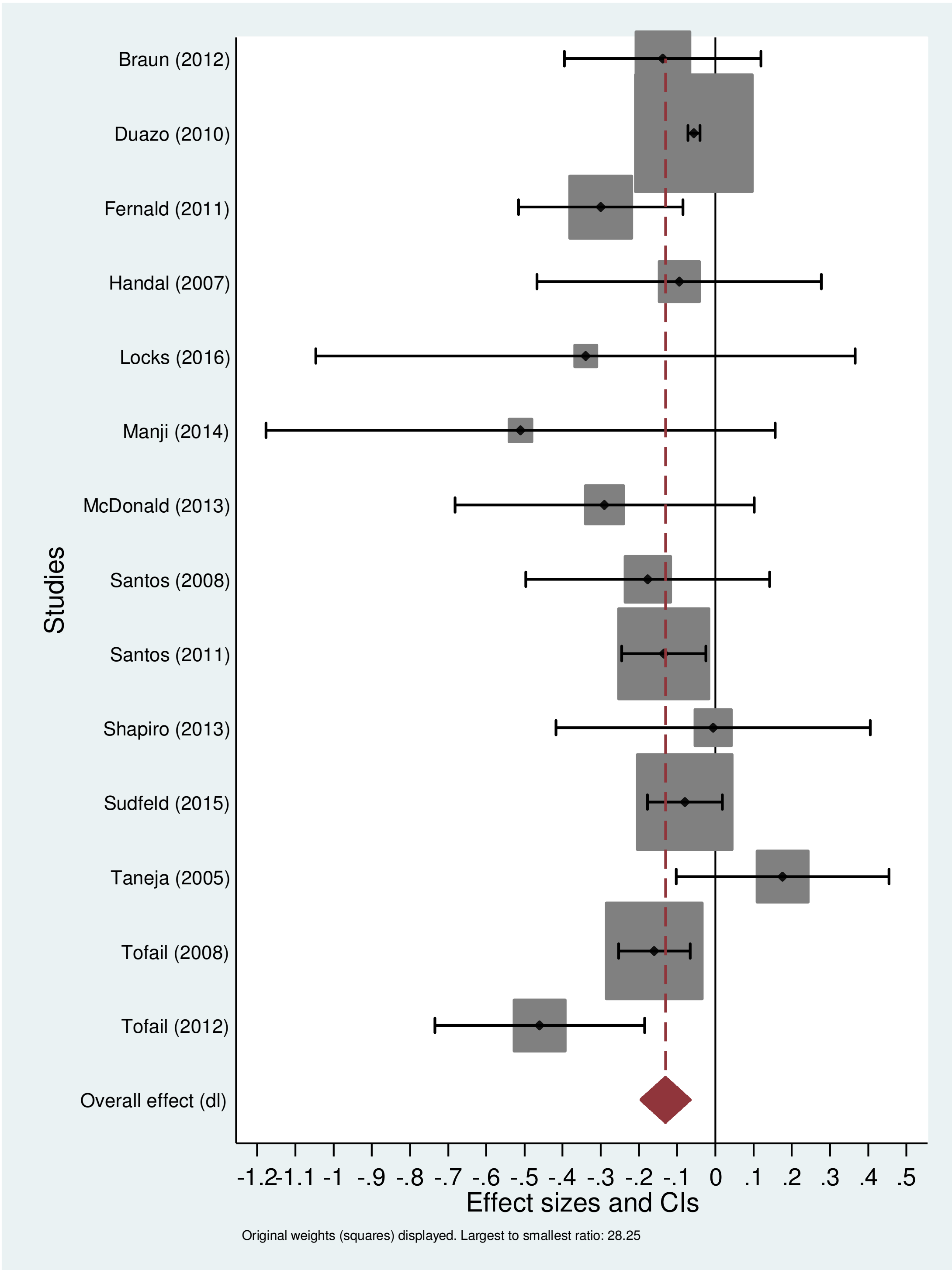

Figure 1: Association between low birth weight (LBW) and (reference: normal birth weight) and cognitive development.

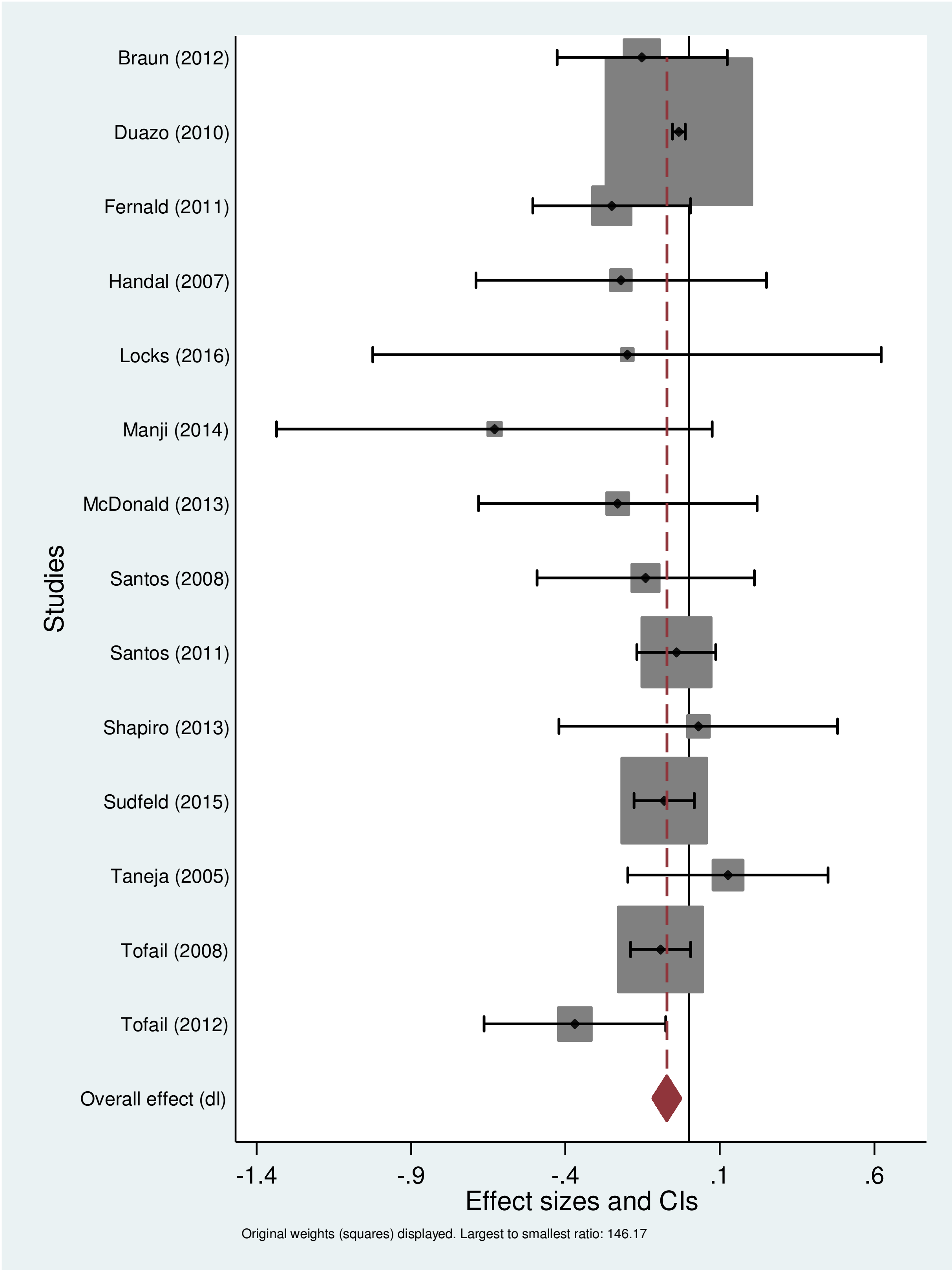

Figure 2: Association between Moderately low birth Weight (reference, normal birth weight) and cognitive development.

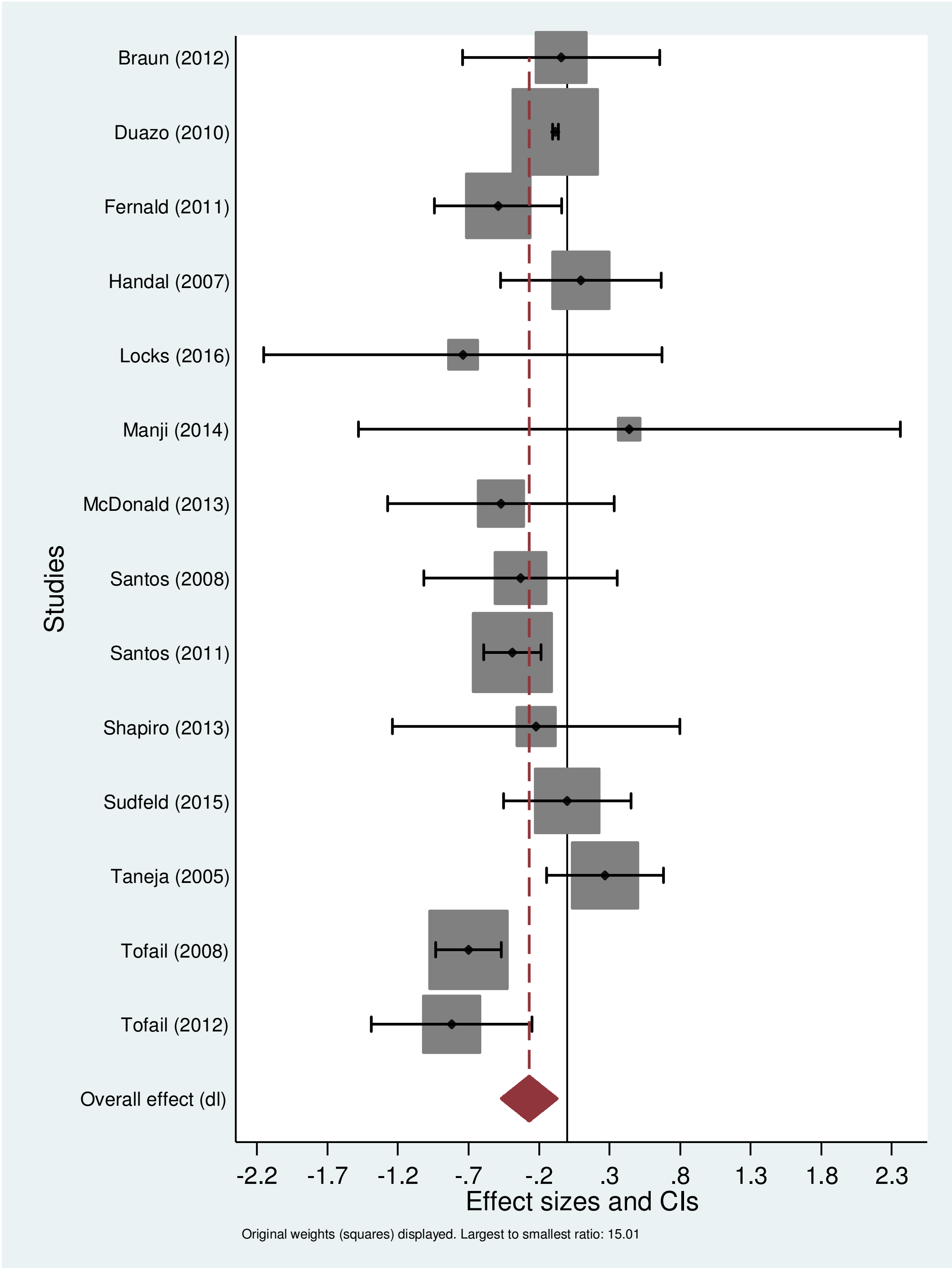

Figure 3: Association between very low Birth weight (reference: normal birth weight)) and cognitive development.

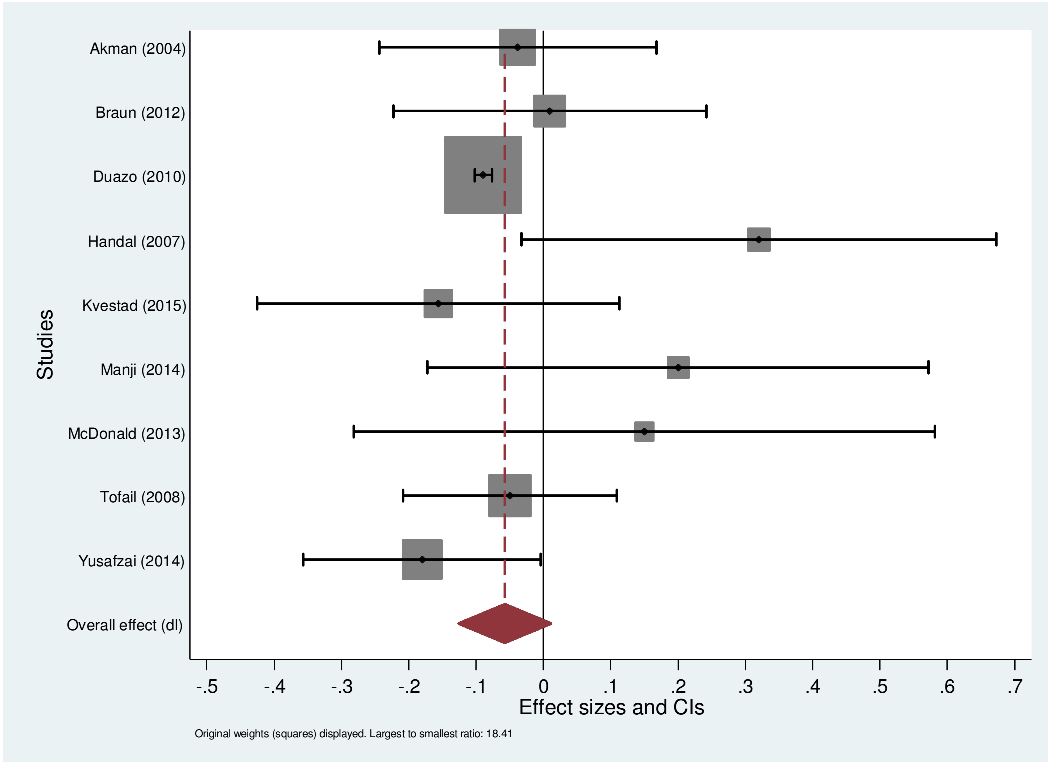

Figure 4: Association between child mild anemia (reference: no anemia) and cognitive development.

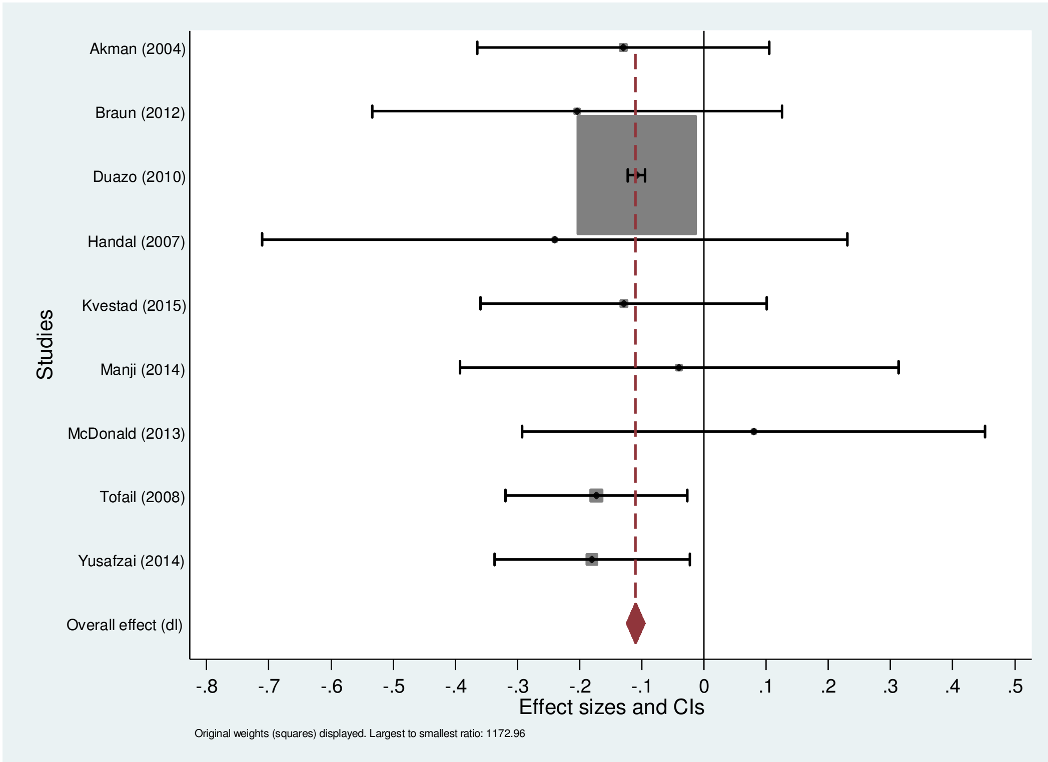

Figure 5: Association between child moderate anemia (reference: no anemia) and cognitive development.

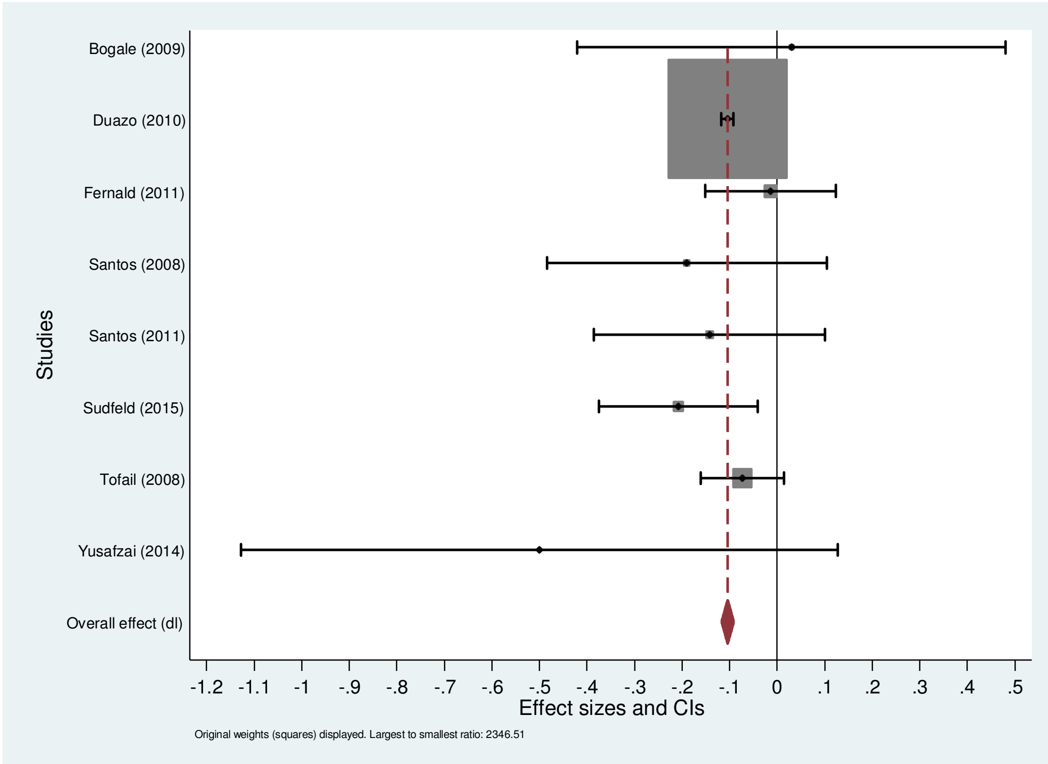

Figure 6: Association between lack of access to clean water (reference: access to clean water) and cognitive development.

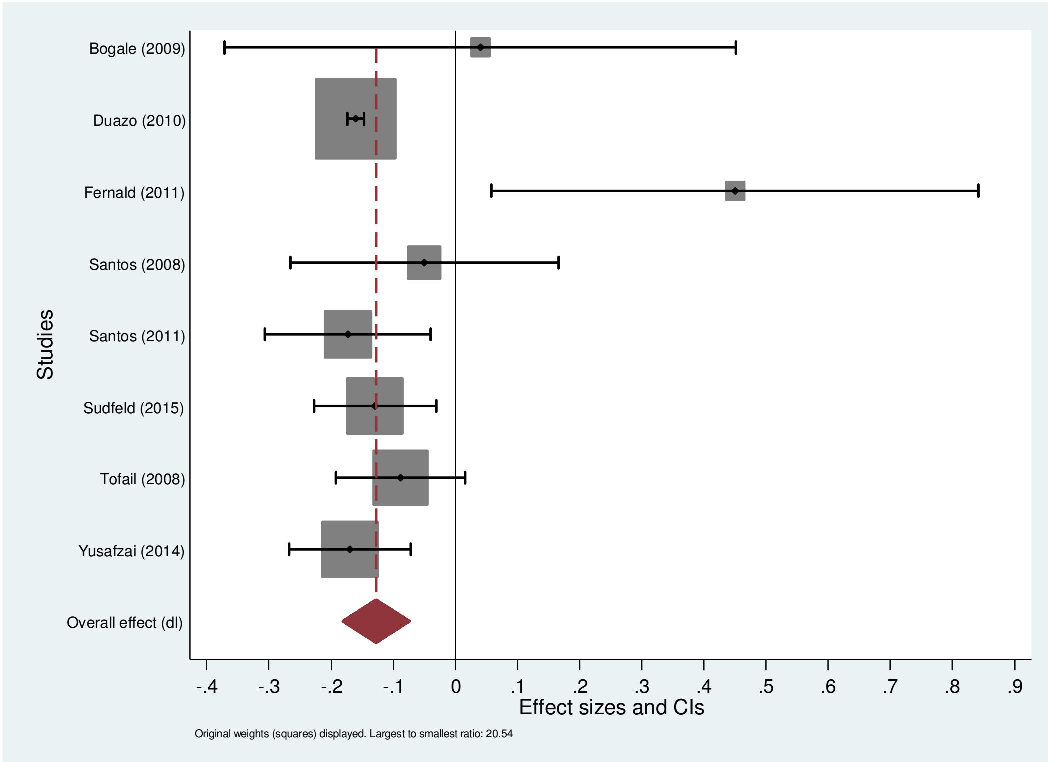

Figure 7: Association between lack of access to sanitation (reference: access to sanitation) and cognitive development.

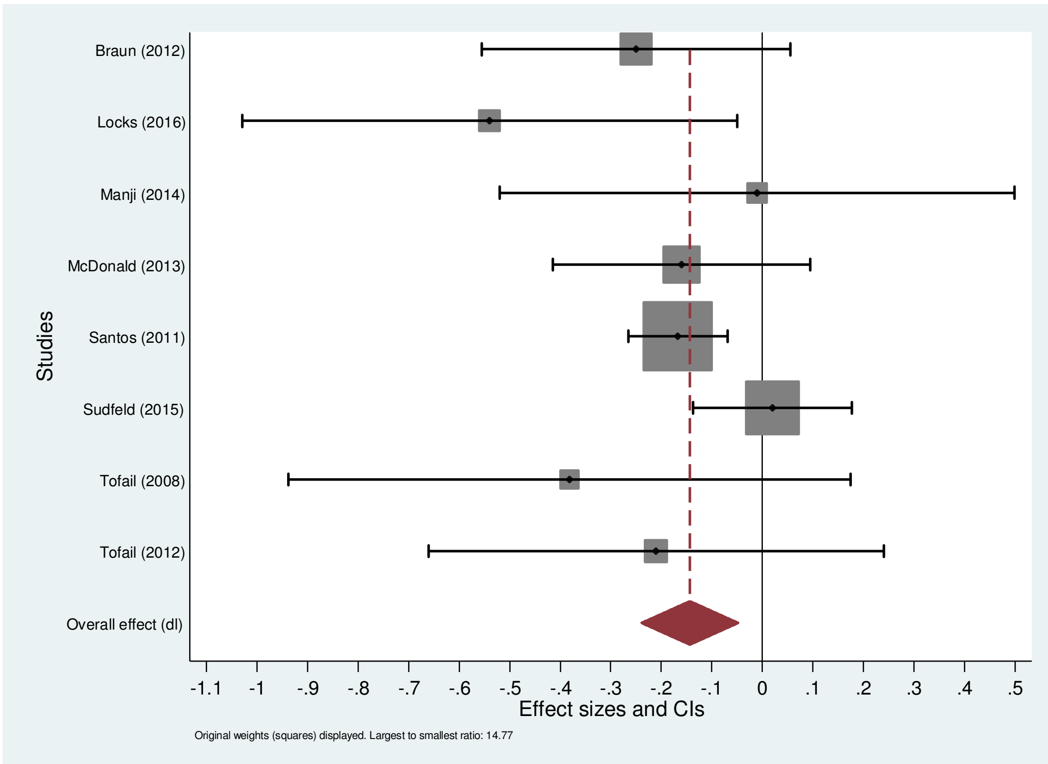

Figure 8: Association between preterm-AGA (reference: term-AGA) and cognitive development.

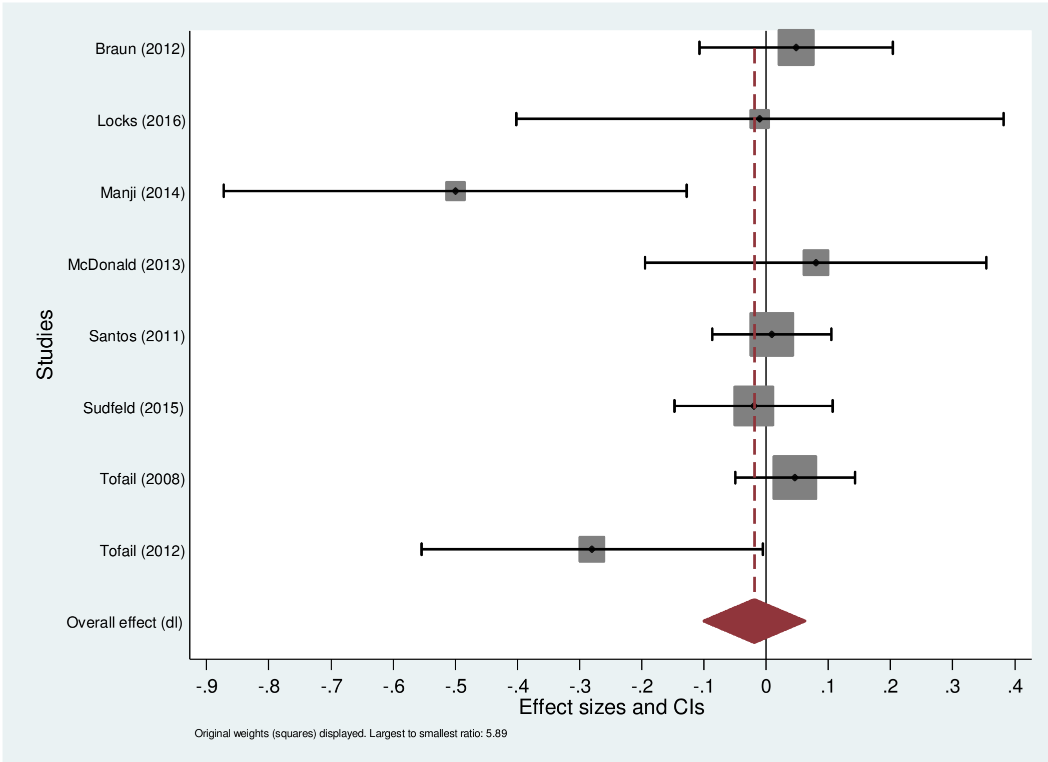

Figure 9: Association between term-SGA (reference: term-AGA) and cognitive development.

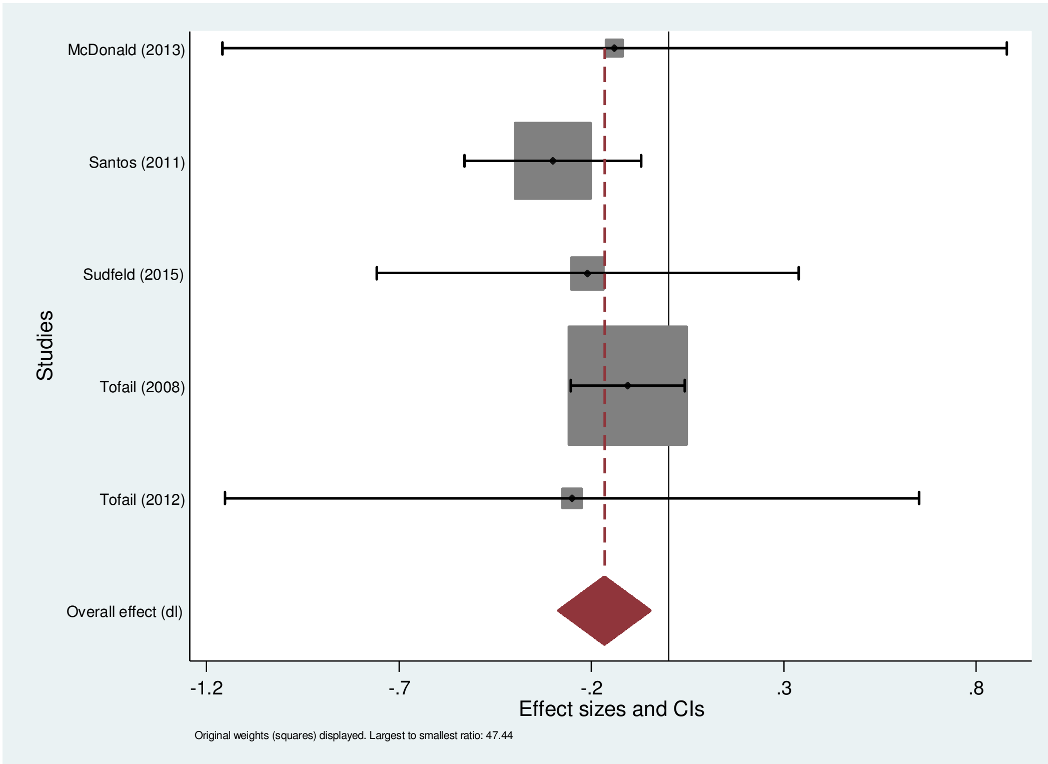

Figure 10: Association between preterm- SGA (reference: term-AGA) and cognitive development.

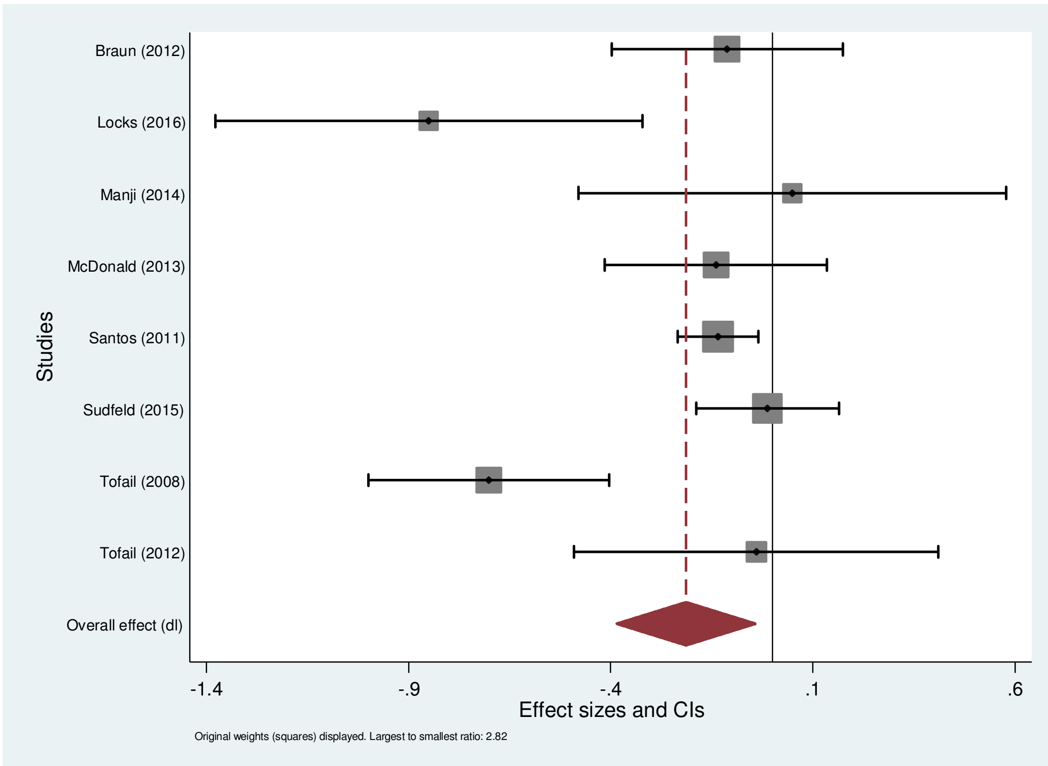

Figure 11: Association between late preterm birth, 34-37 weeks (reference: term) and cognitive development.

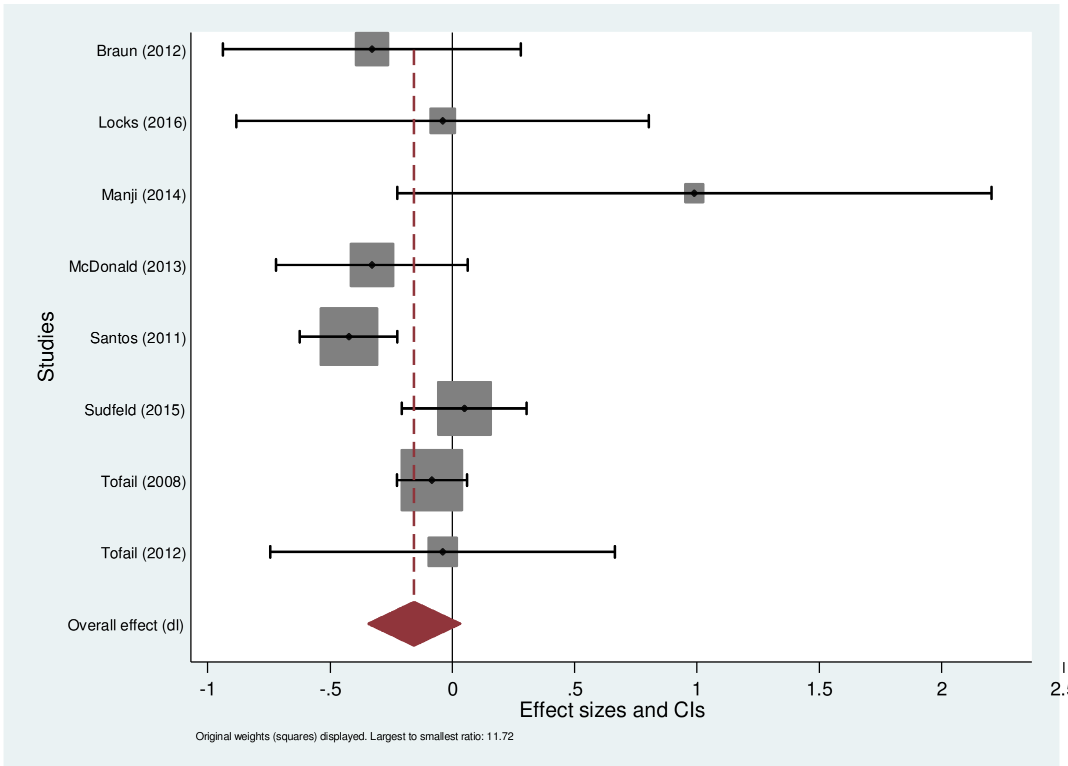

Figure 12: Association between early preterm birth, < 34 weeks (reference: term) and cognitive development.

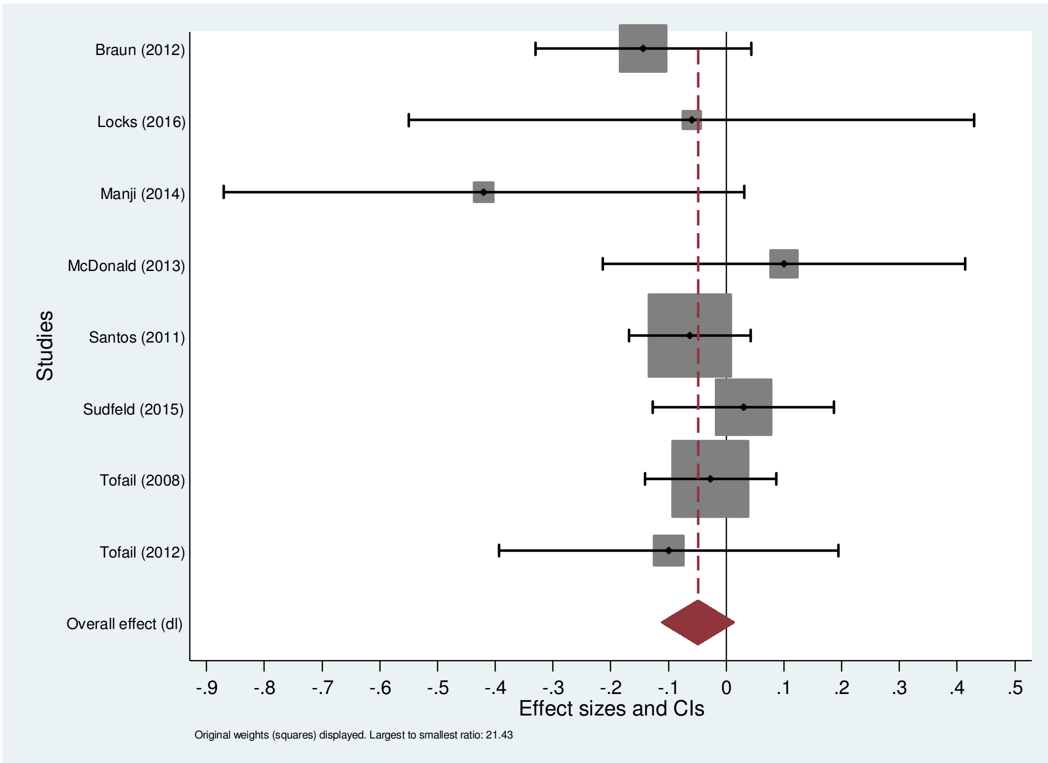

Figure 13: Association between moderate SGA (reference: AGA) and cognitive development.

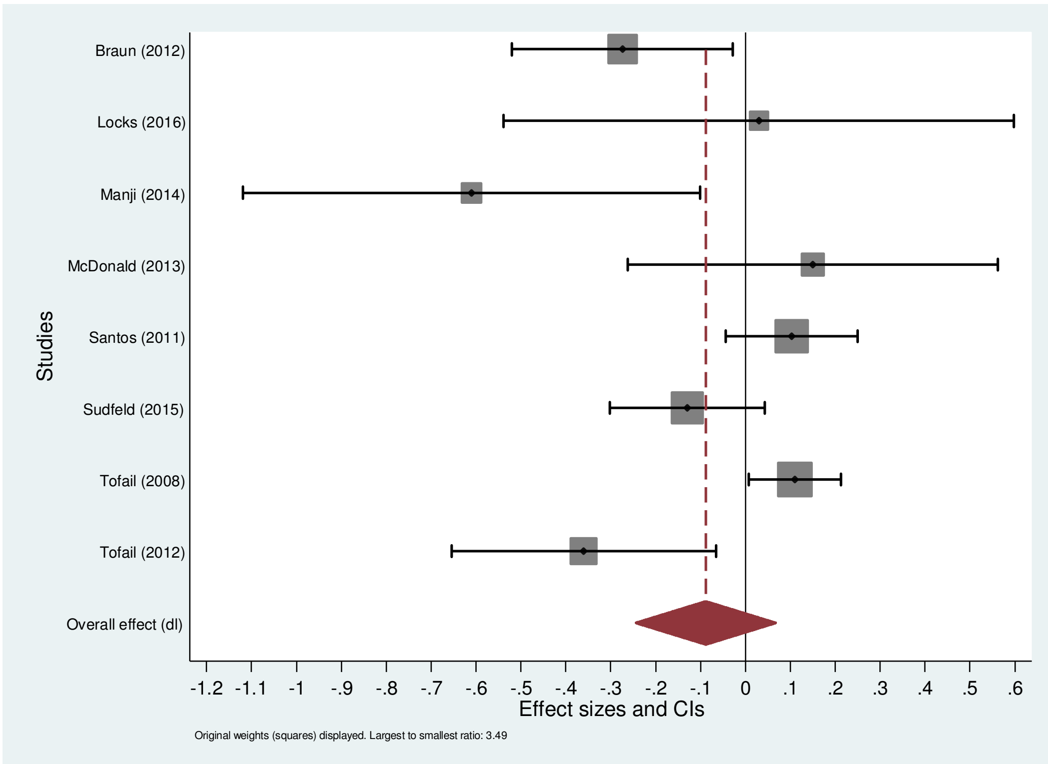

Figure 14: Association between severe SGA (reference: AGA) and cognitive development.

2. Child Risk Factors on Child's Motor Development

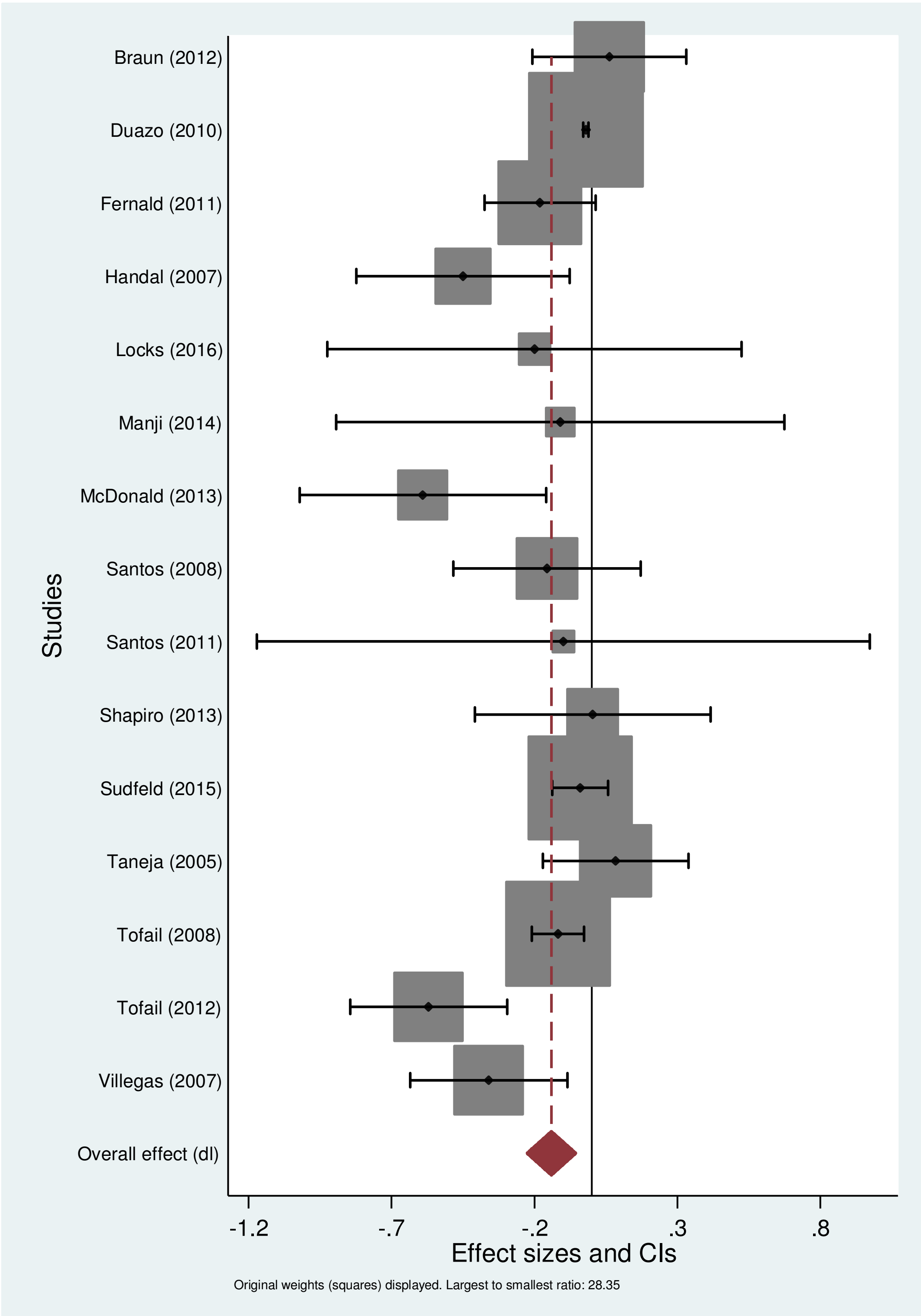

Figure 15: Association between low birth weight (reference: normal birth weight) and motor development.

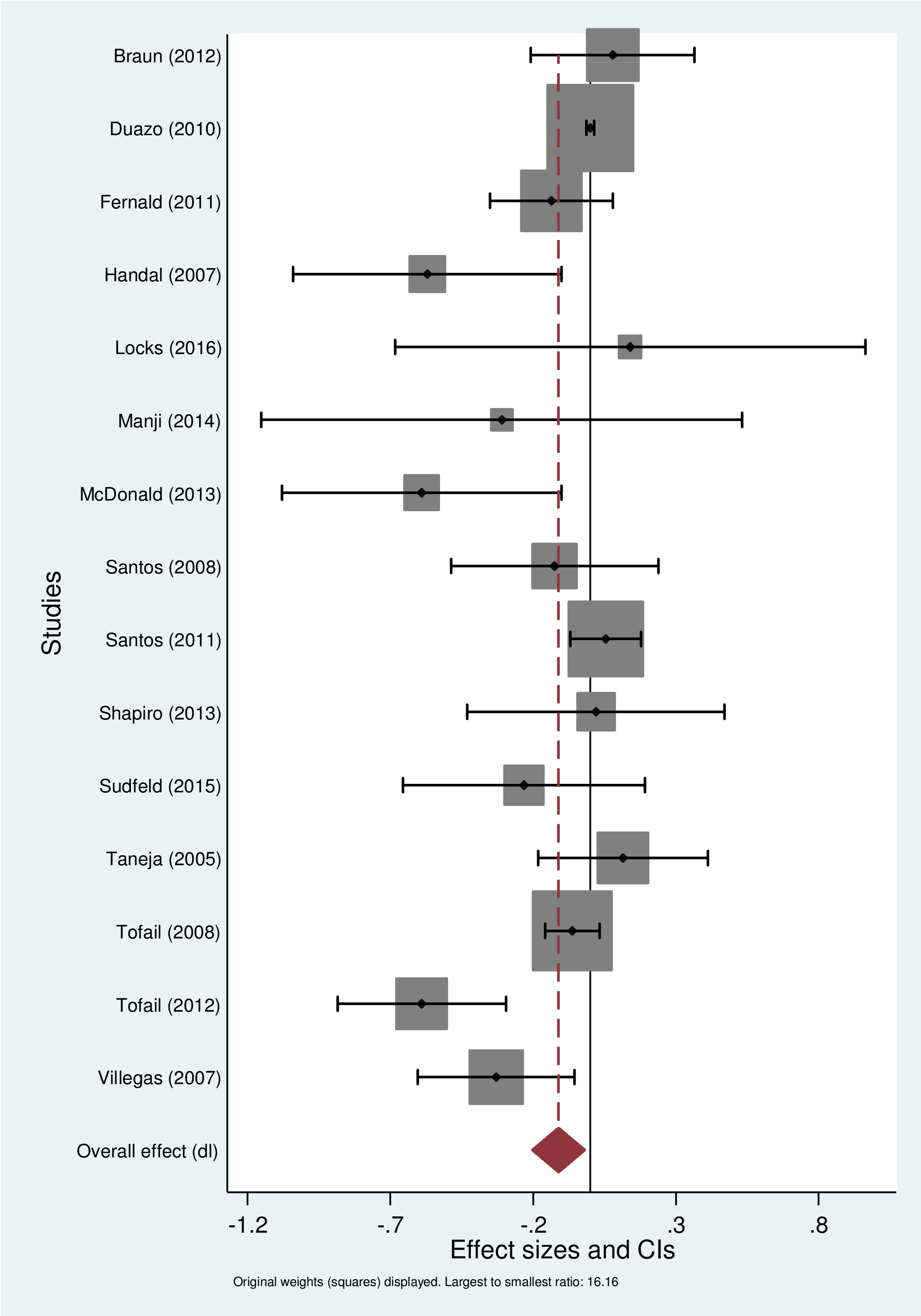

Figure 16: Association between moderately low birth weight (reference: normal birth weight) and motor development.

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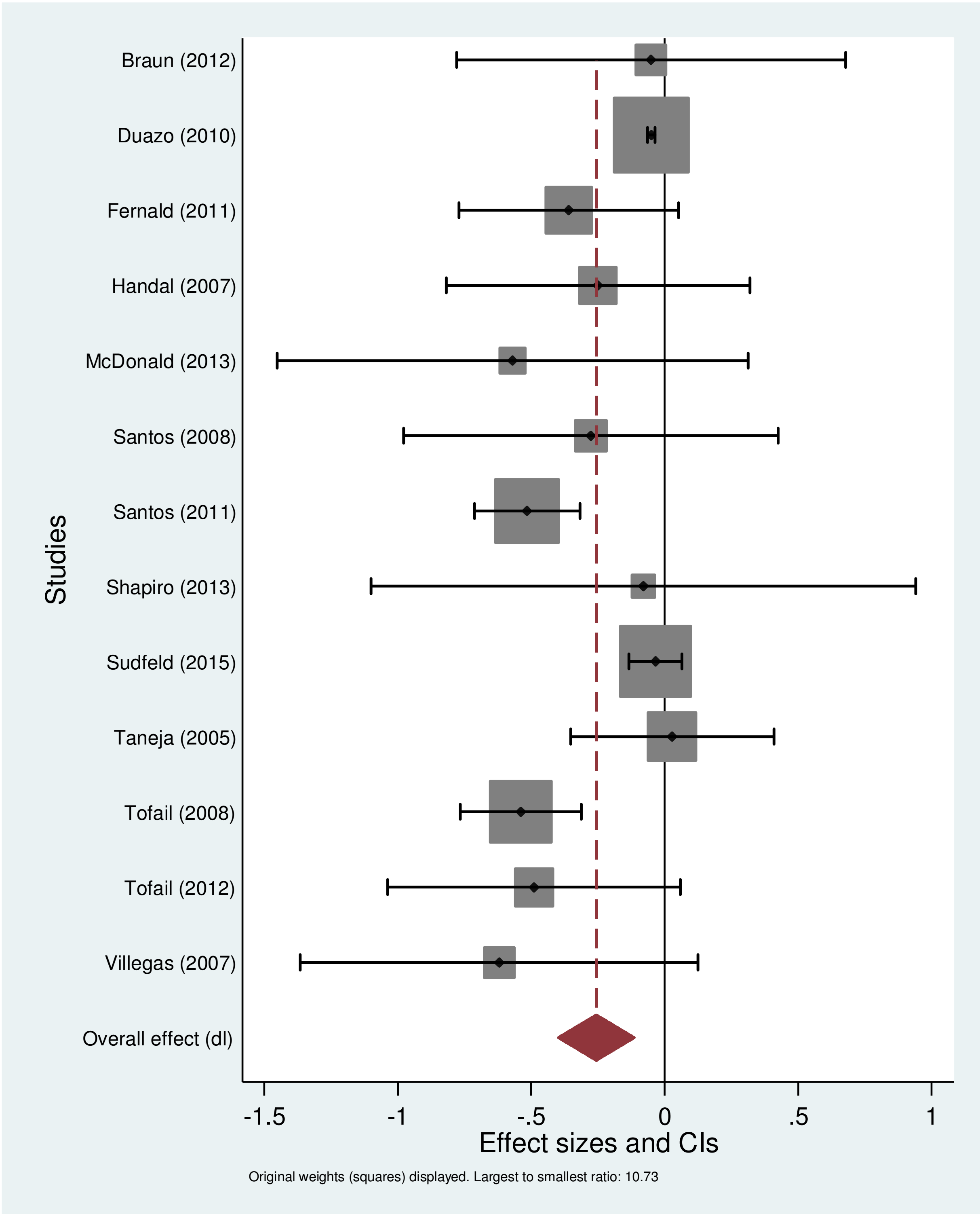

Figure 17: Association between very low birth weight (reference: normal birth weight) and motor development.

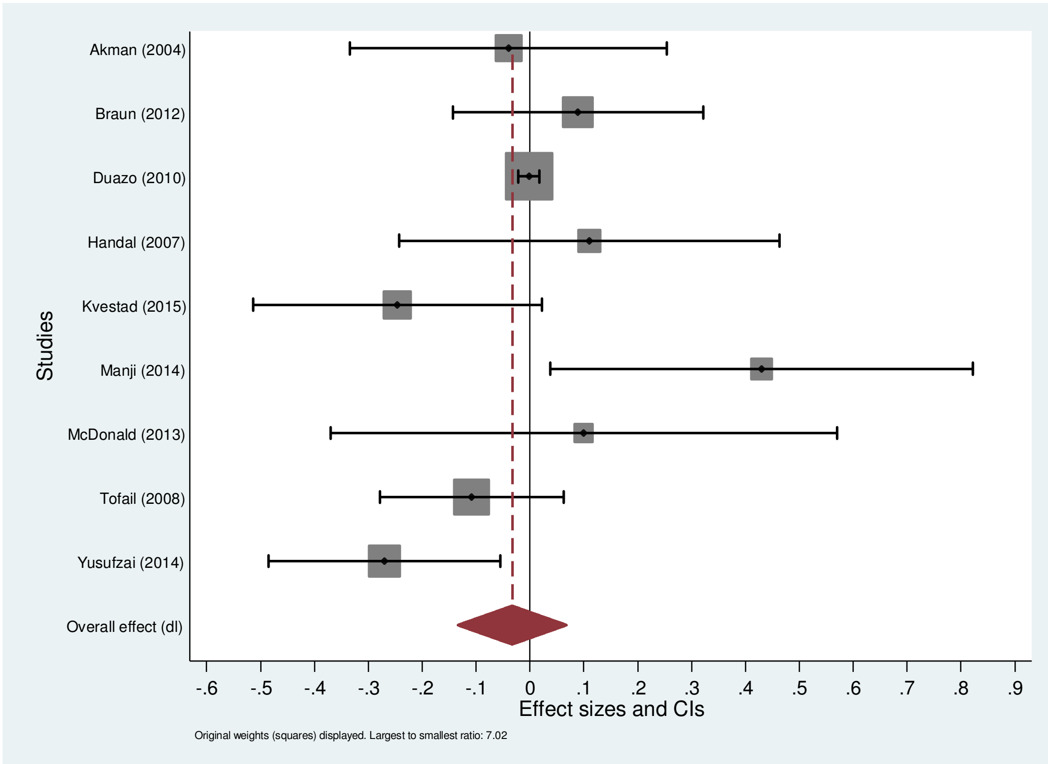

Figure 18: Association between child mild anemia (reference: no anemia) and motor development.

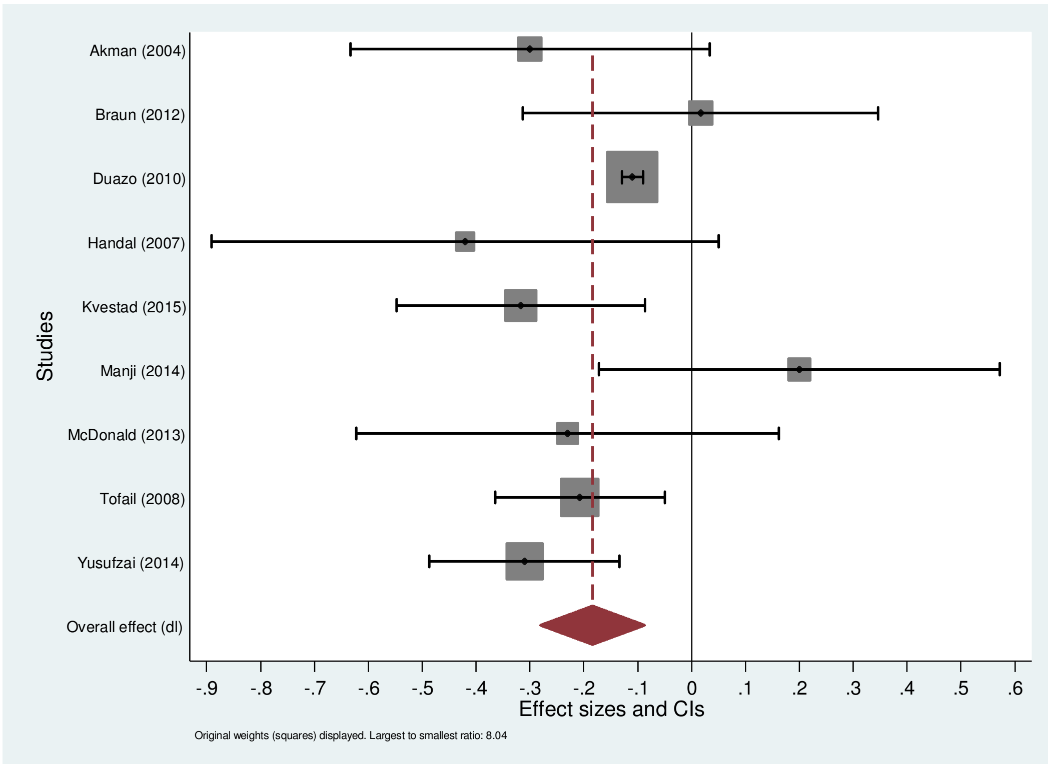

Figure 19: Association between child moderate anemia (reference: no anemia) and motor development.

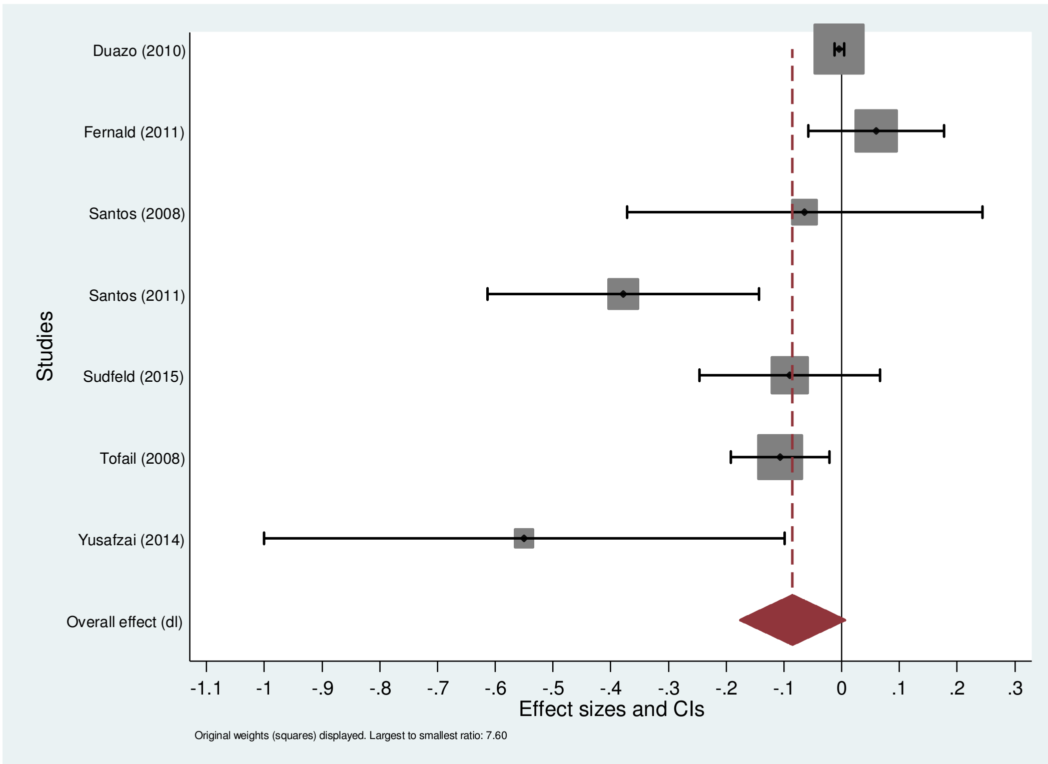

Figure 20: Association between lack of access to clean water (reference: access to clean water) and motor development.

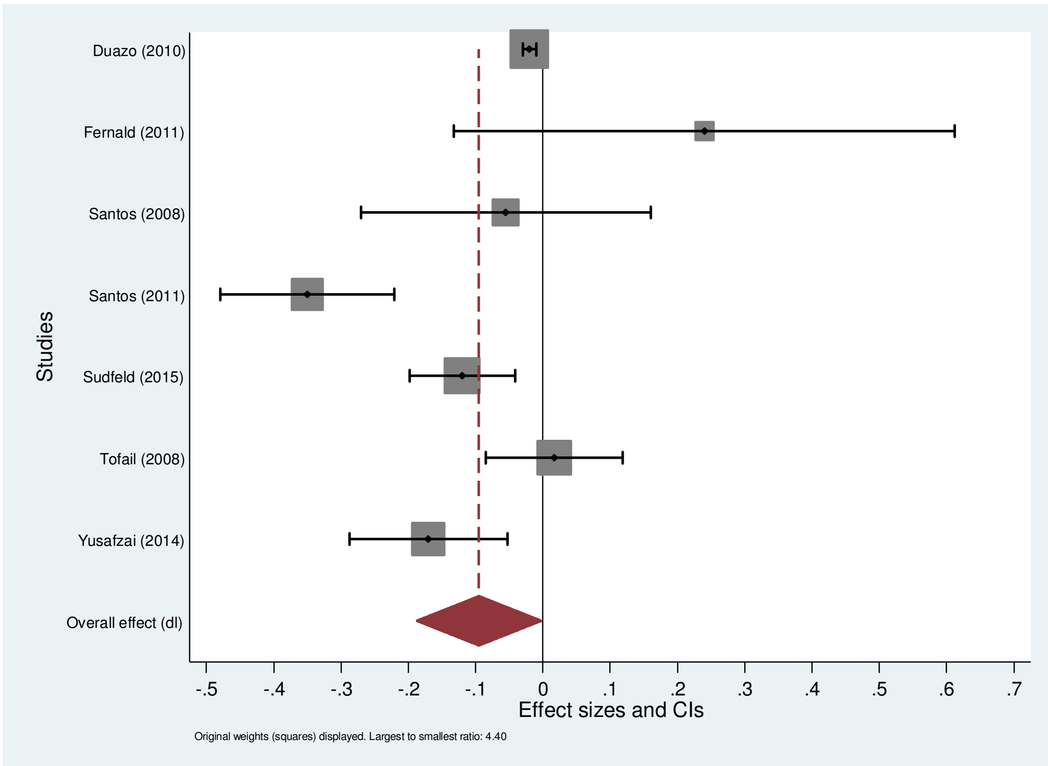

Figure 21: Association between lack of access to sanitation (reference: access to sanitation) and motor development.

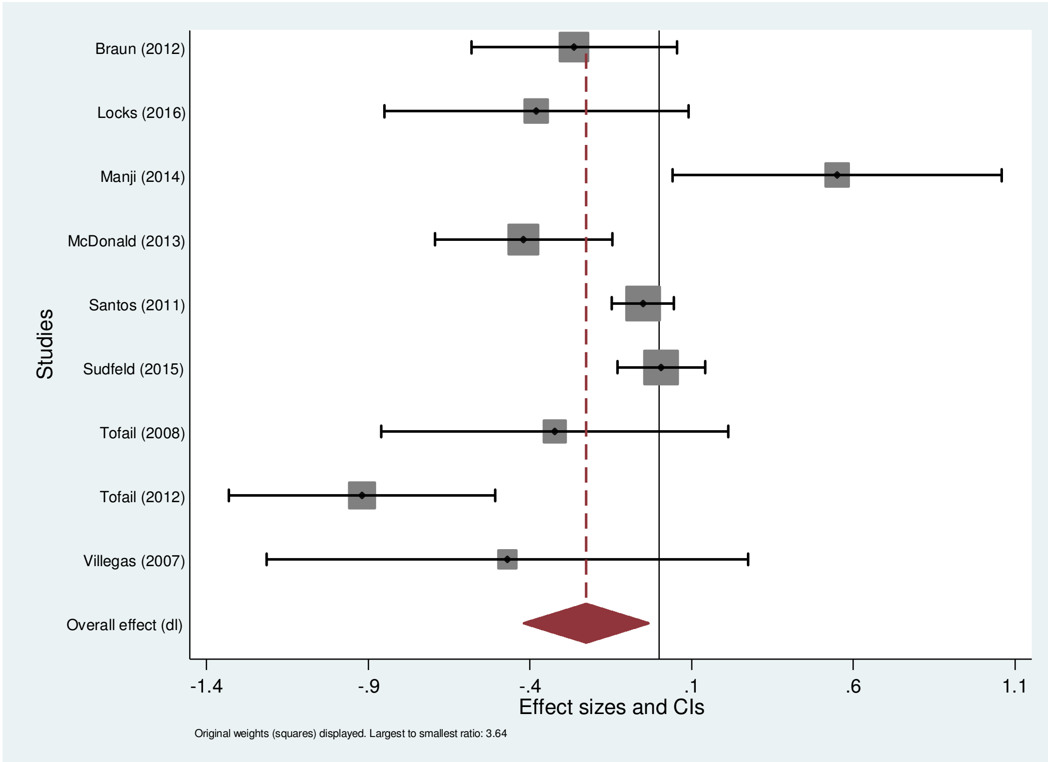

Figure 22: Association between preterm-AGA (reference: term-AGA) and motor development.

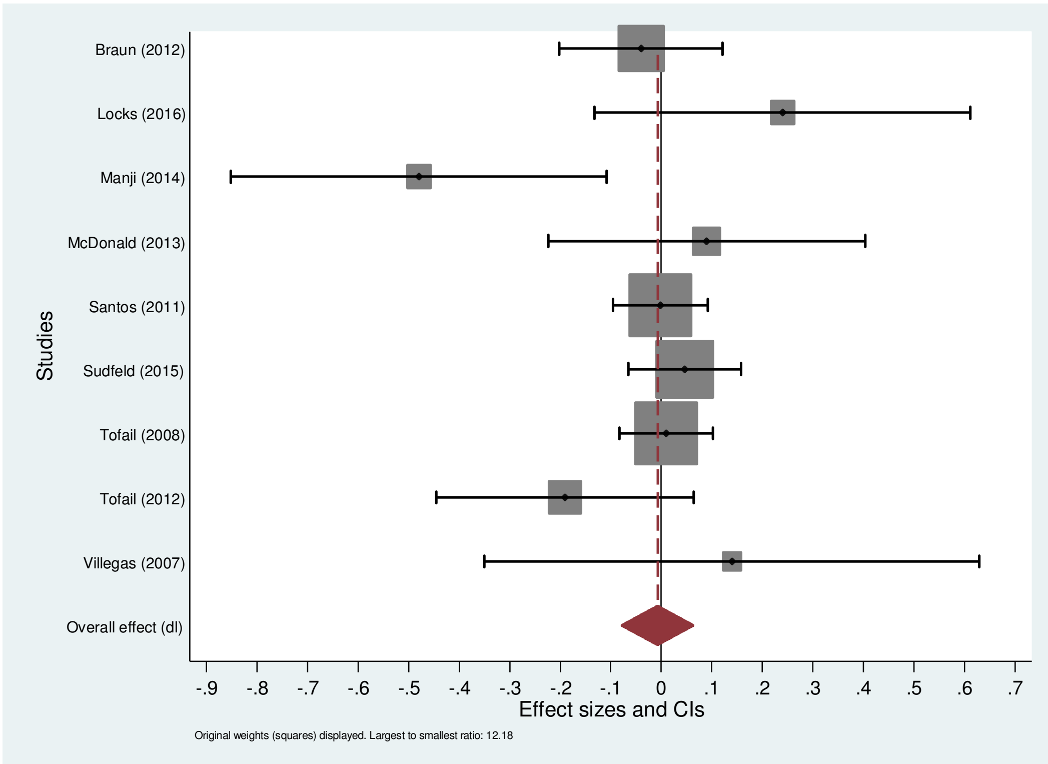

Figure 23: Association between term-SGA (reference: term-AGA) and motor development.

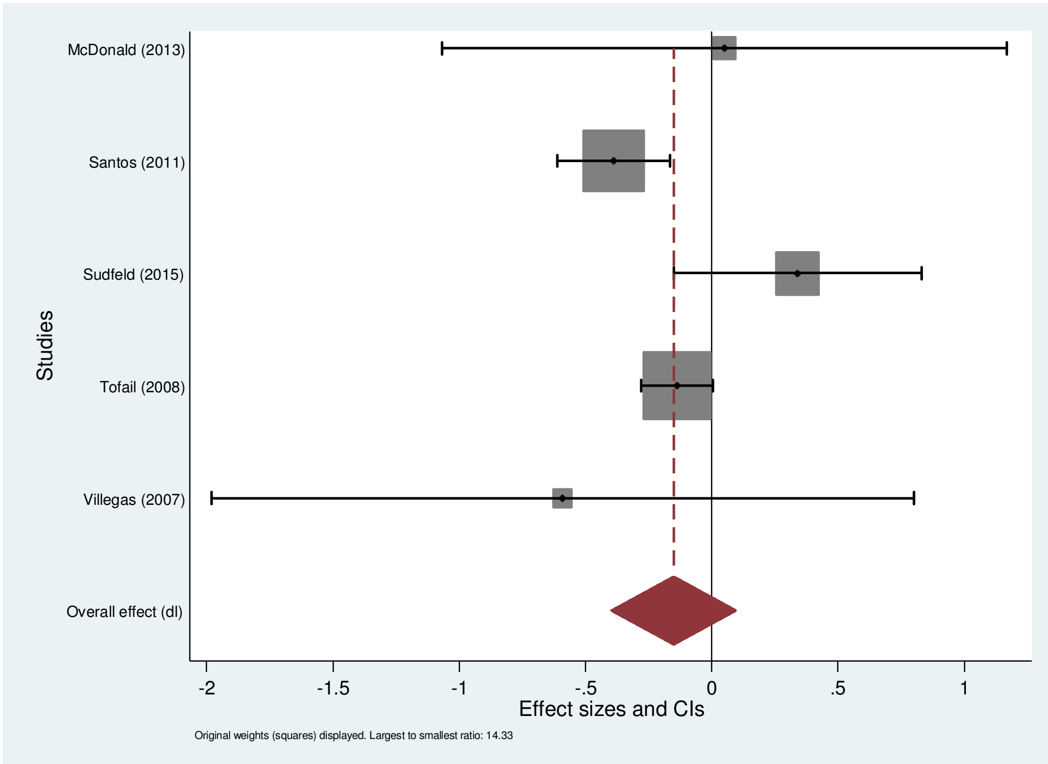

Figure 24: Association between preterm-SGA (reference: term-AGA) and motor development.

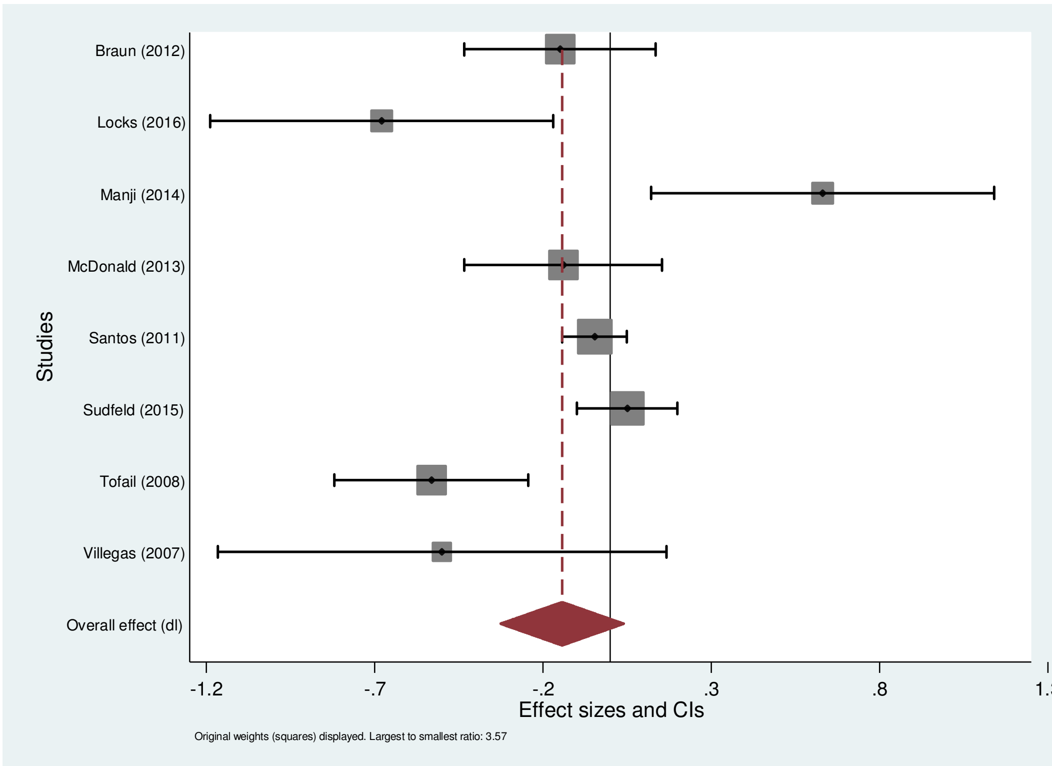

Figure 25: Association between late preterm birth, 34-37 weeks (reference: term) and motor development.

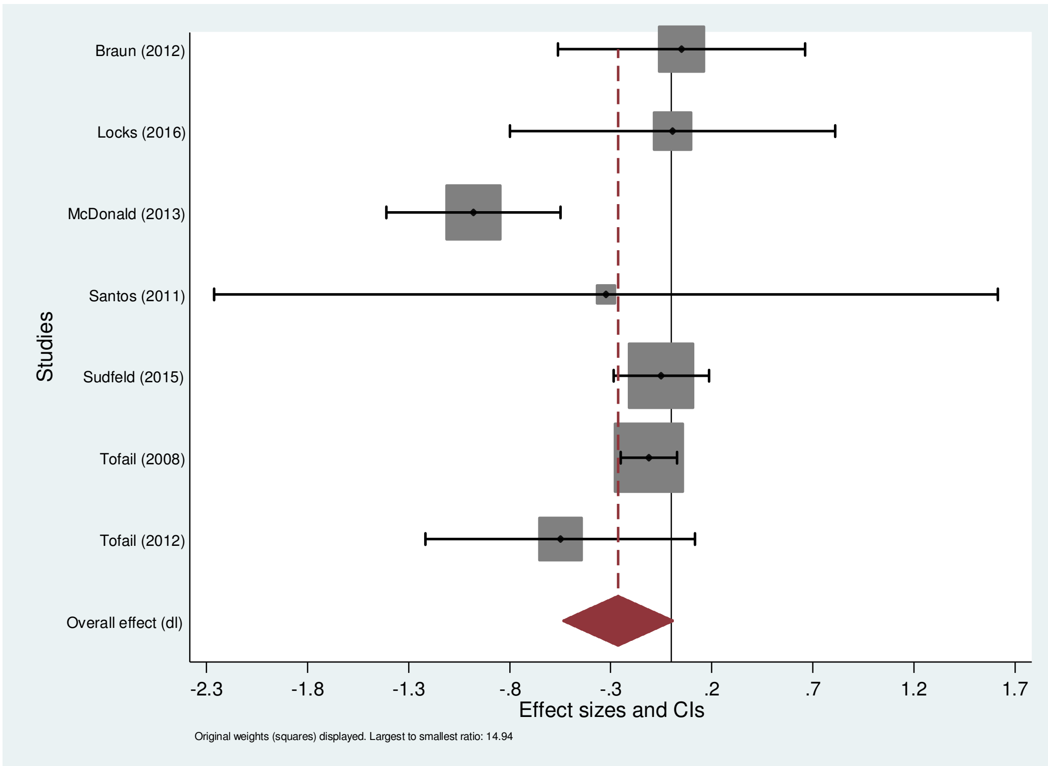

Figure 26: Association between early preterm birth, < 34 weeks (reference: term) and motor development.

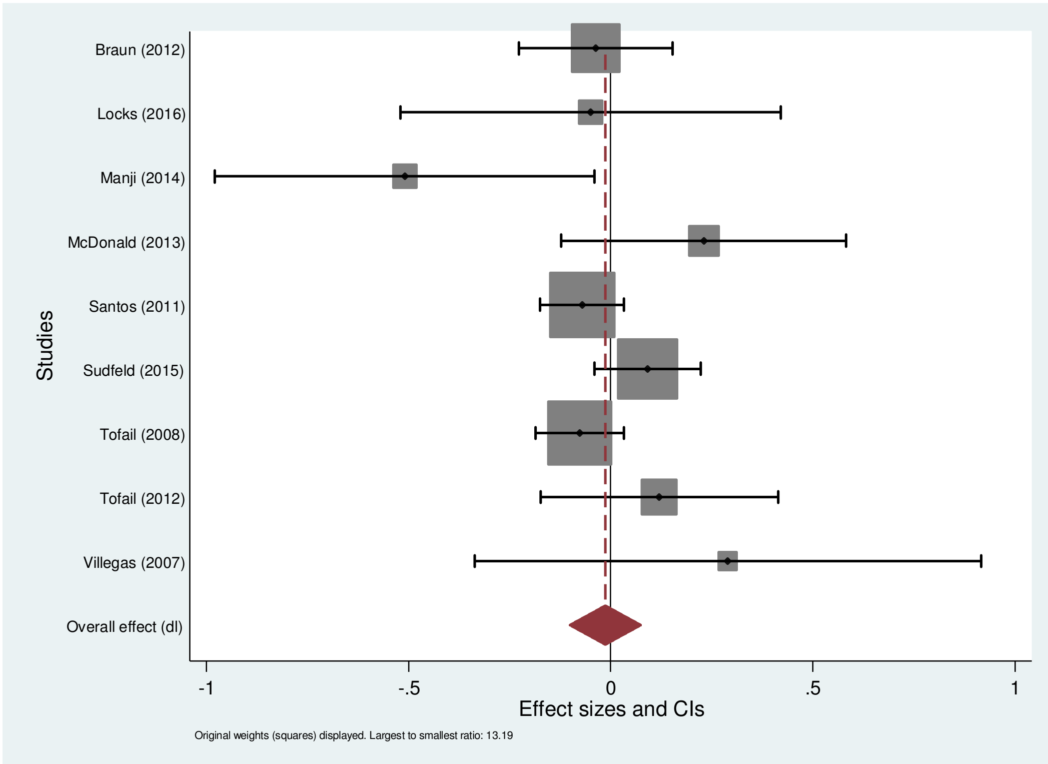

Figure 27: Association between moderate SGA (reference: AGA) and motor development.

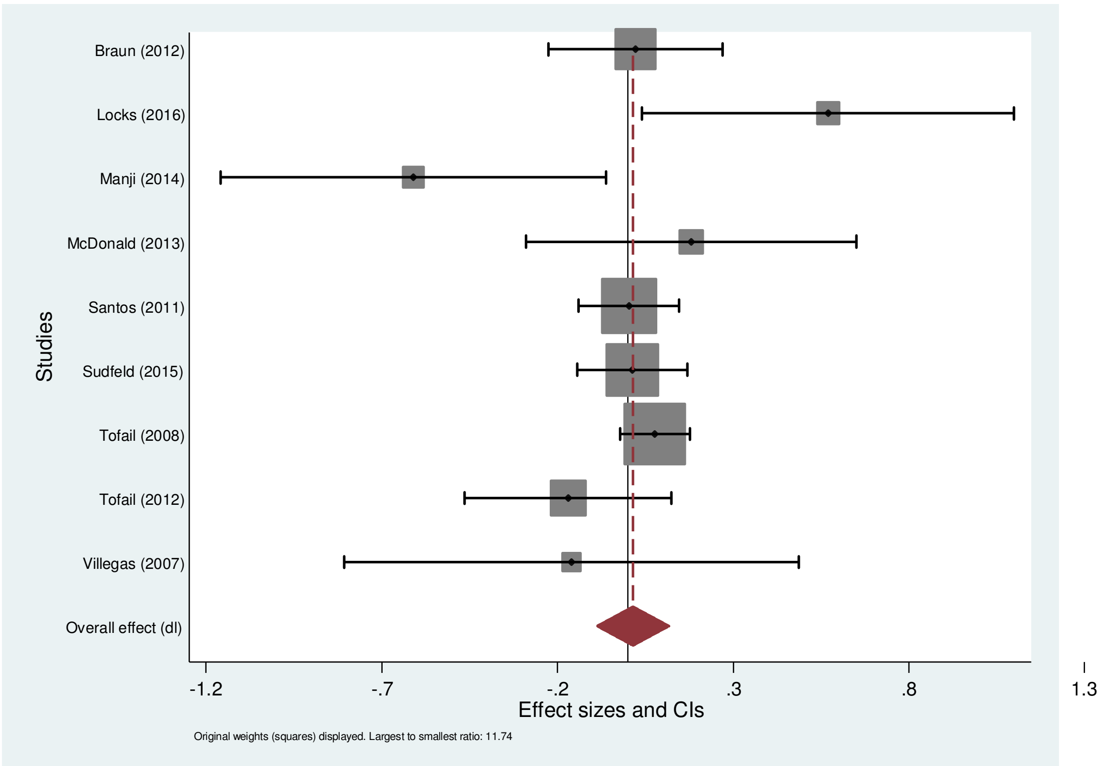

Figure 28: Association between severe SGA (reference: AGA) and motor development.

3. Child Risk Factors on Child's Language Development

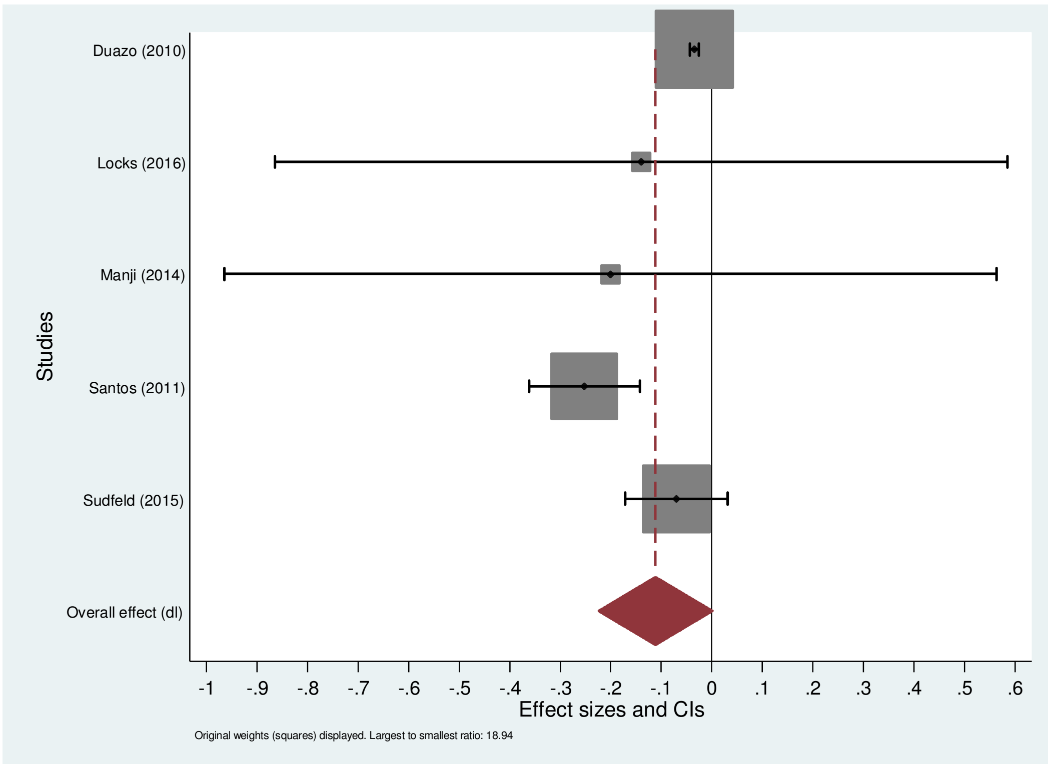

Figure 29: Association between low birth weight (LBW) and (reference: normal birth weight) and language development.

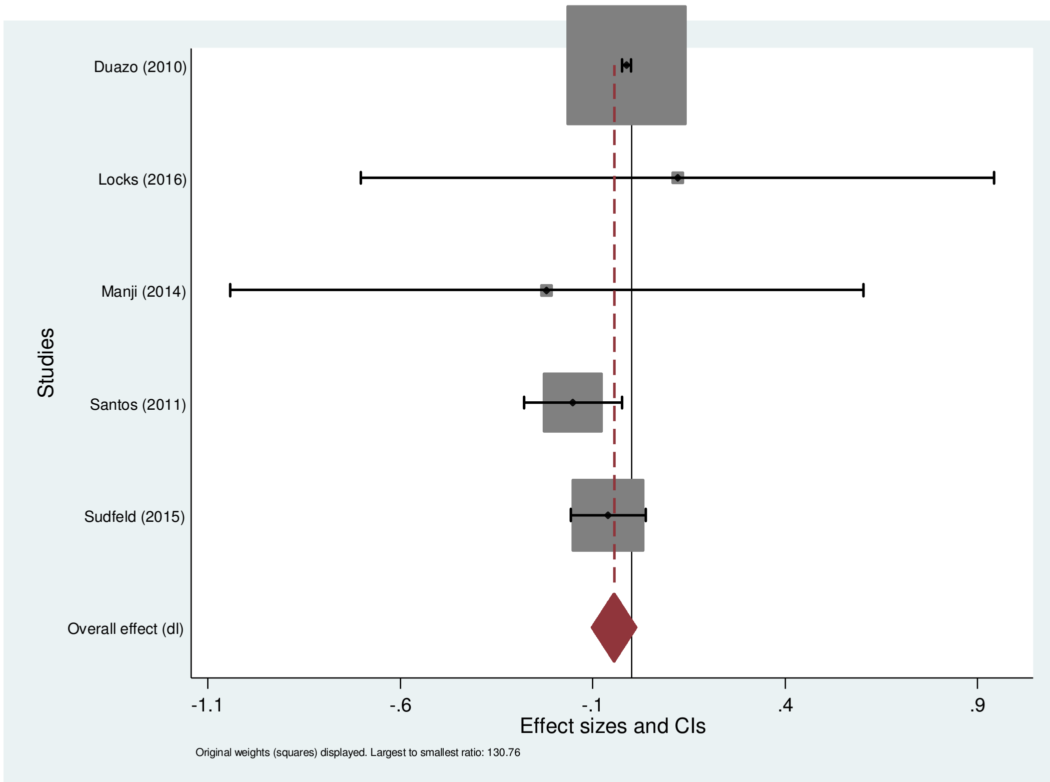

Figure 30: Association between moderately low birth weight and (reference: normal birth weight) and language development.

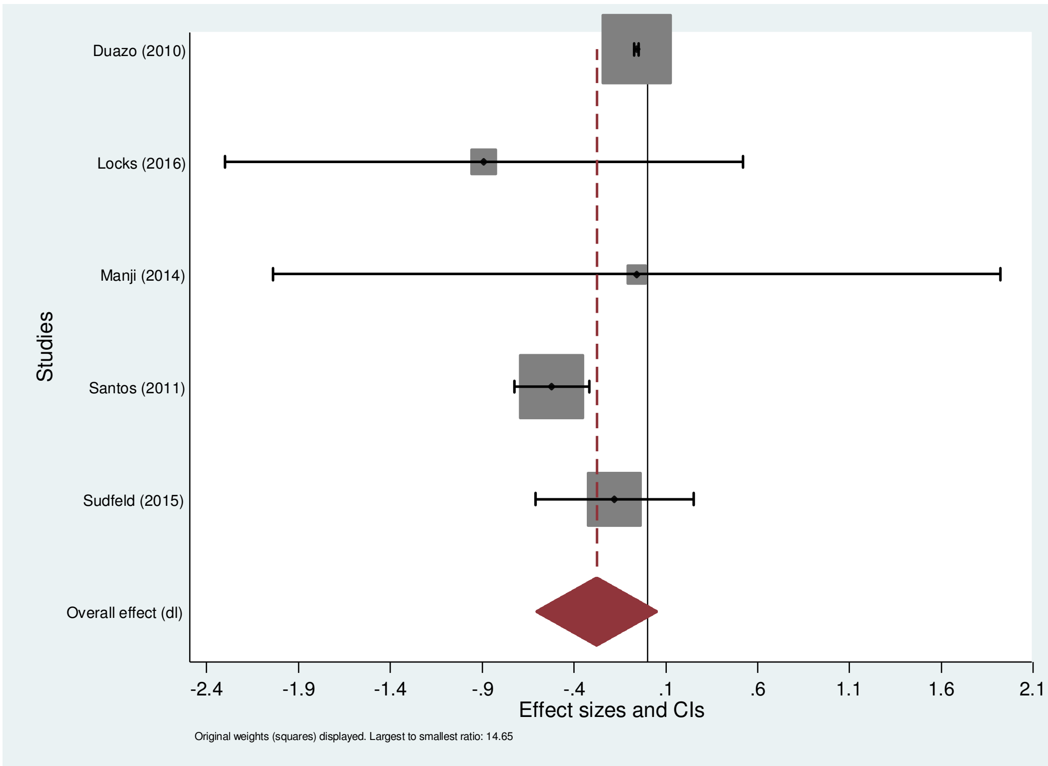

Figure 31: Association between very low birth weight and (reference: normal birth weight) and language development.

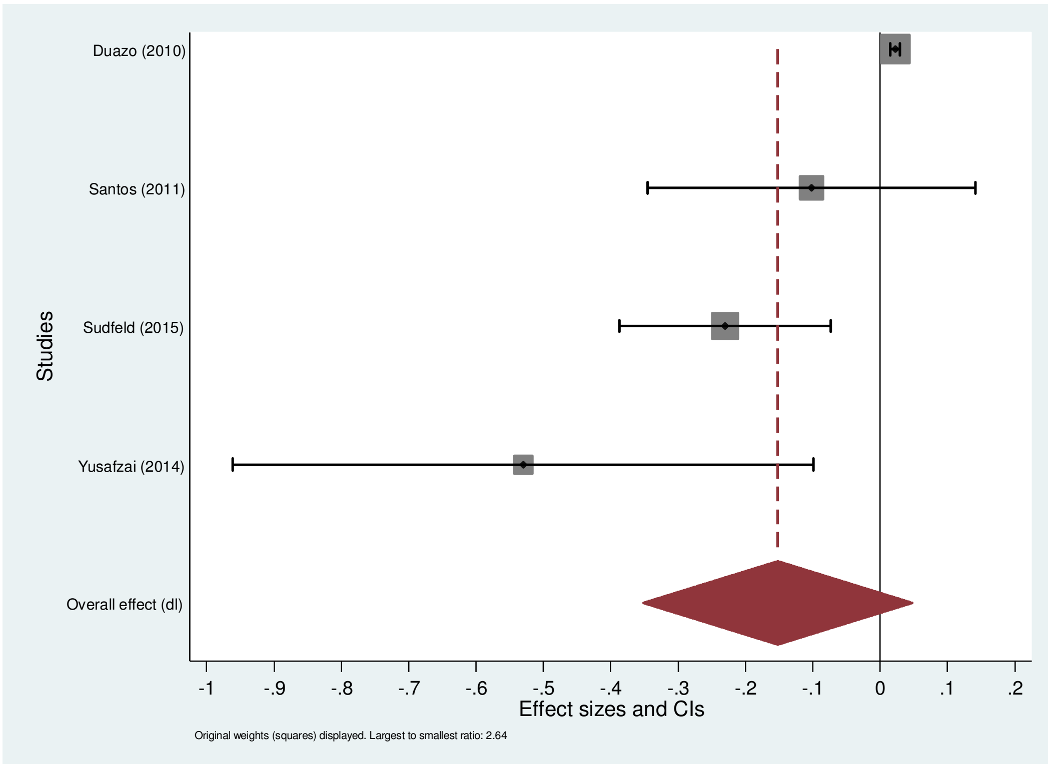

Figure 32: Association between lack of access to clean water (reference: access to clean water) and language development.

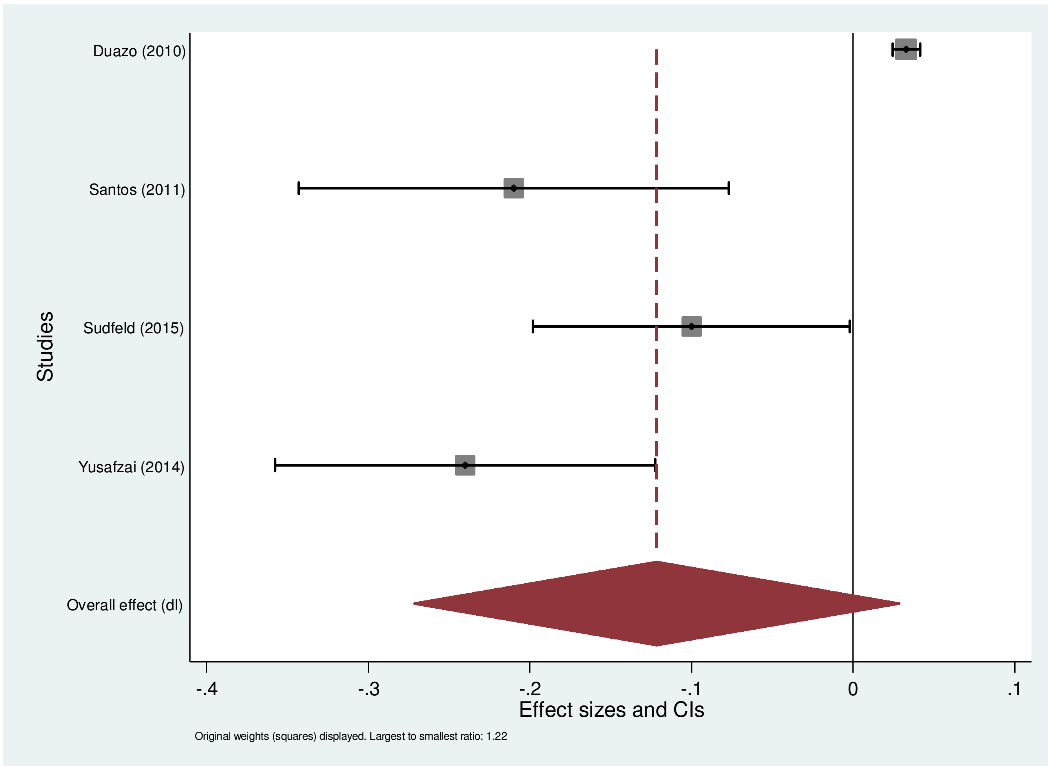

Figure 33: Association between lack of access to sanitation (reference: access to sanitation) and language development.

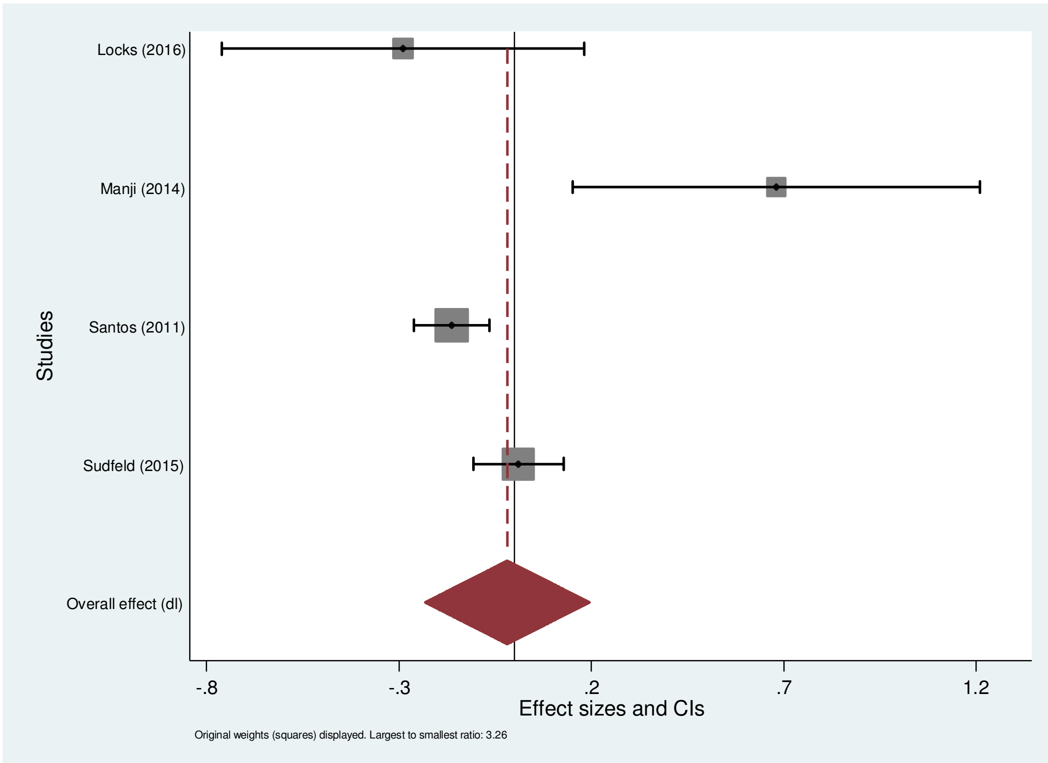

Figure 34: Association between preterm-AGA (reference: term-AGA) and language development.

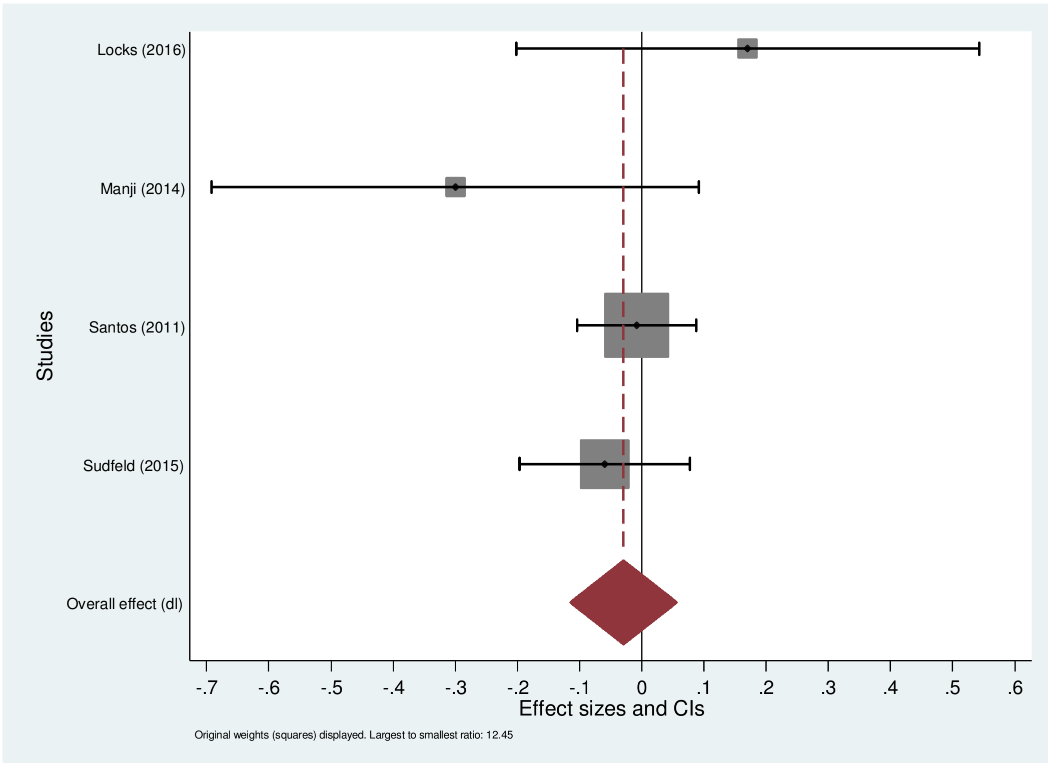

Figure 35: Association between term-SGA (reference: term-AGA) and language development.

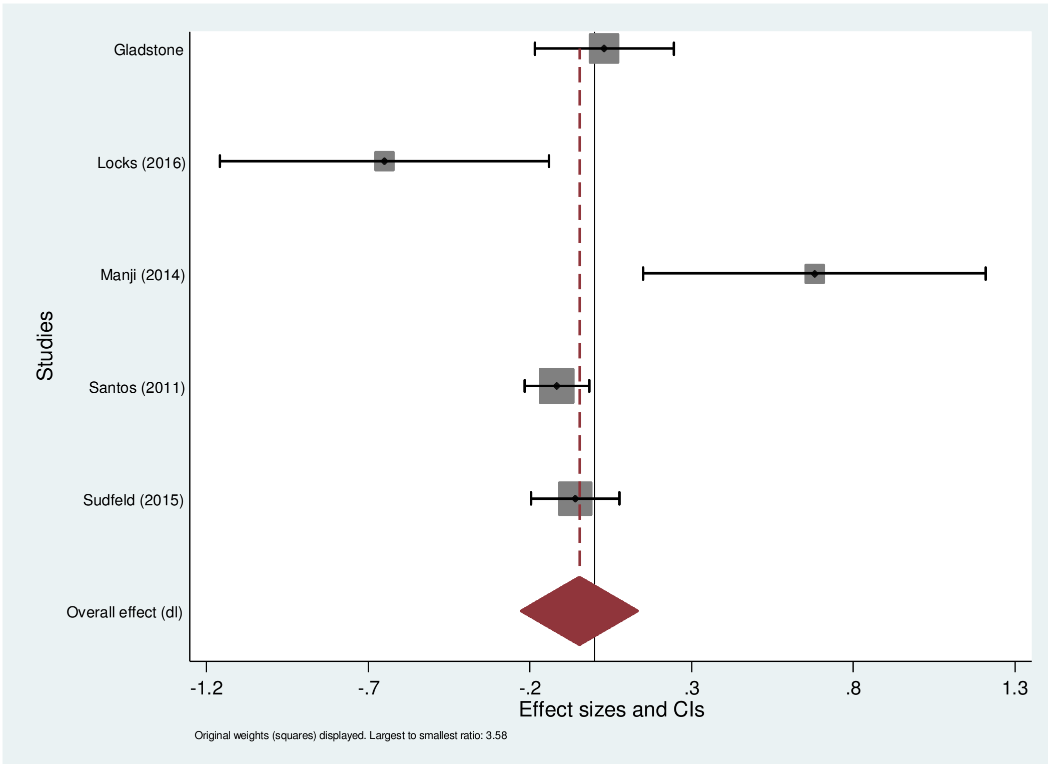

Figure 36: Association between late preterm birth, 34-37 weeks (reference: term) and language development.

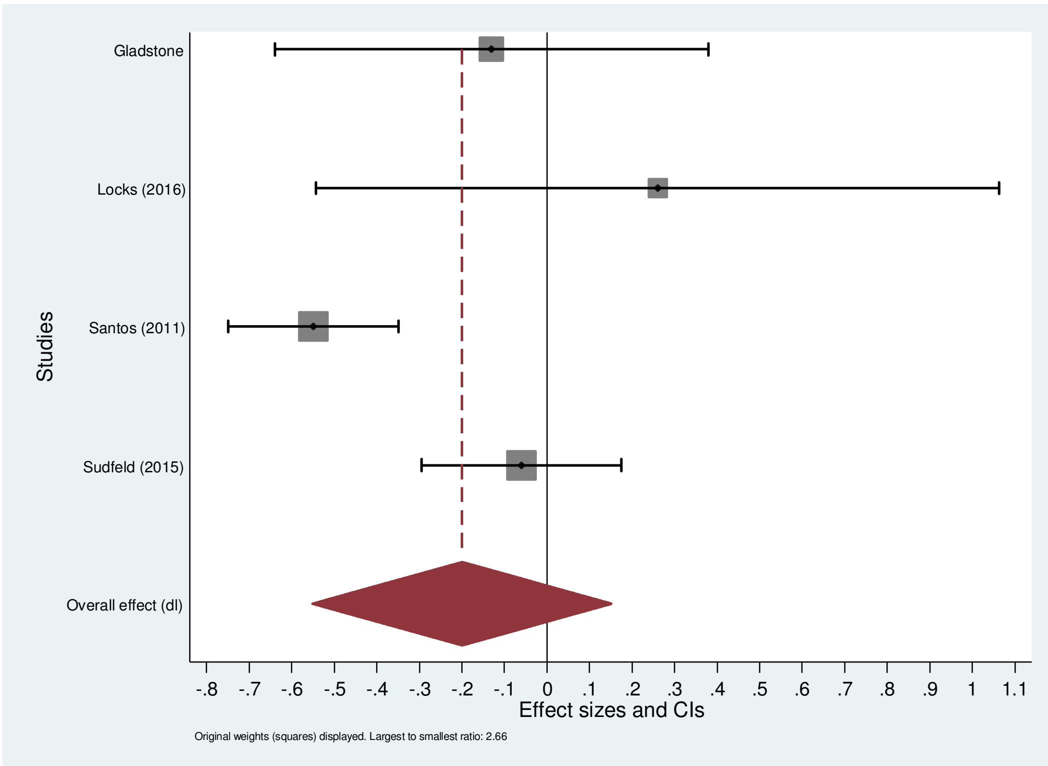

Figure 37: Association between early preterm birth, < 34 weeks (reference: term) and language development.

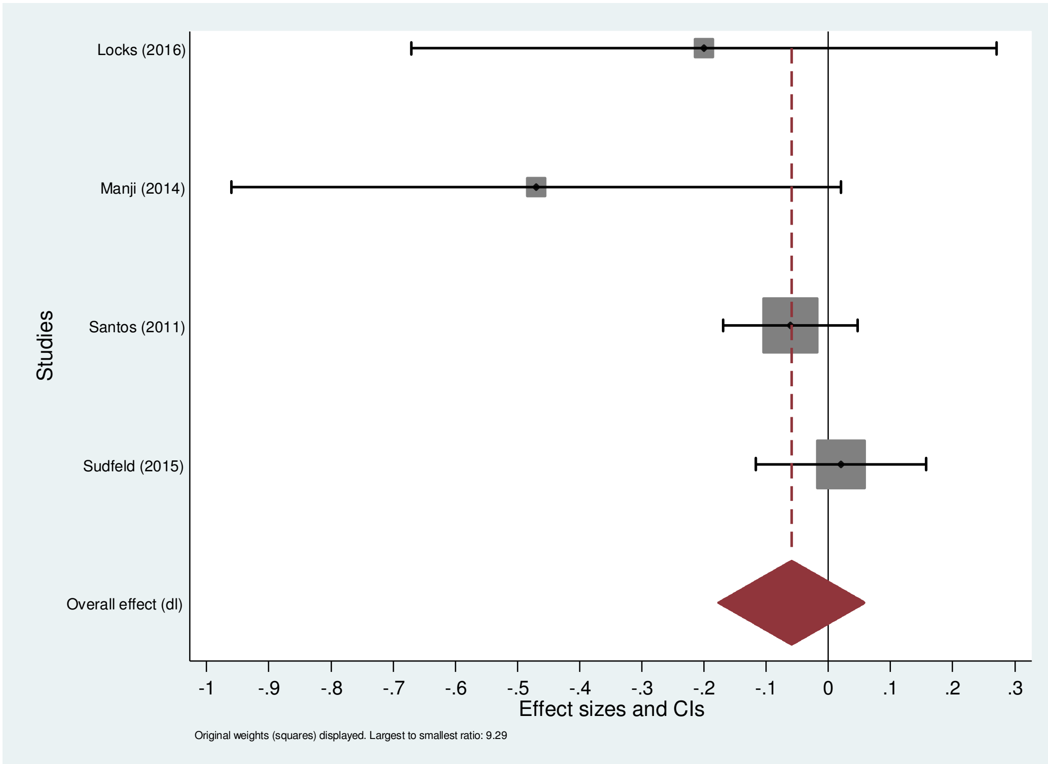

Figure 38: Association between moderate SGA (reference: AGA) and language development.

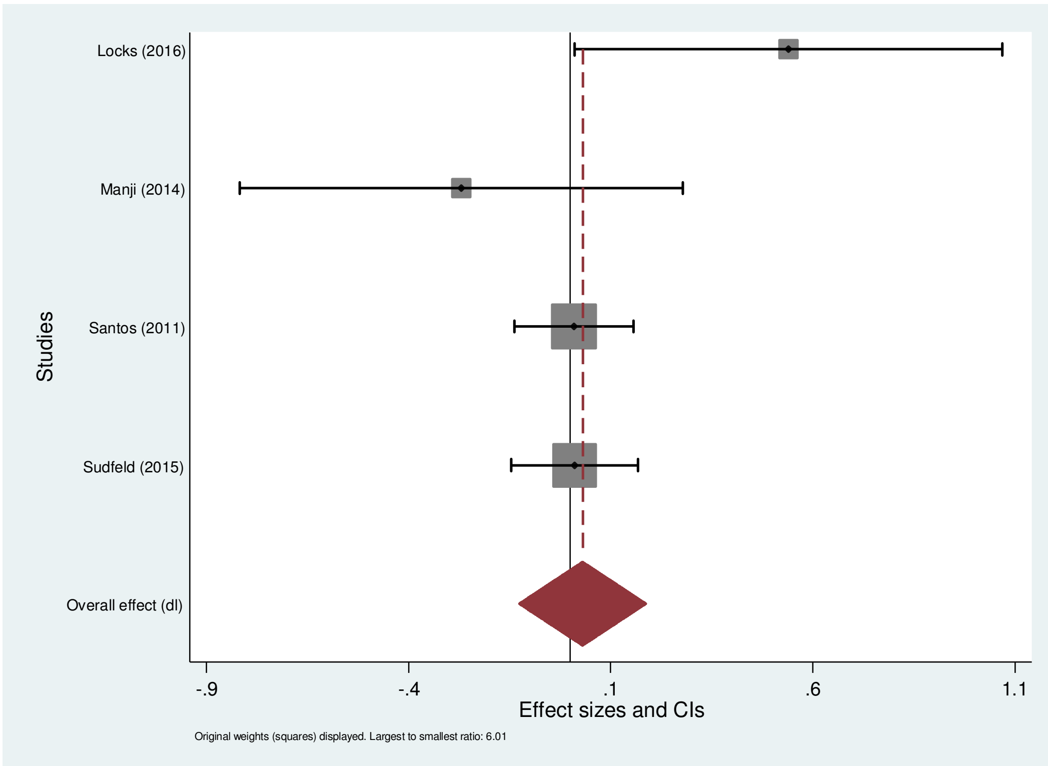

Figure 39: Association between severe SGA (reference: AGA) and language development.

4. Parental Risk Factors on Child's Cognitive Development

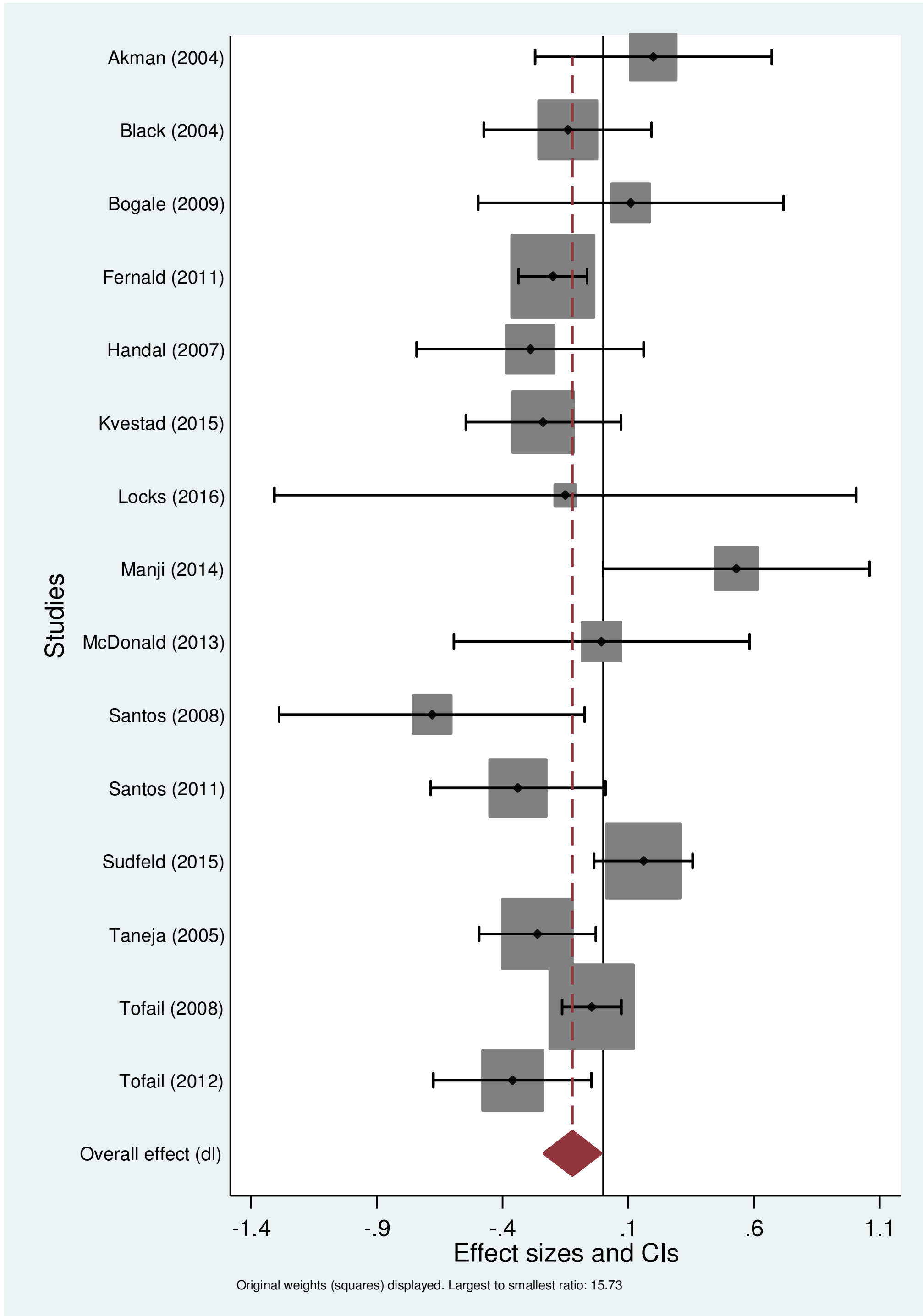

Figure 40: Association between no maternal education (reference: primary education) and cognitive development.

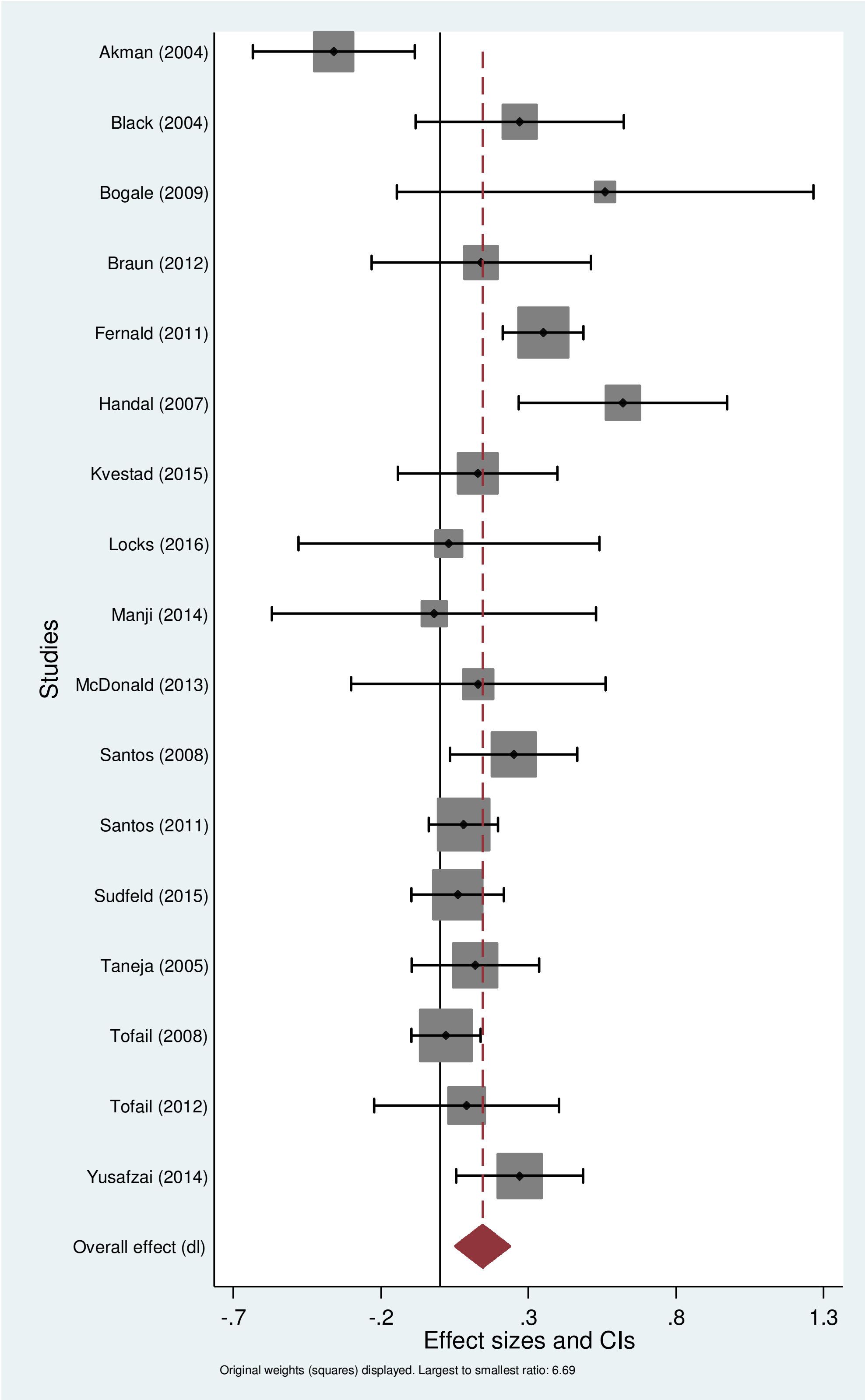

Figure 41: Association between maternal secondary education (reference: primary education) and cognitive development.

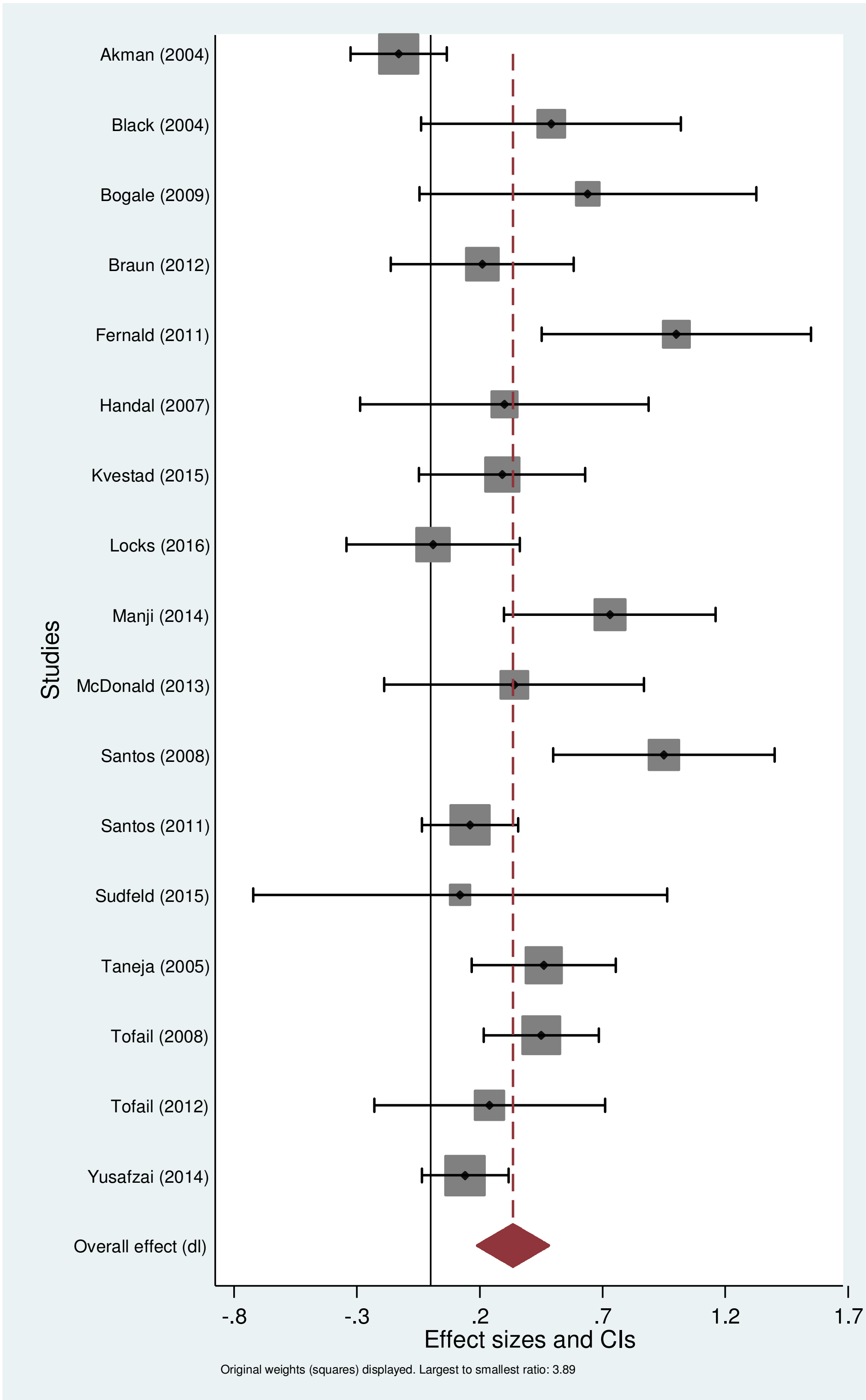

Figure 42: Association between maternal higher education (reference: primary education) and cognitive development.

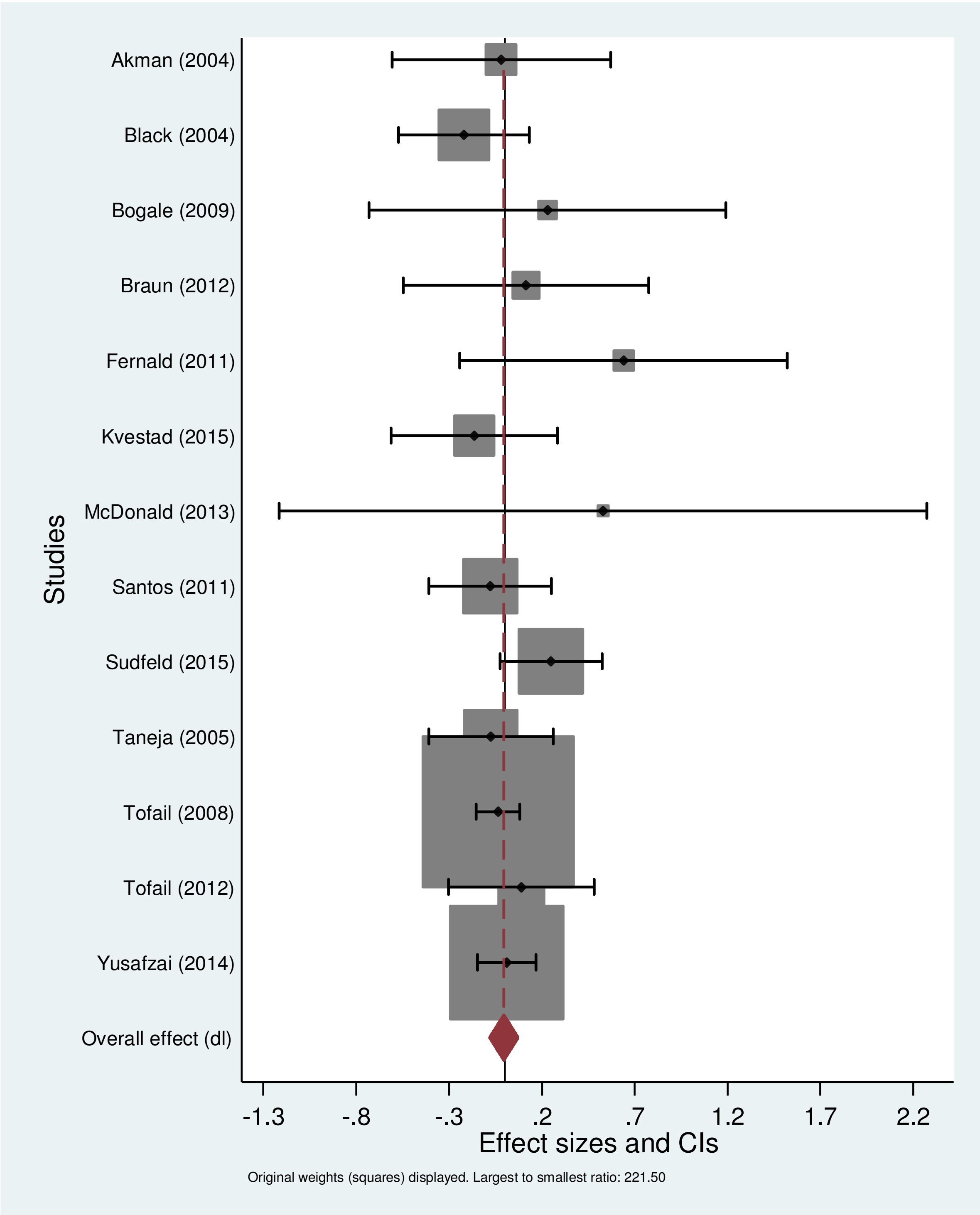

Figure 43: Association between no paternal education (reference: primary education) and cognitive development.

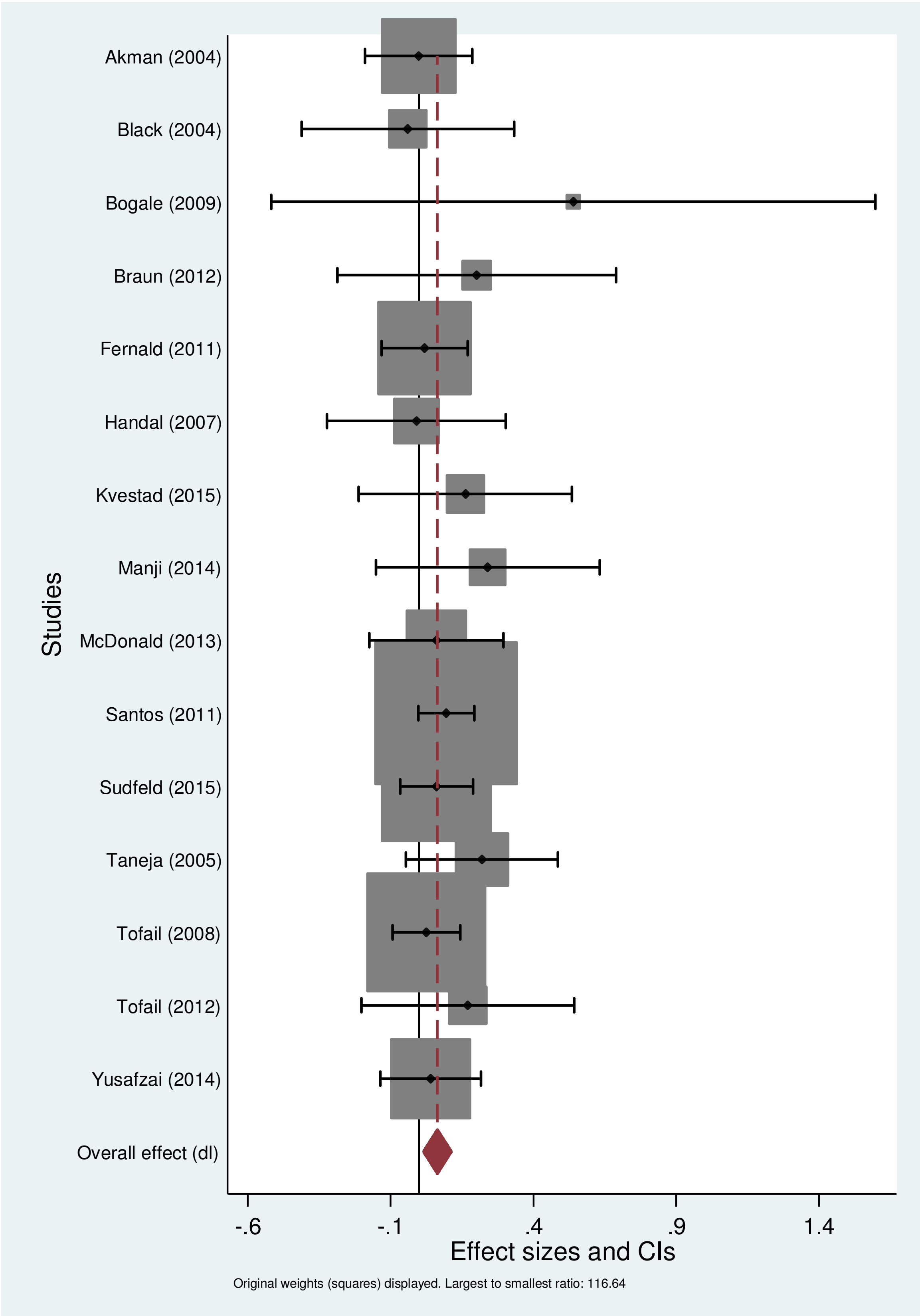

Figure 44: Association between paternal secondary education (reference: primary education) and cognitive development.

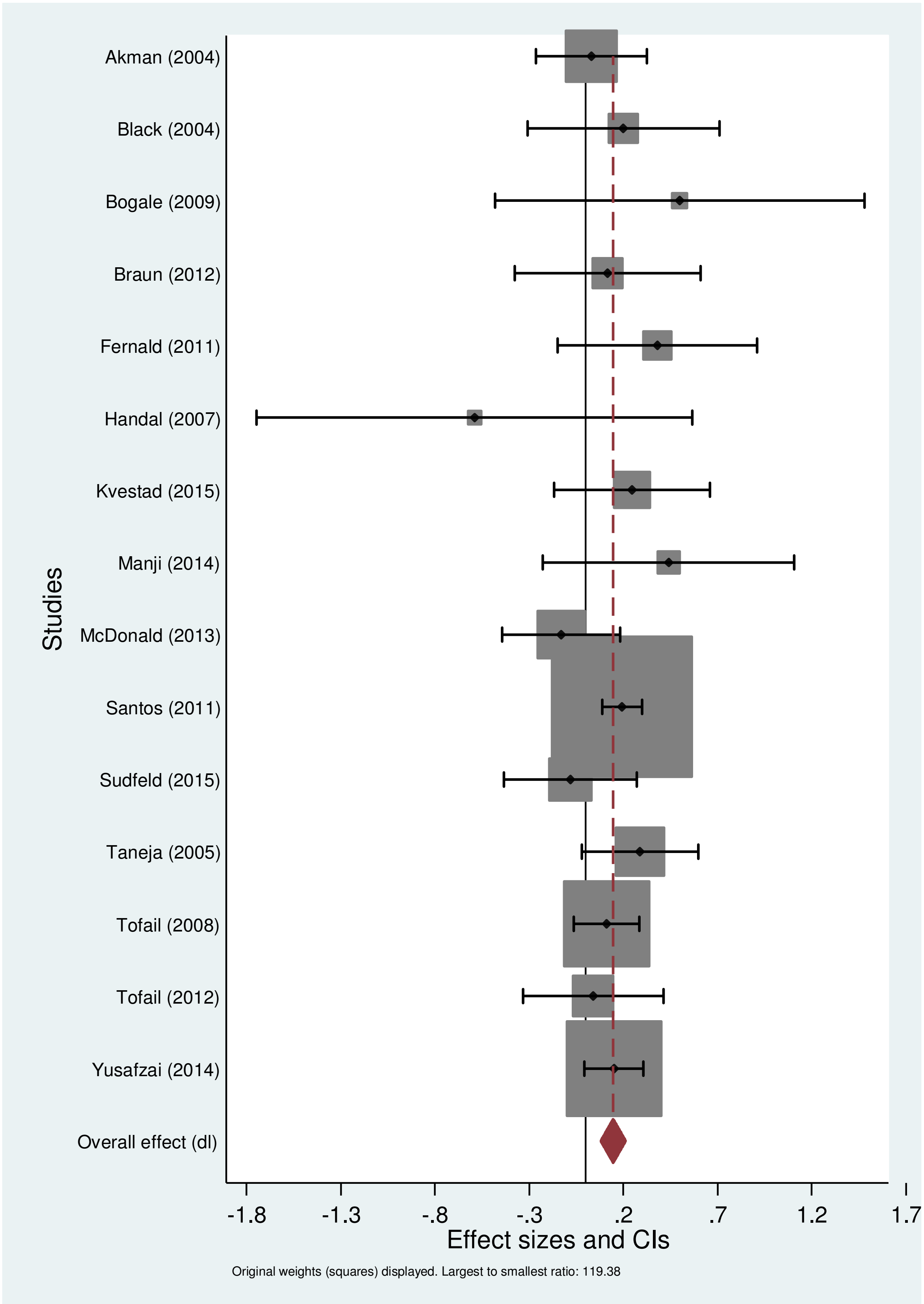

Figure 45: Association between paternal higher education (reference: primary education) and cognitive development.

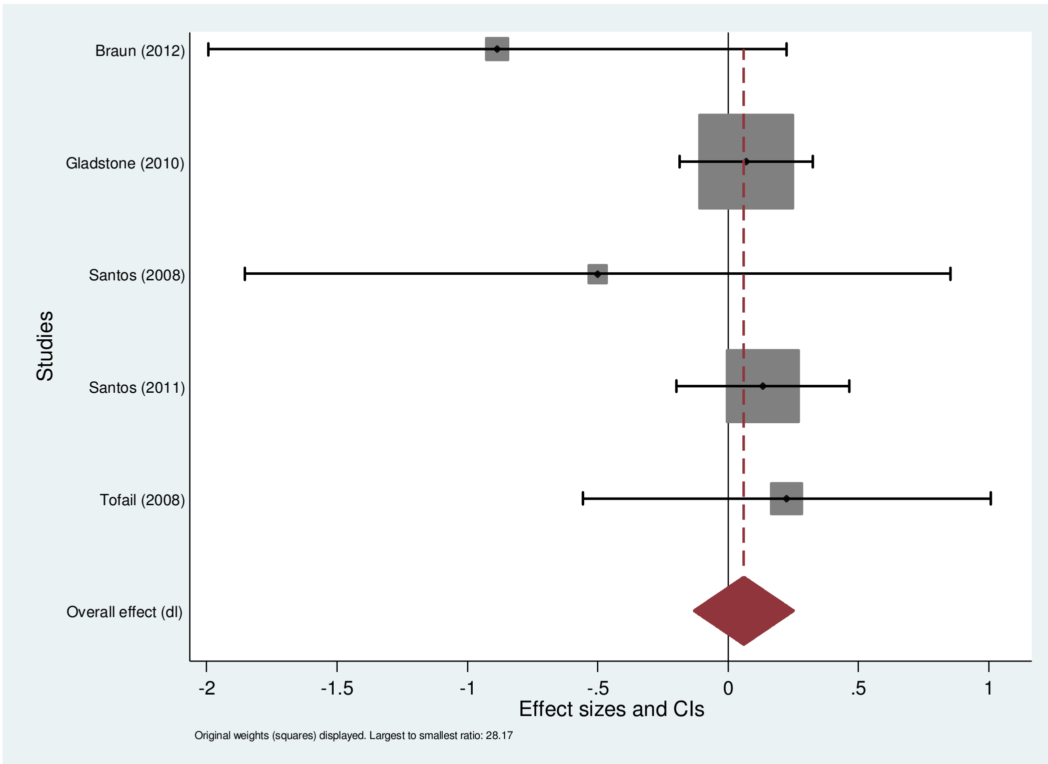

Figure 46: Association between maternal ages < 15 (reference: ages 20-34) and cognitive development.

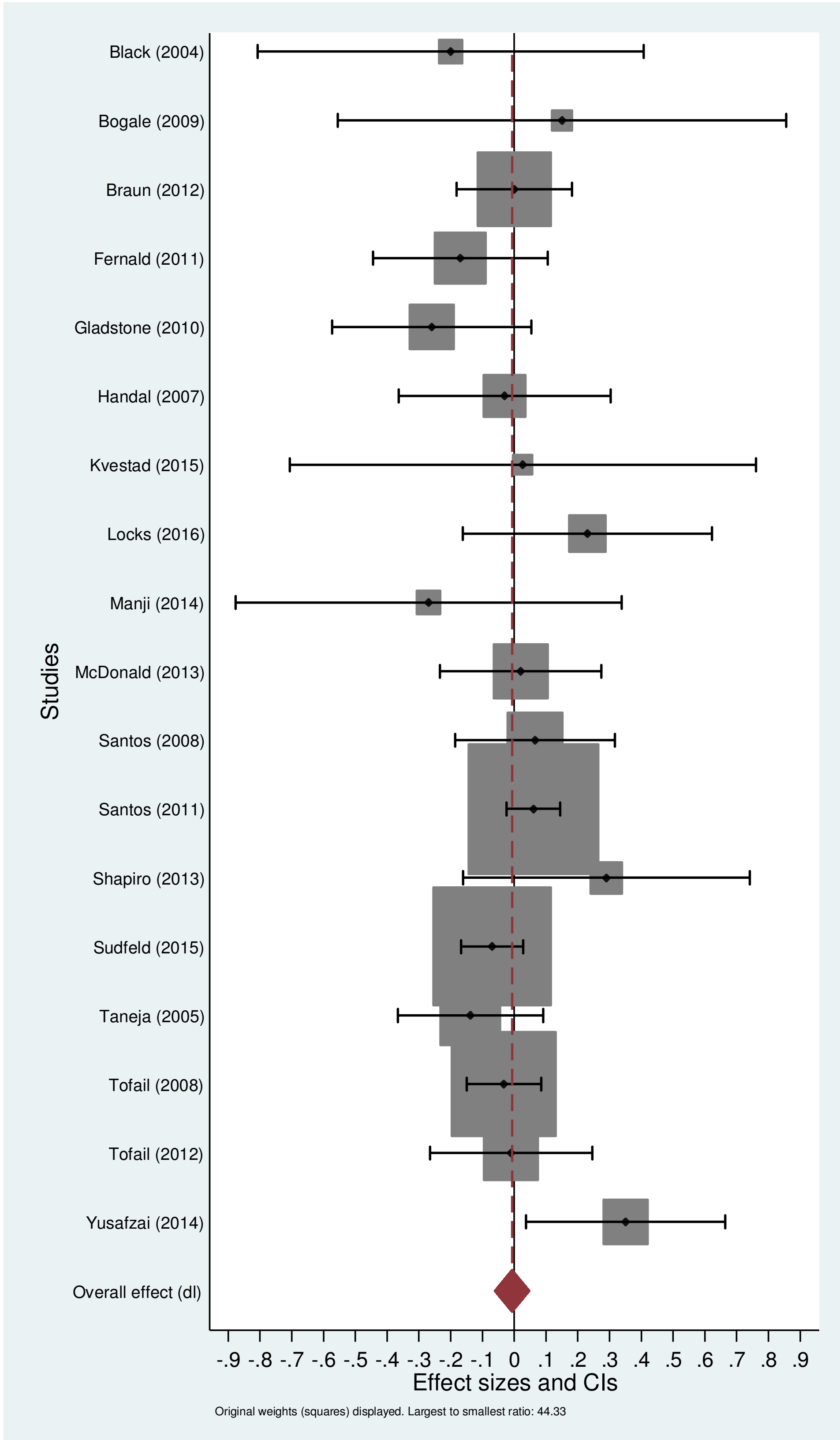

Figure 47: Association between maternal ages 15-20 (reference: ages 20-34) and cognitive development.

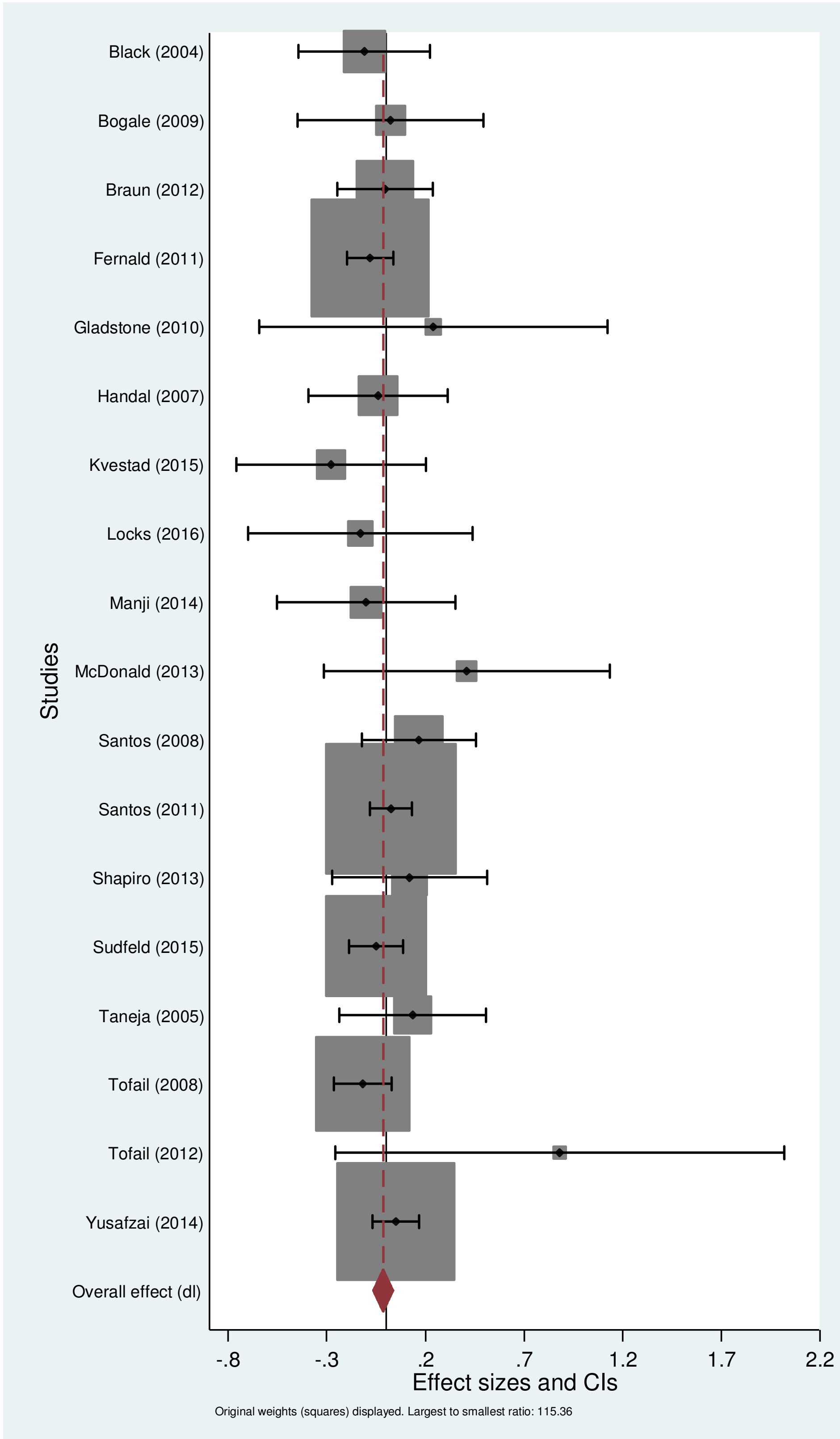

Figure 48: Association between maternal ages >35 (reference: ages 20-34) and cognitive development.

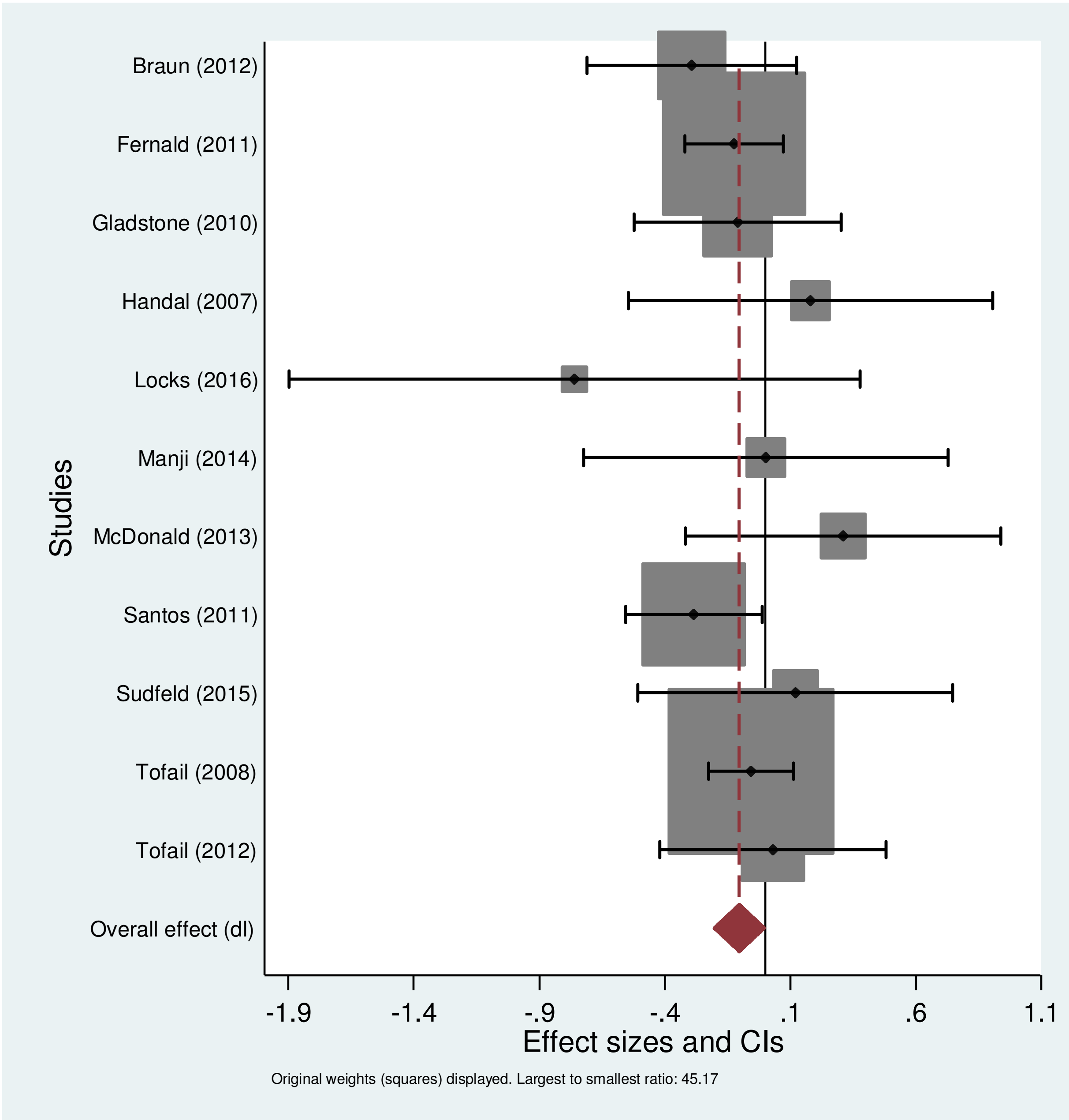

Figure 49: Association between maternal height < 145cm (reference: >155 cm) and cognitive development.

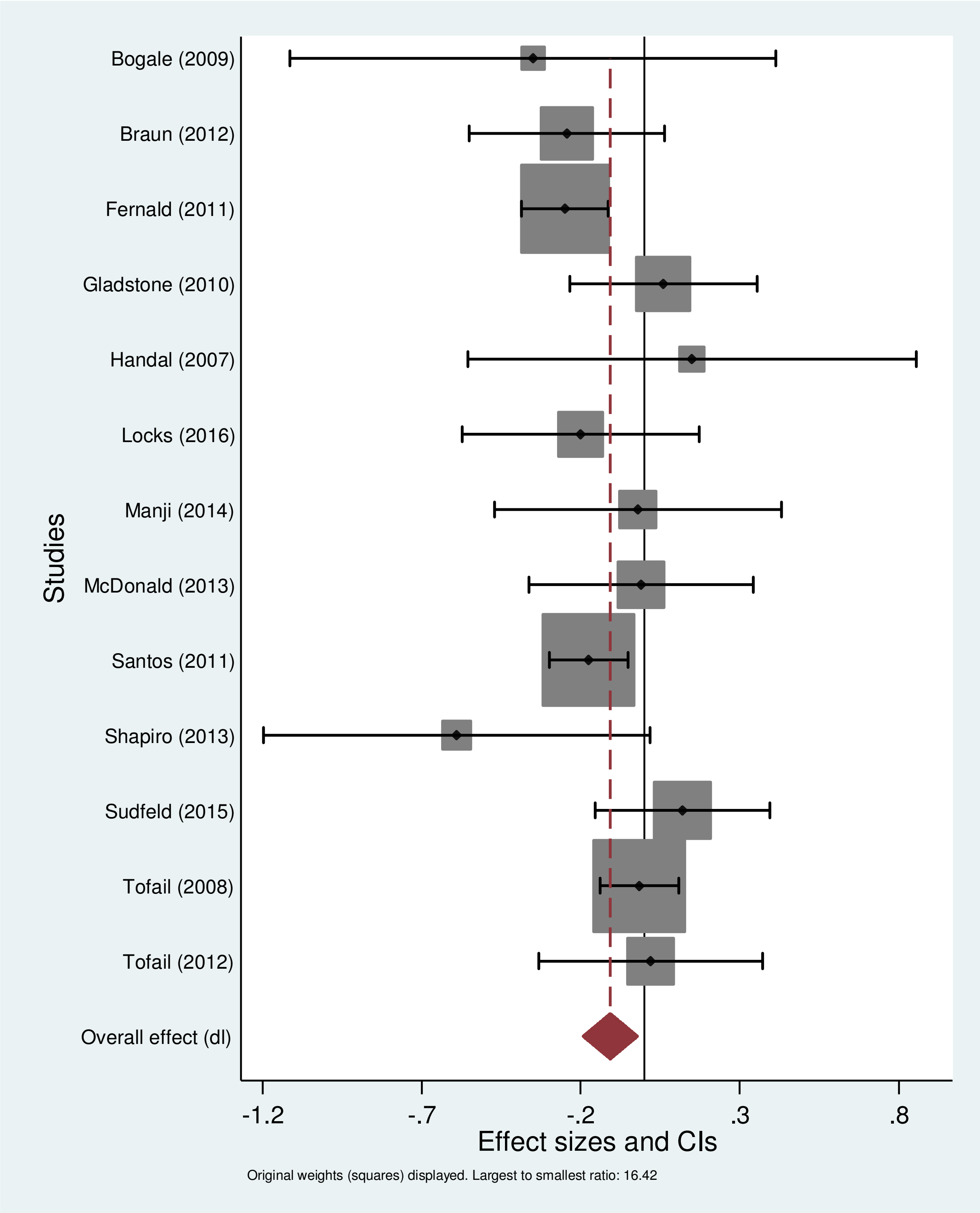

Figure 50: Association between maternal height 145-150cm (reference: >155 cm) and cognitive development.

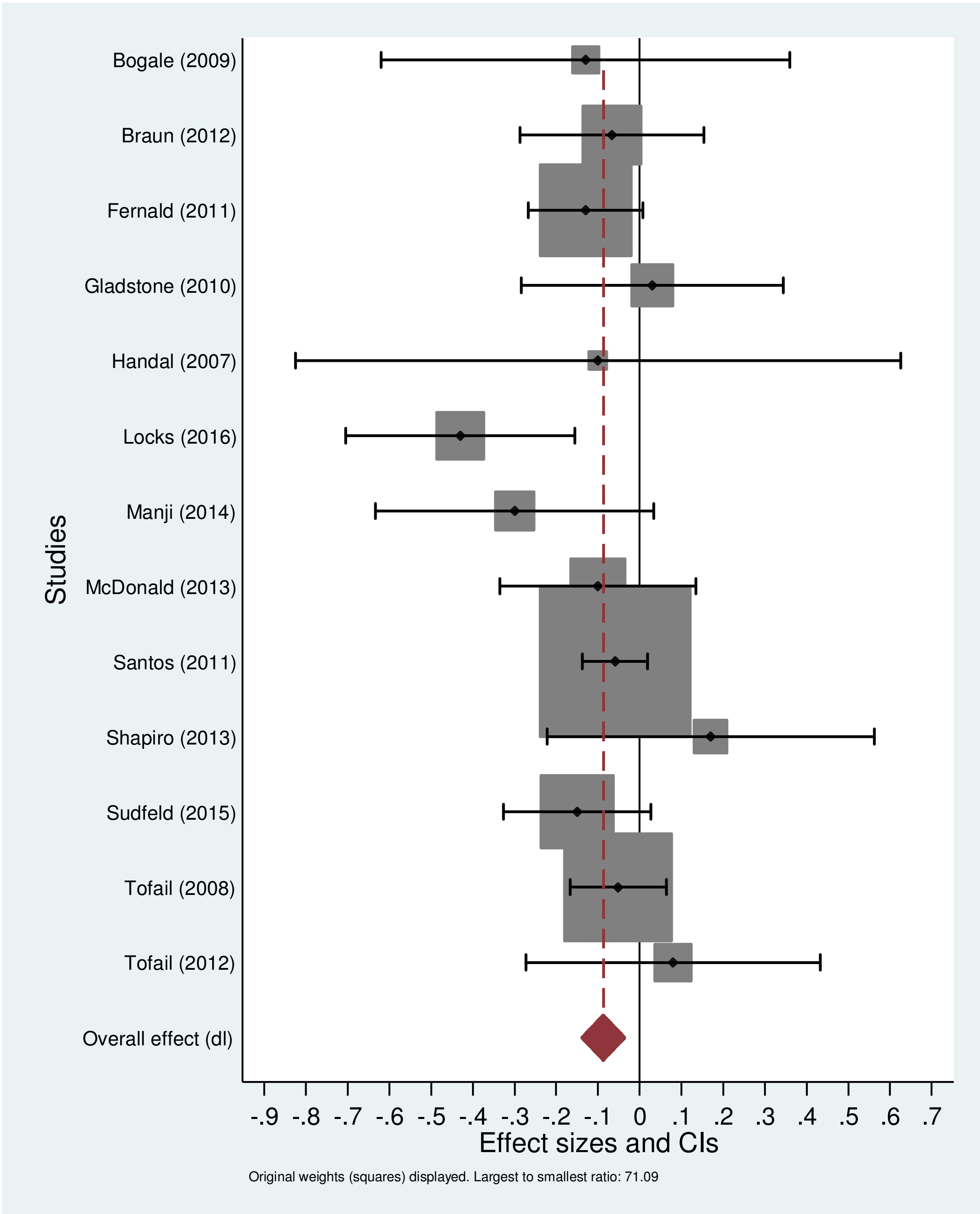

Figure 51: Association between maternal height 150-155 cm (reference: >155 cm) and cognitive development.

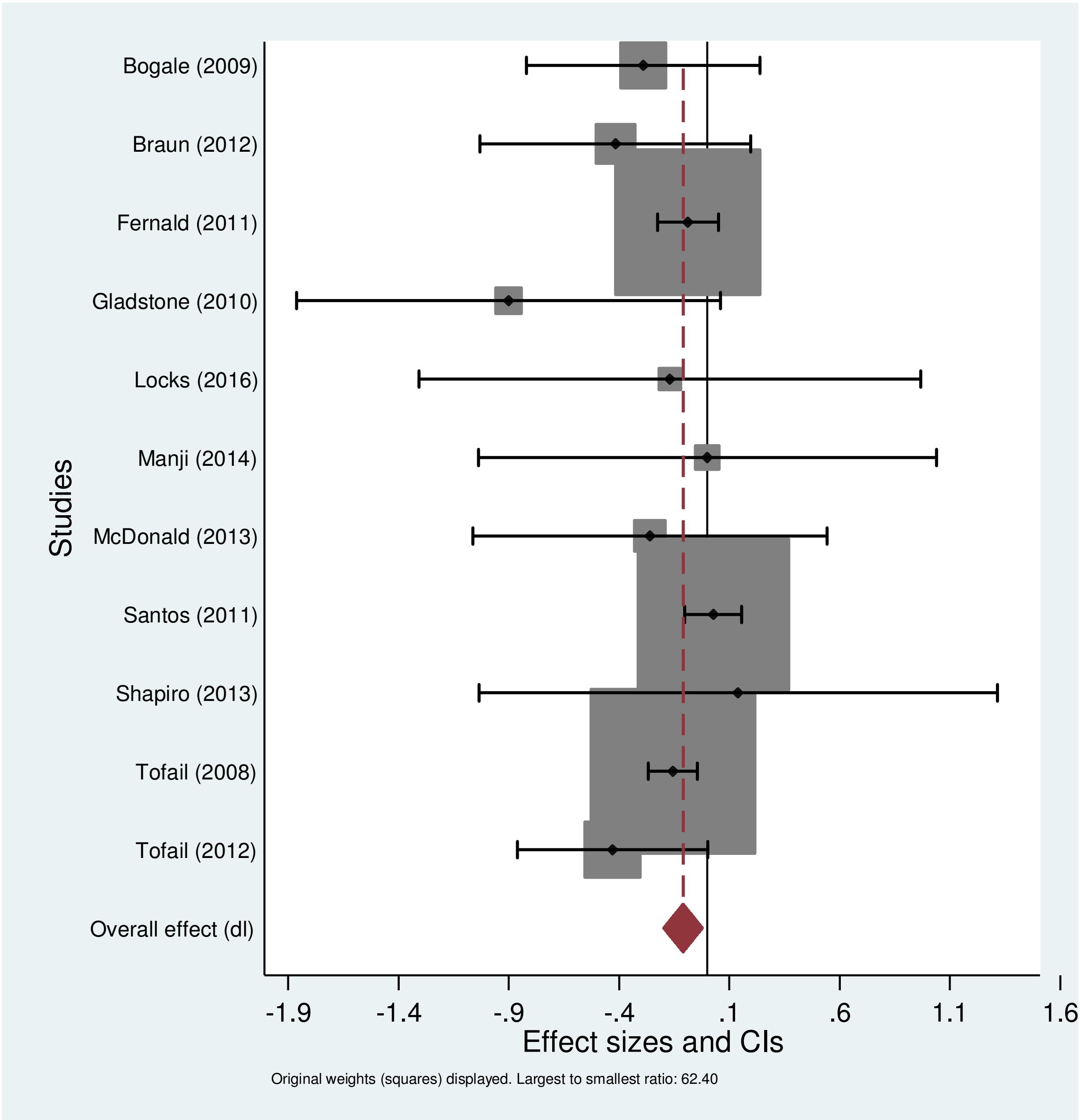

Figure 52: Association between maternal BMI <18.5 kg/m² (reference: 18.5-25) and cognitive development.

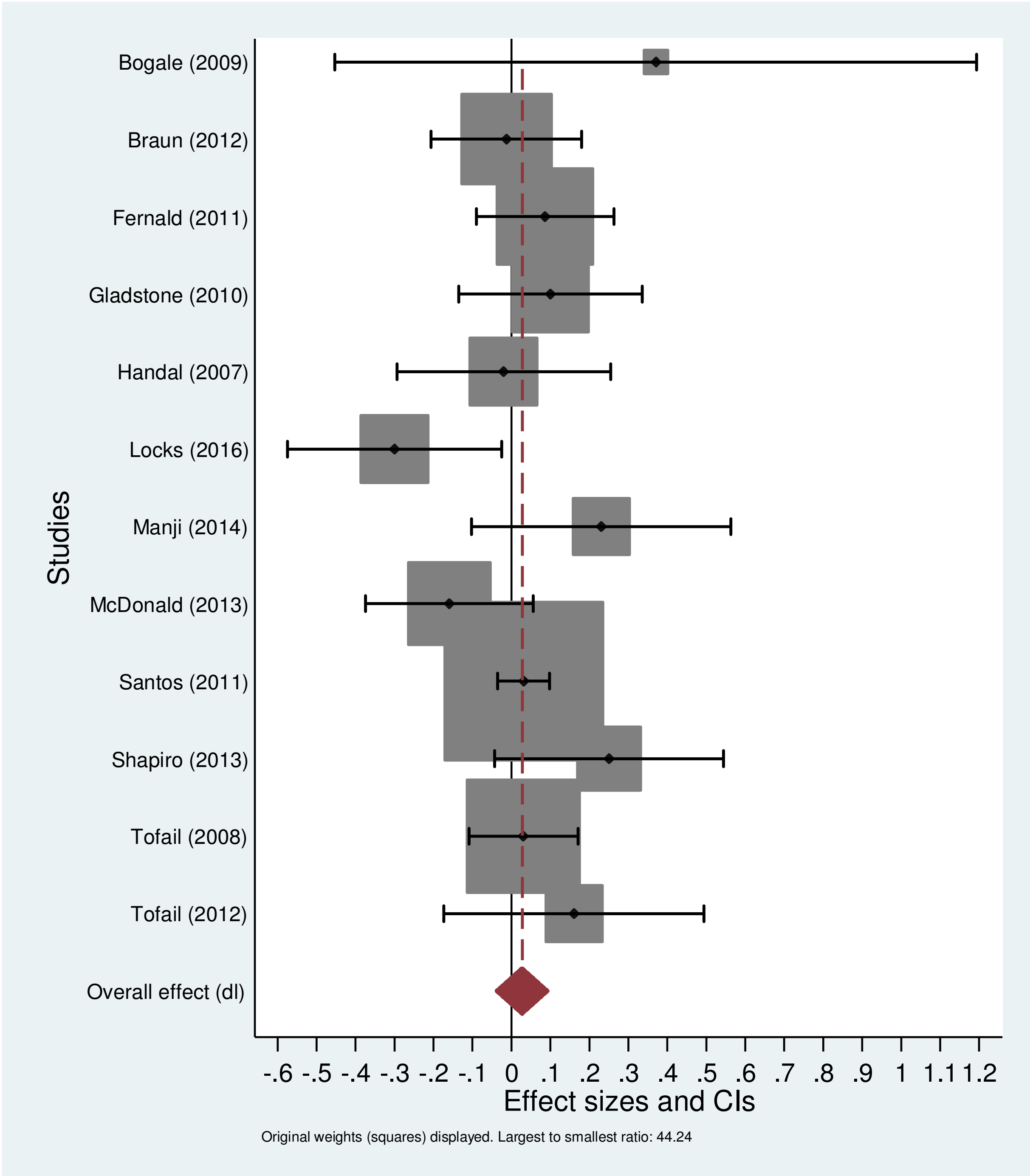

Figure 53: Association between maternal BMI 25-30 kg/m² (reference: 18.5-25) and cognitive development.

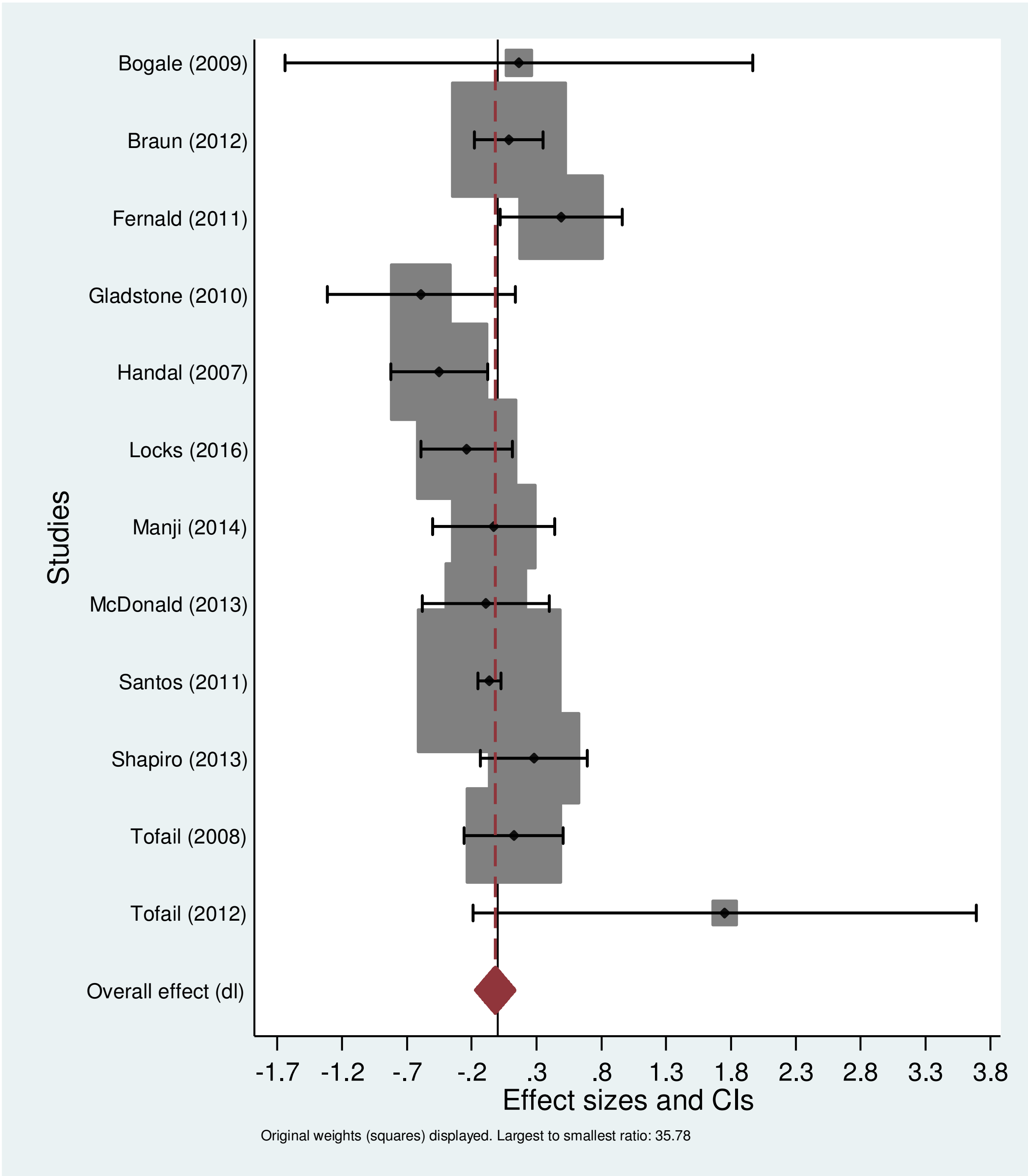

Figure 54: Association between maternal BMI >30 kg/m² (reference: 18.5-25) and cognitive development.

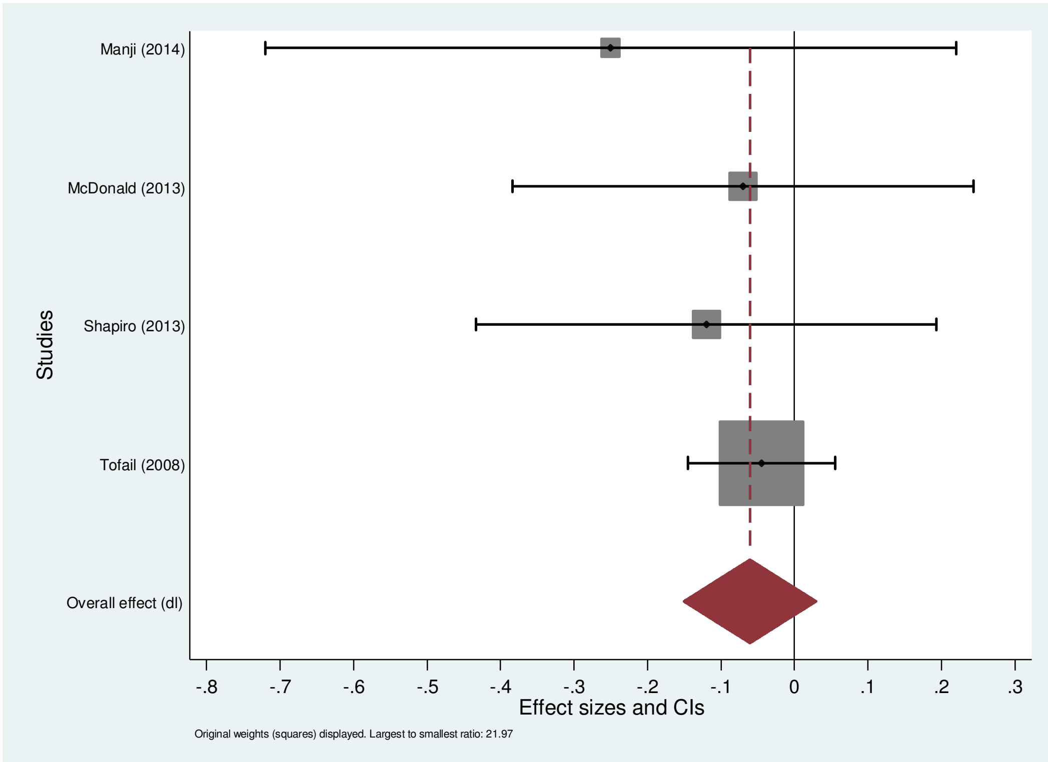

Figure 55: Association between mild anemia in pregnancy (reference: no anemia) and cognitive development.

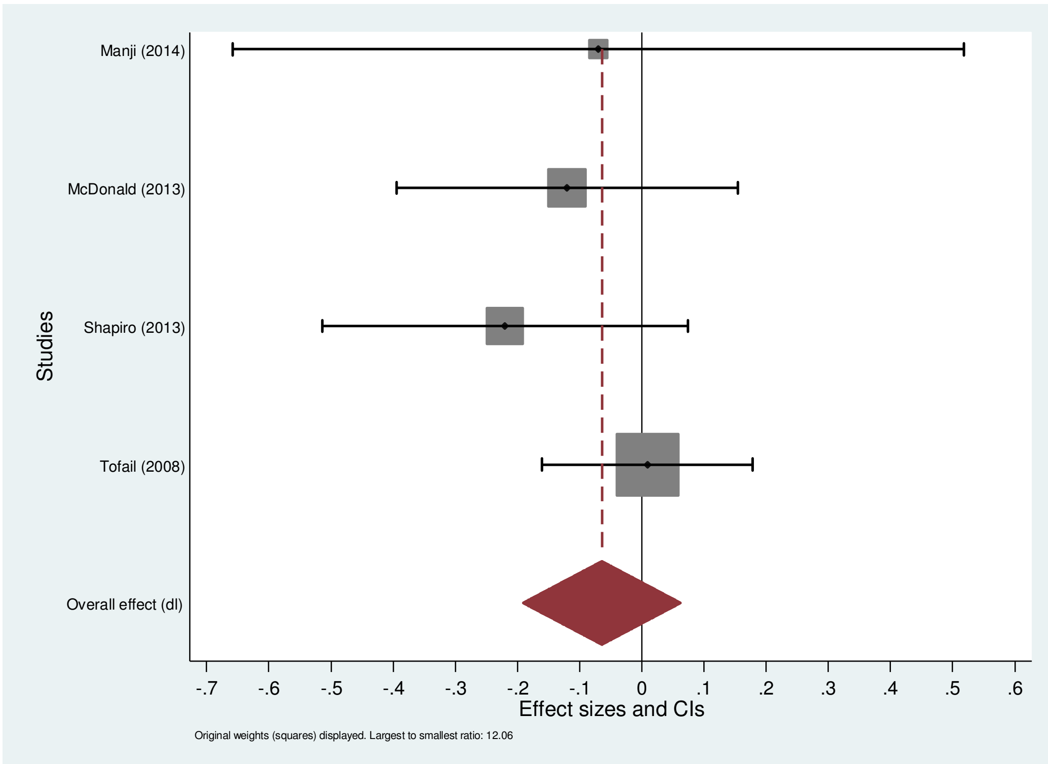

Figure 56: Association between maternal moderate anemia (reference: no anemia) and cognitive development.

5. Parental Risk Factors on Child's Motor Development

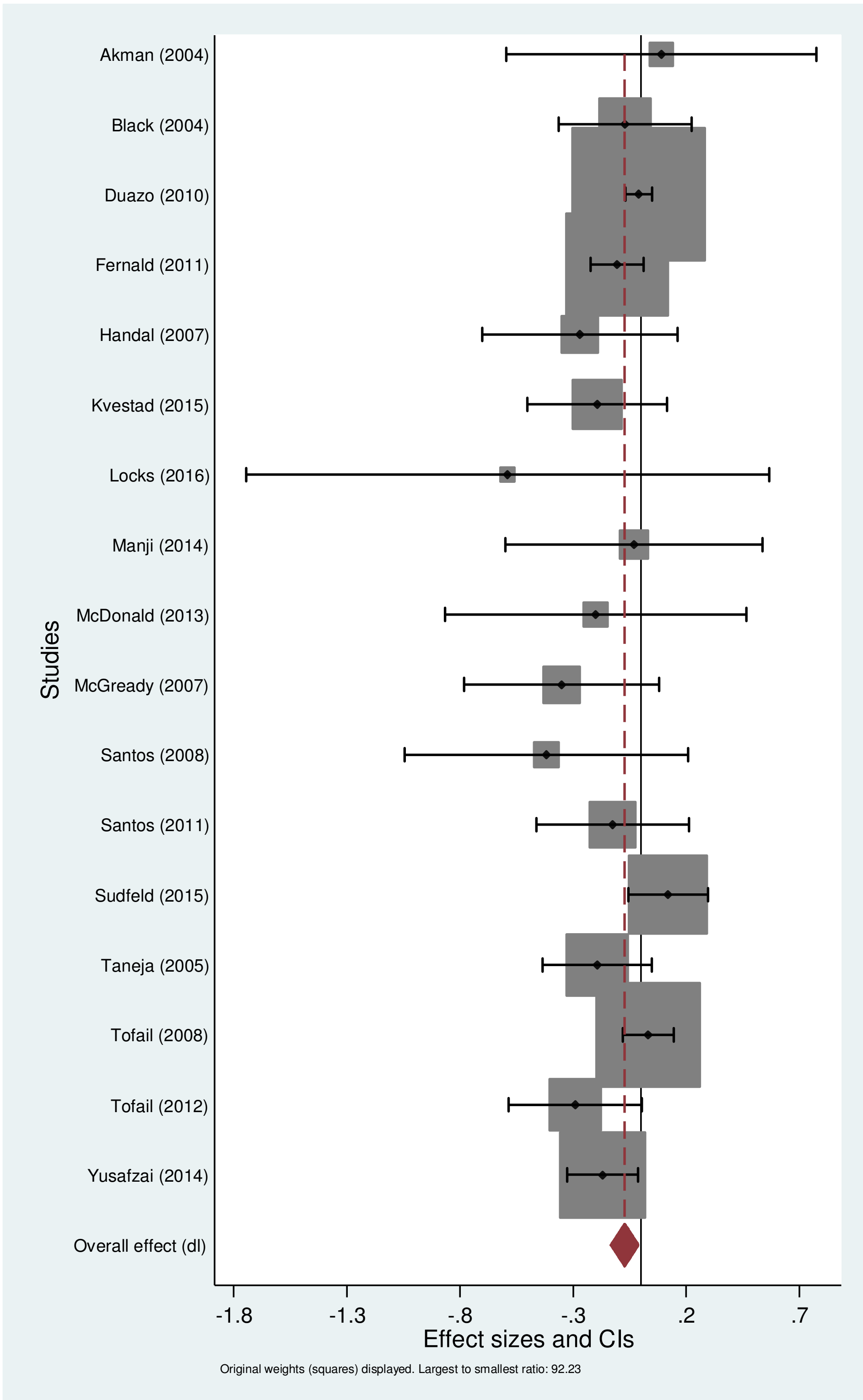

Figure 57: Association between no maternal education (reference: primary education) and motor development.

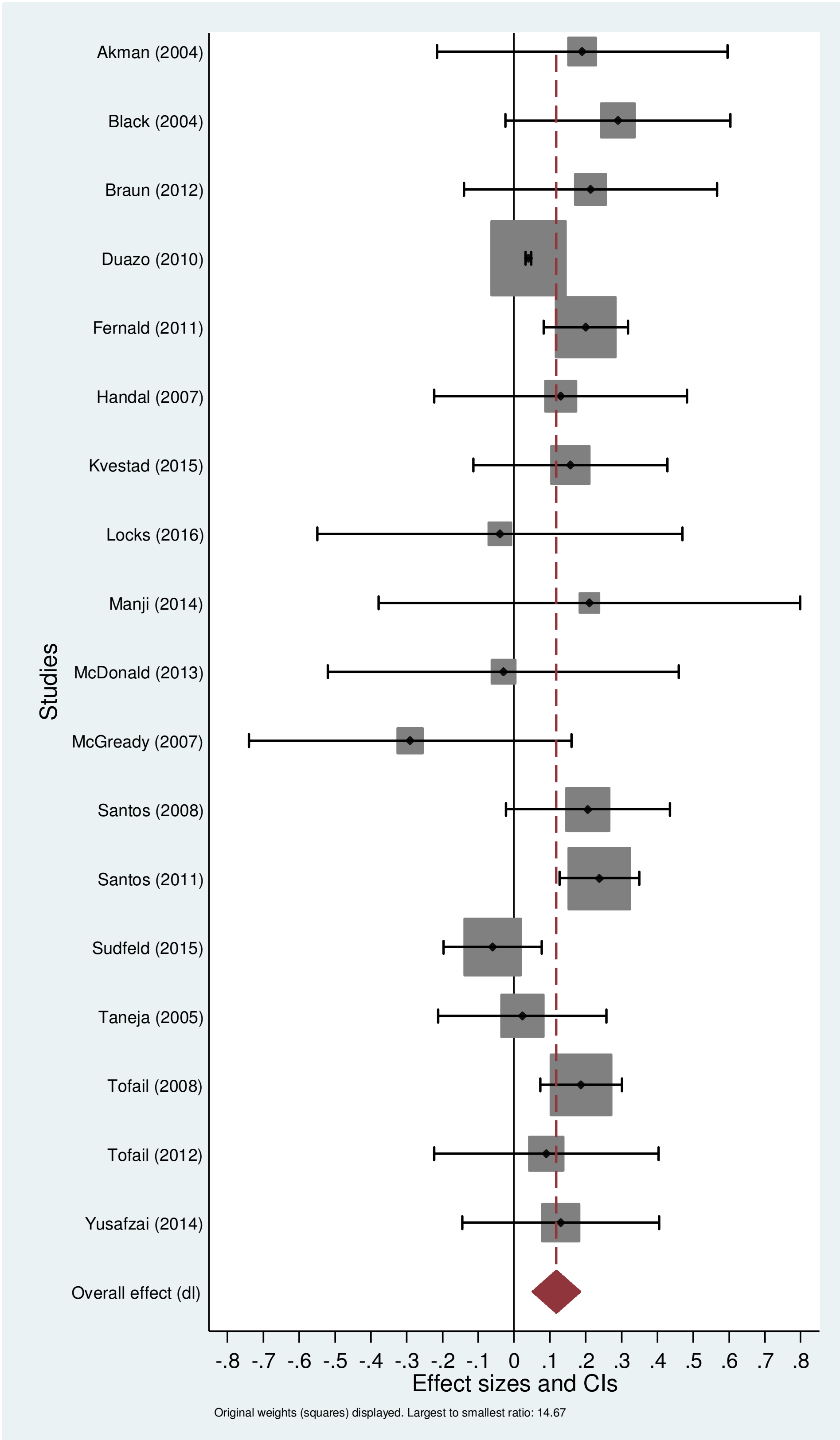

Figure 58: Association between maternal secondary education (reference: primary education) and motor development.

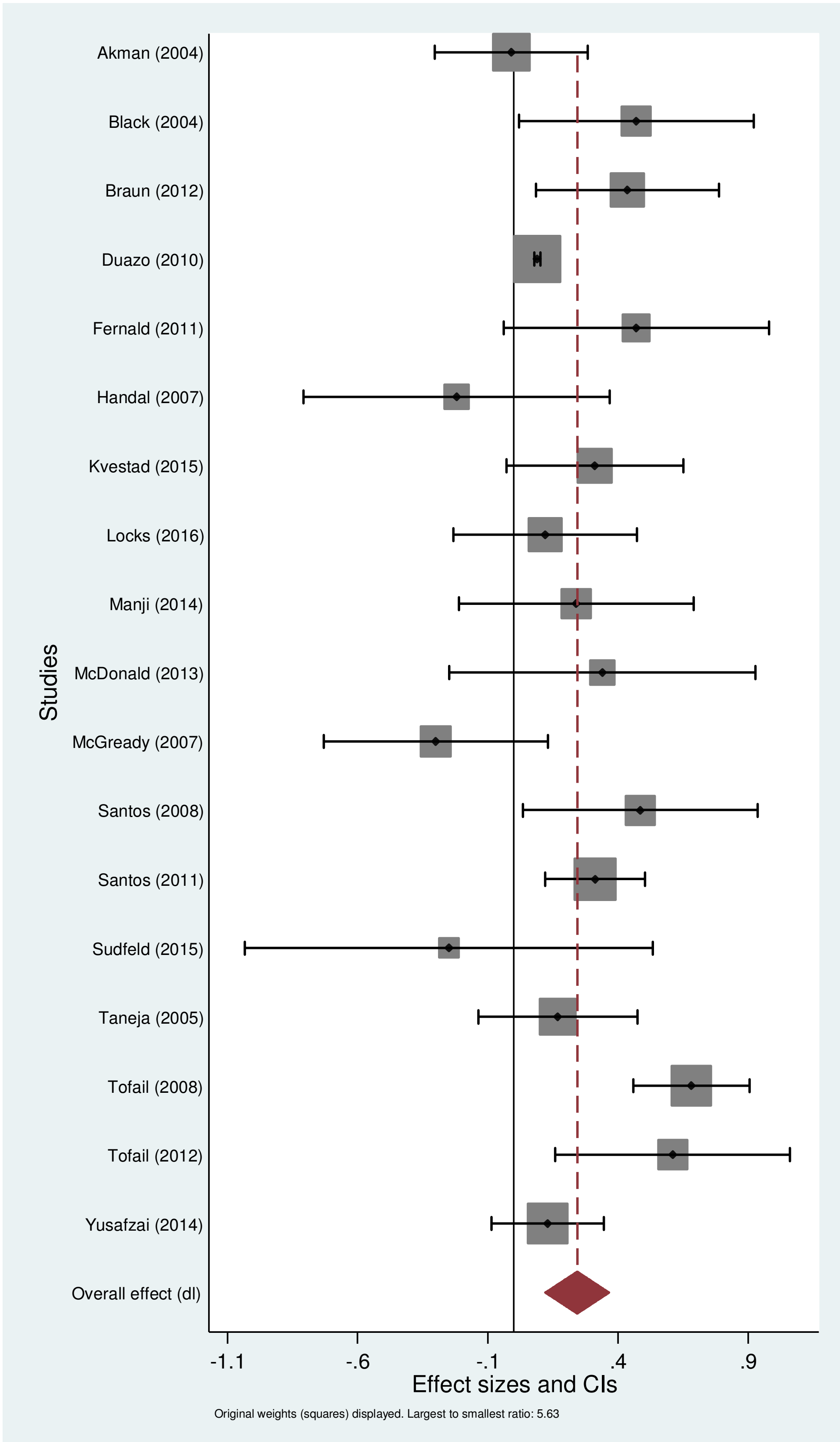

Figure 59: Association between maternal higher education (reference: primary education) and motor development.

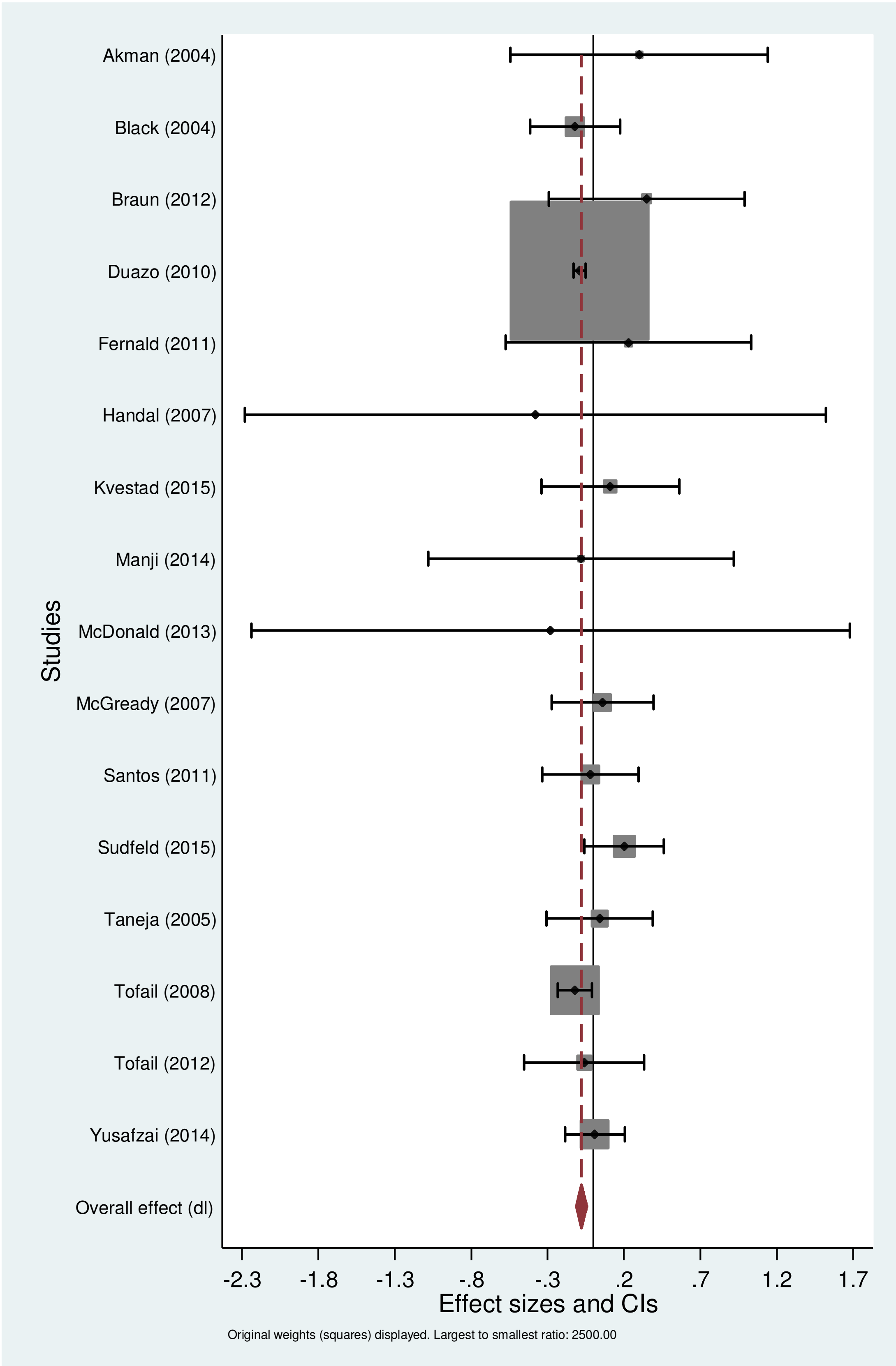

Figure 60: Association between no paternal education (reference: primary education) and motor development.

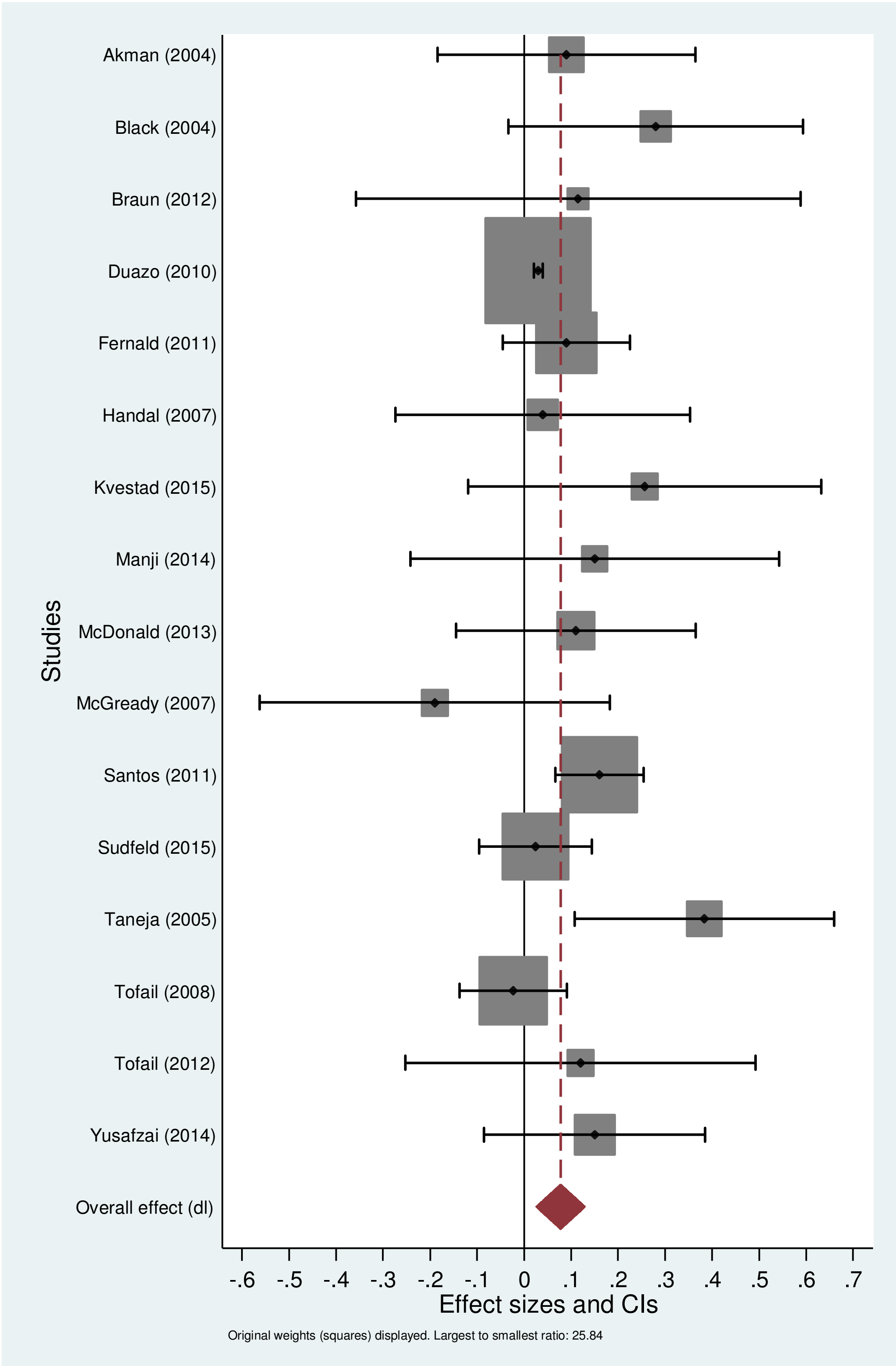

Figure 61: Association between paternal secondary education (reference: primary education) and motor development.

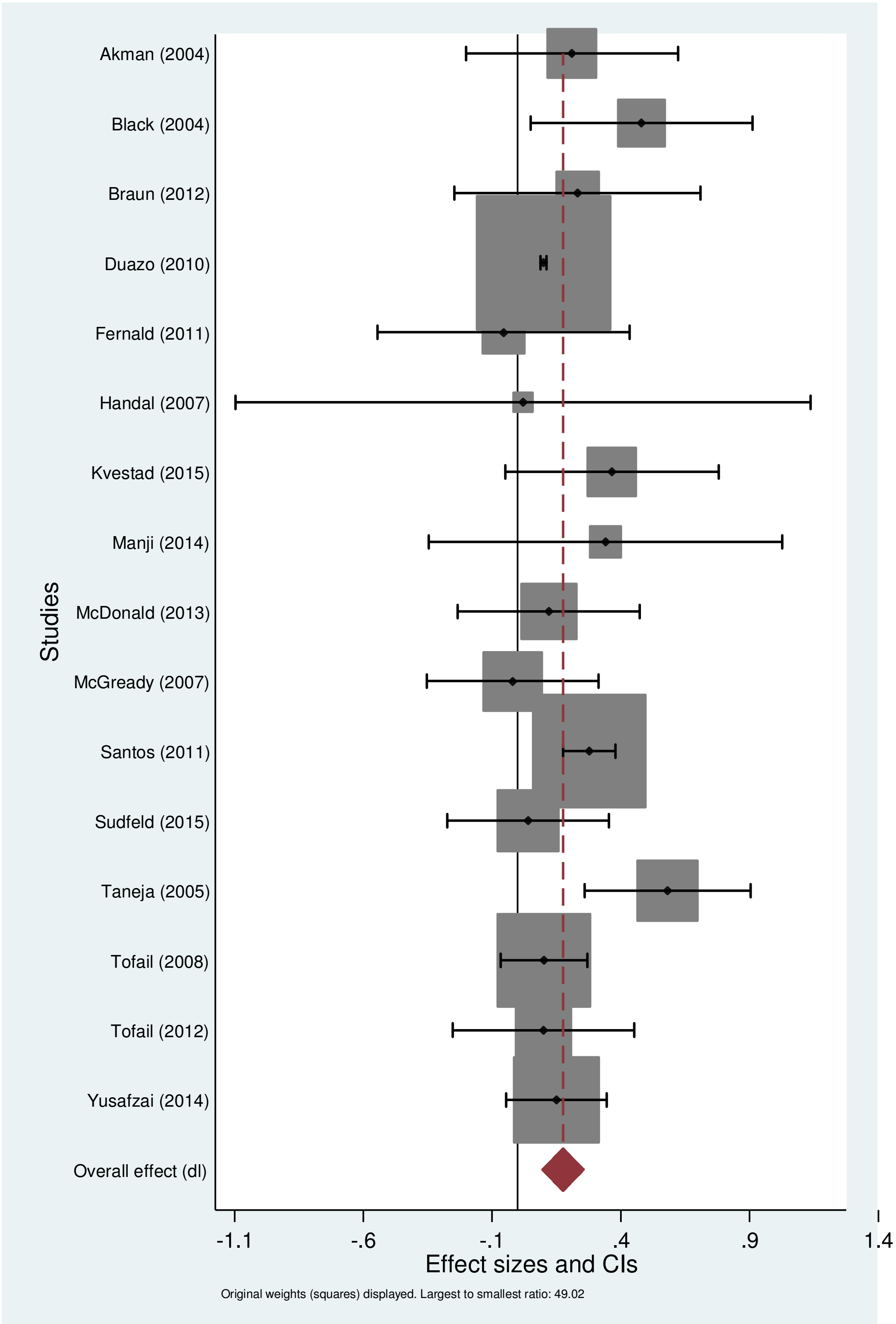

Figure 62: Association between paternal higher education (reference: primary education) and motor development.

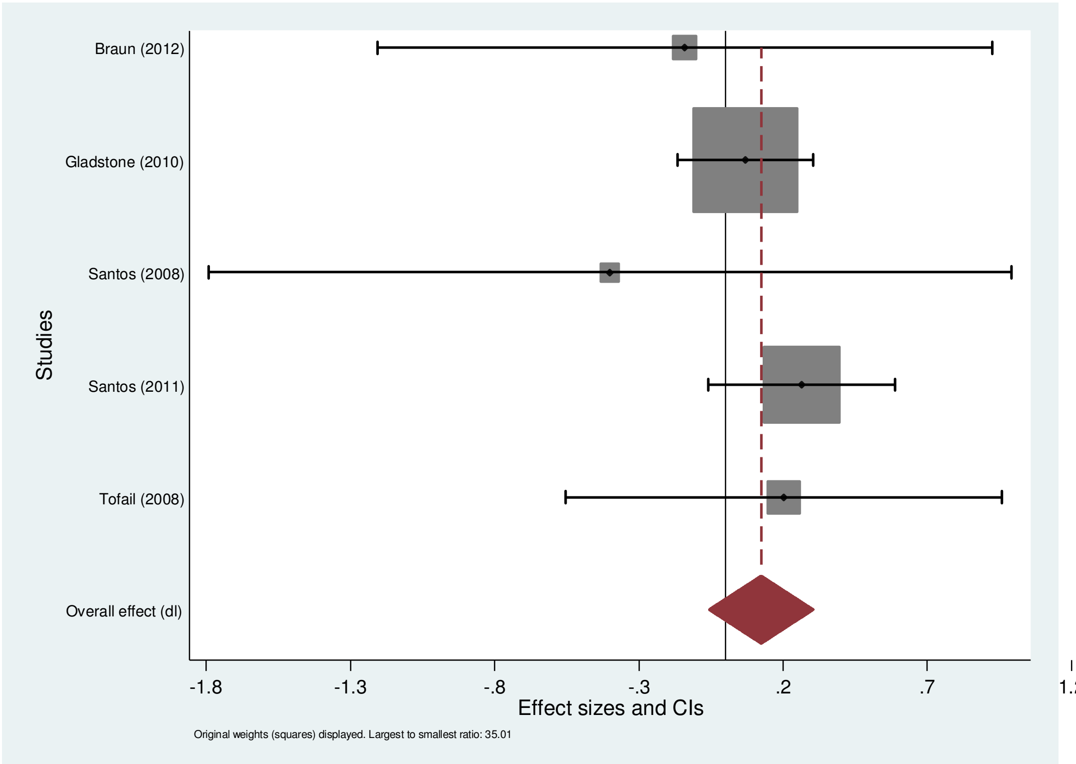

Figure 63: Association between maternal ages < 15 (reference: ages 20-34) and motor development.

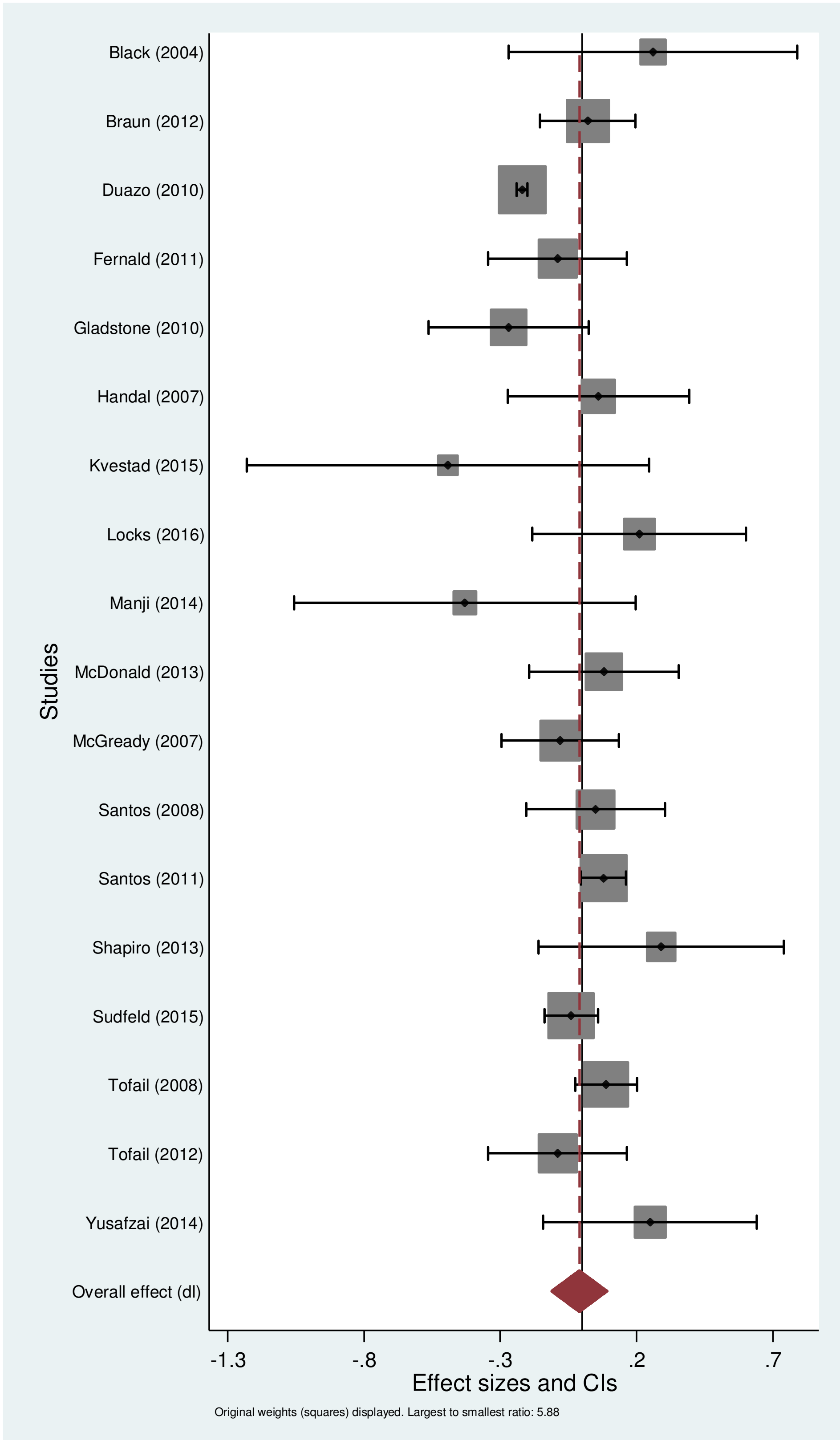

Figure 64: Association between maternal ages 15-20 (reference: ages 20-34) and motor development.

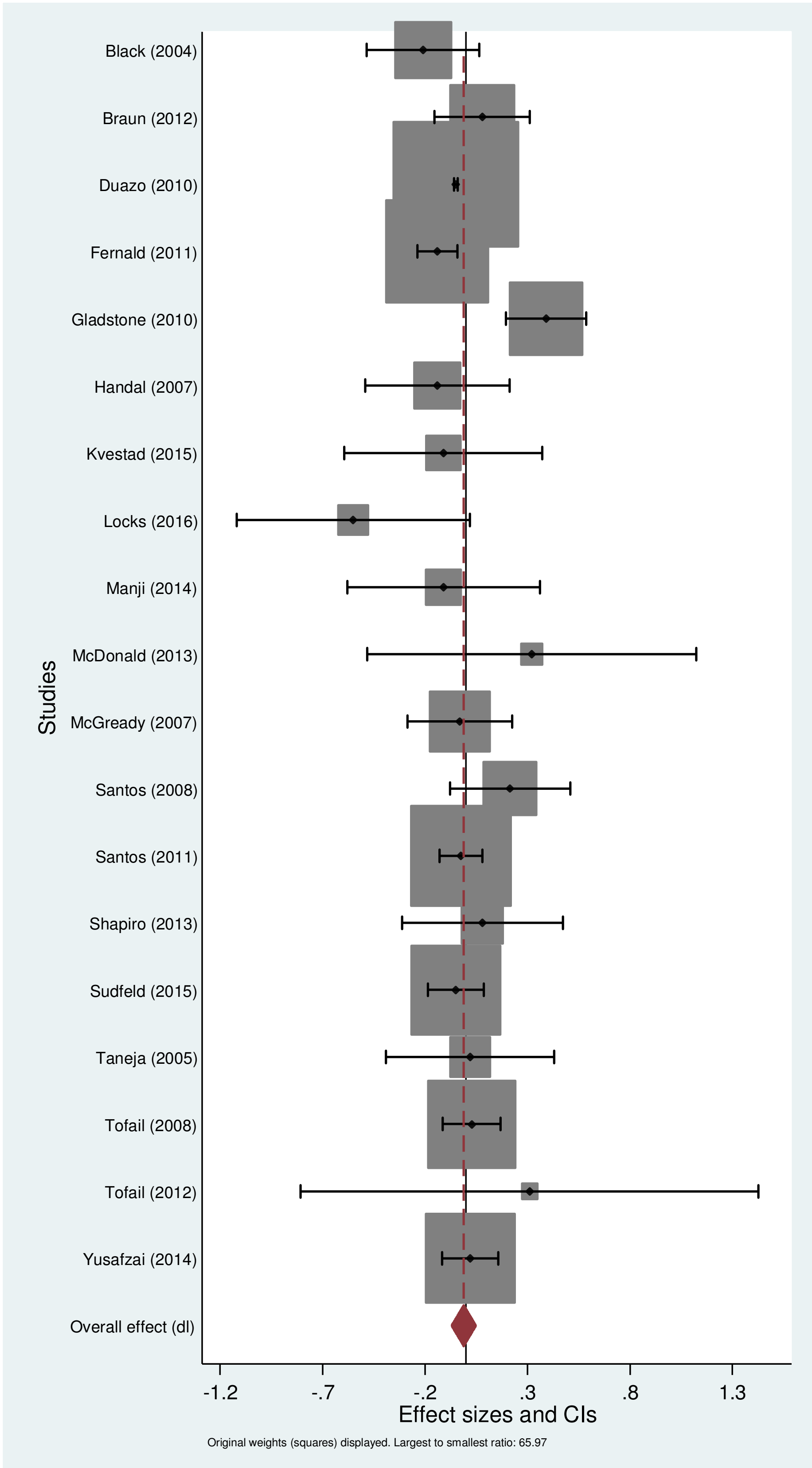

Figure 65: Association between maternal ages >35 (reference: ages 20-34) and motor development.

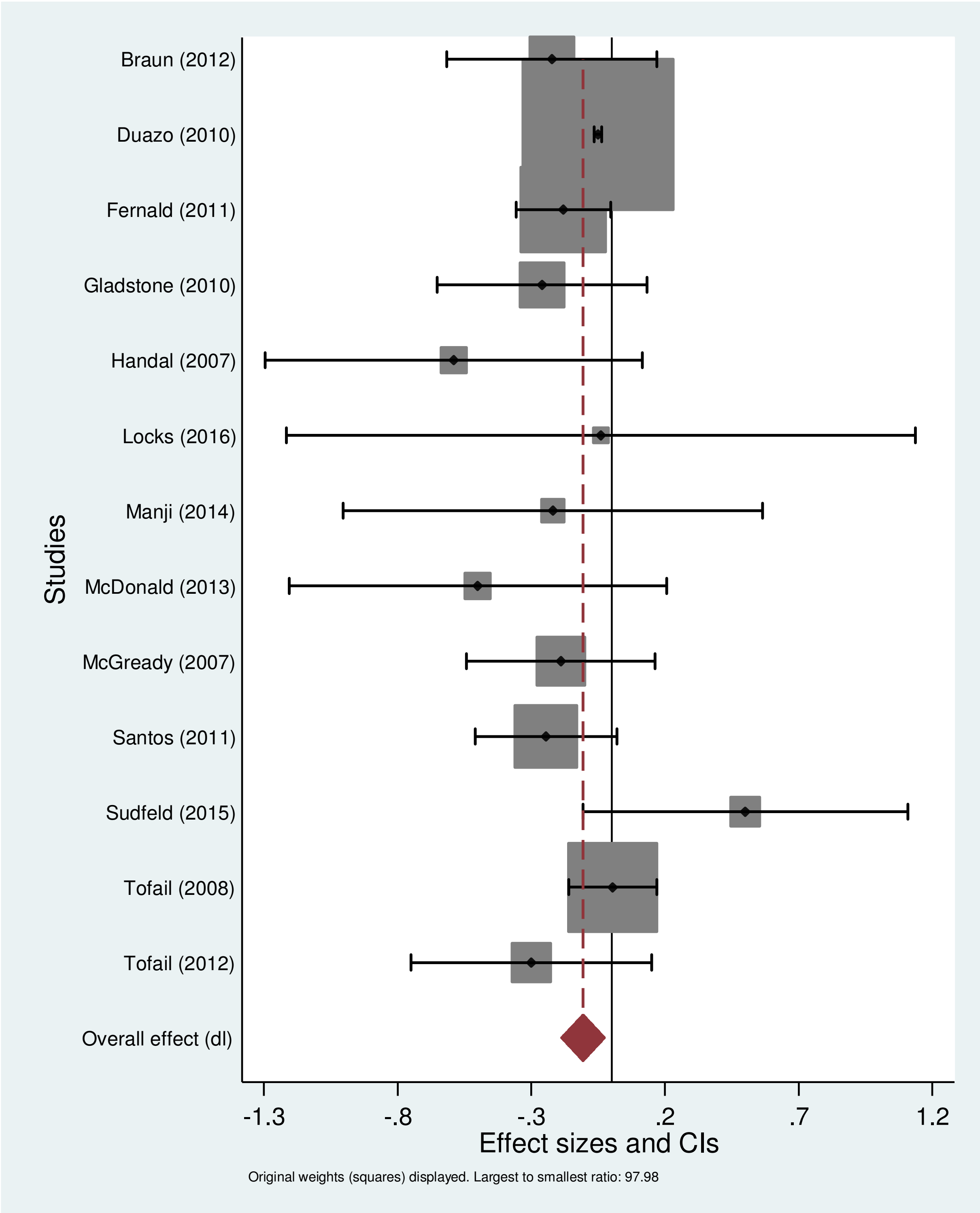

Figure 66: Association between maternal height <145 (reference: >155 cm) and motor development.

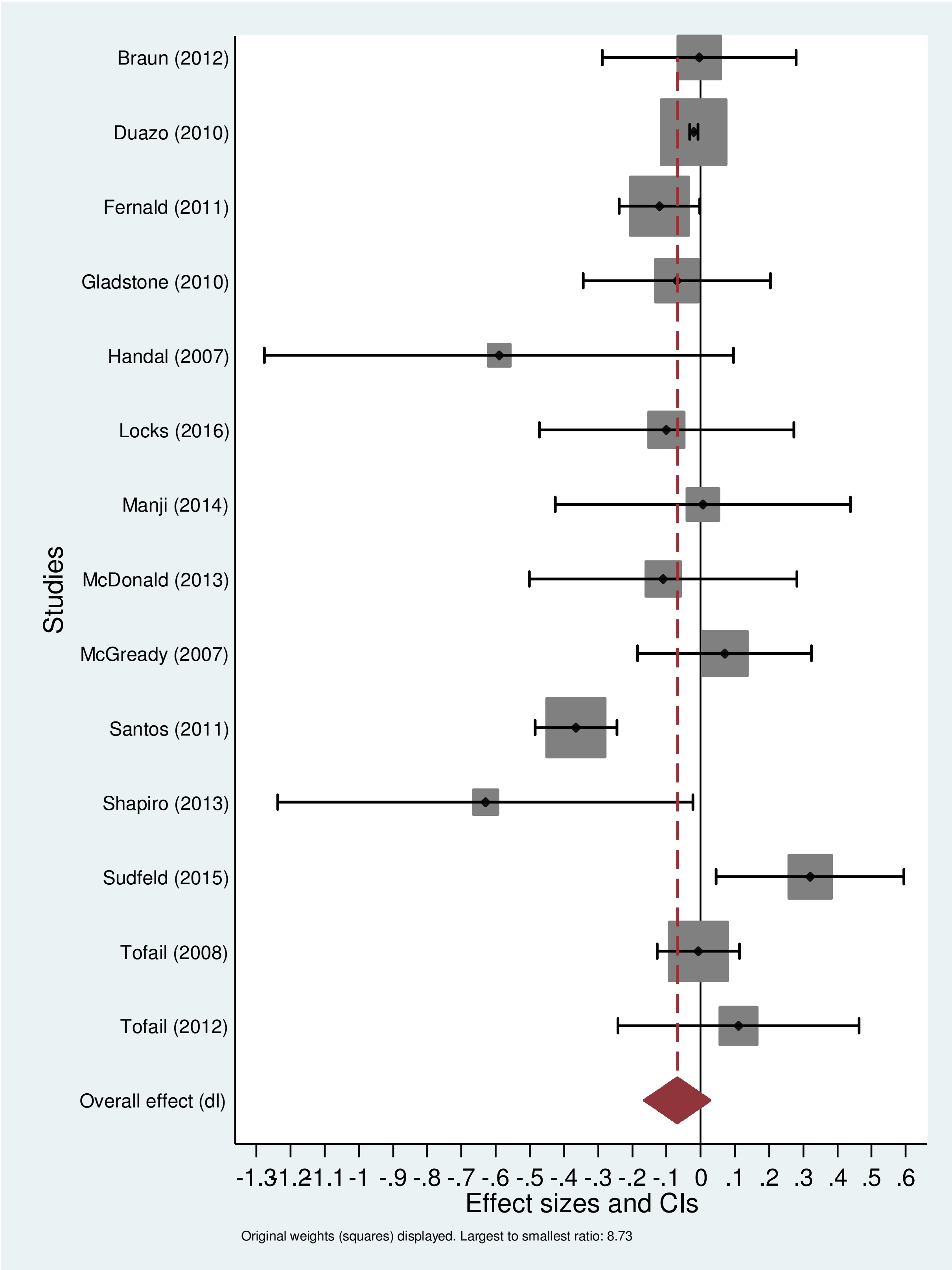

Figure 67: Association between maternal height 145-150 (reference: >155 cm) and motor development.

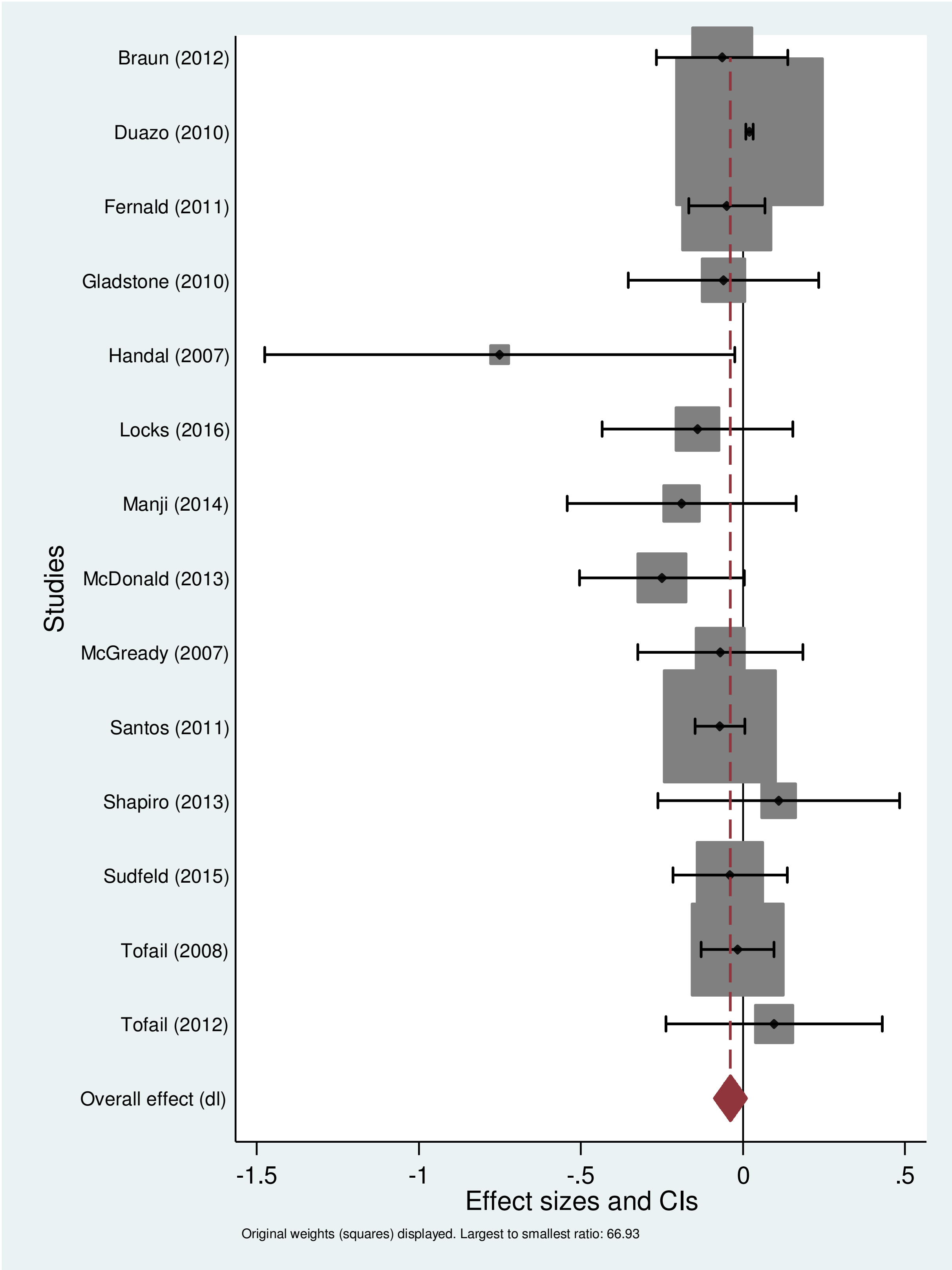

Figure 68: Association between maternal height 150-155 (reference: >155 cm) and motor development.

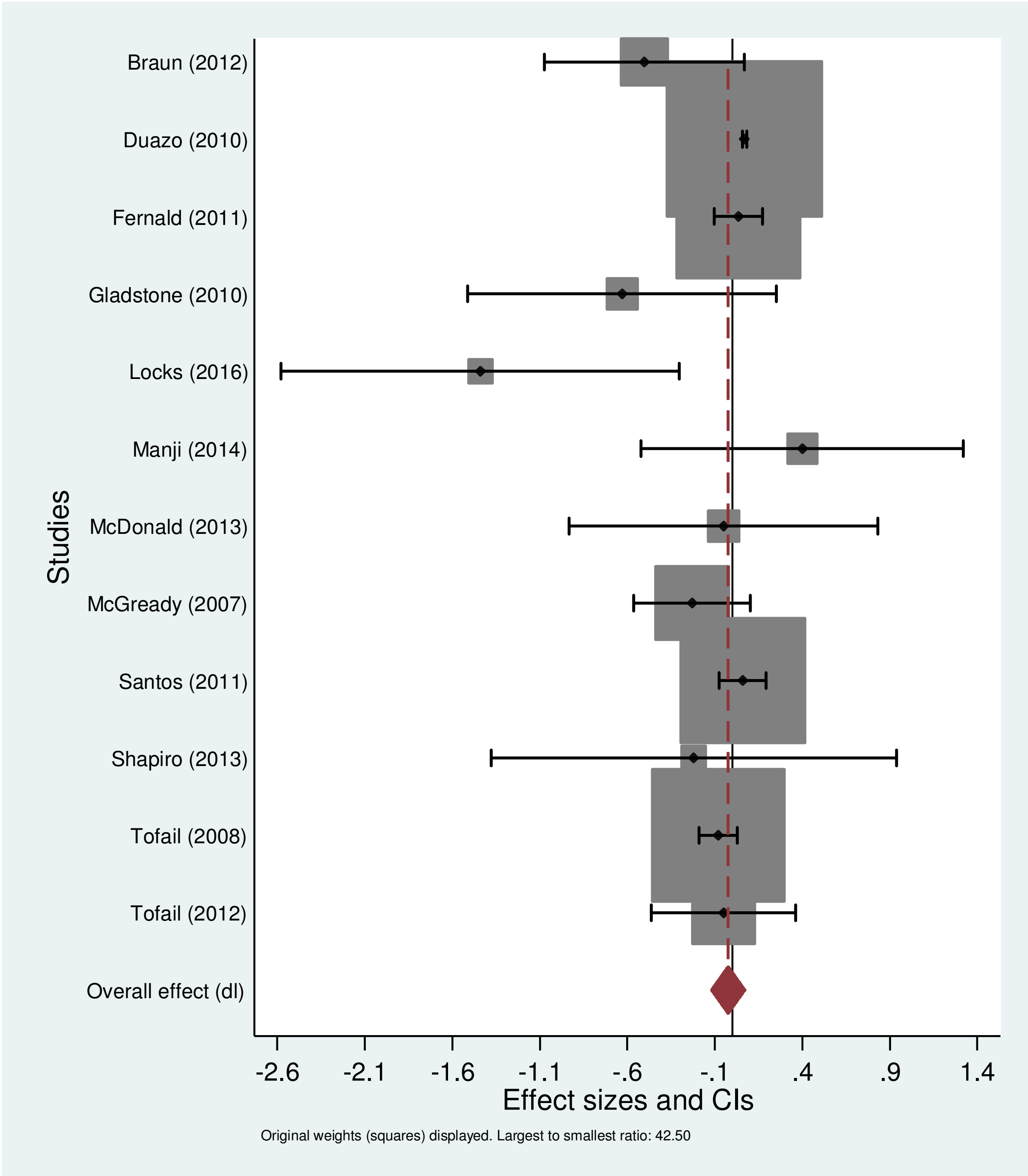

Figure 69: Association between maternal BMI <18.5 kg/m² (reference: 18.5-25) and motor development.

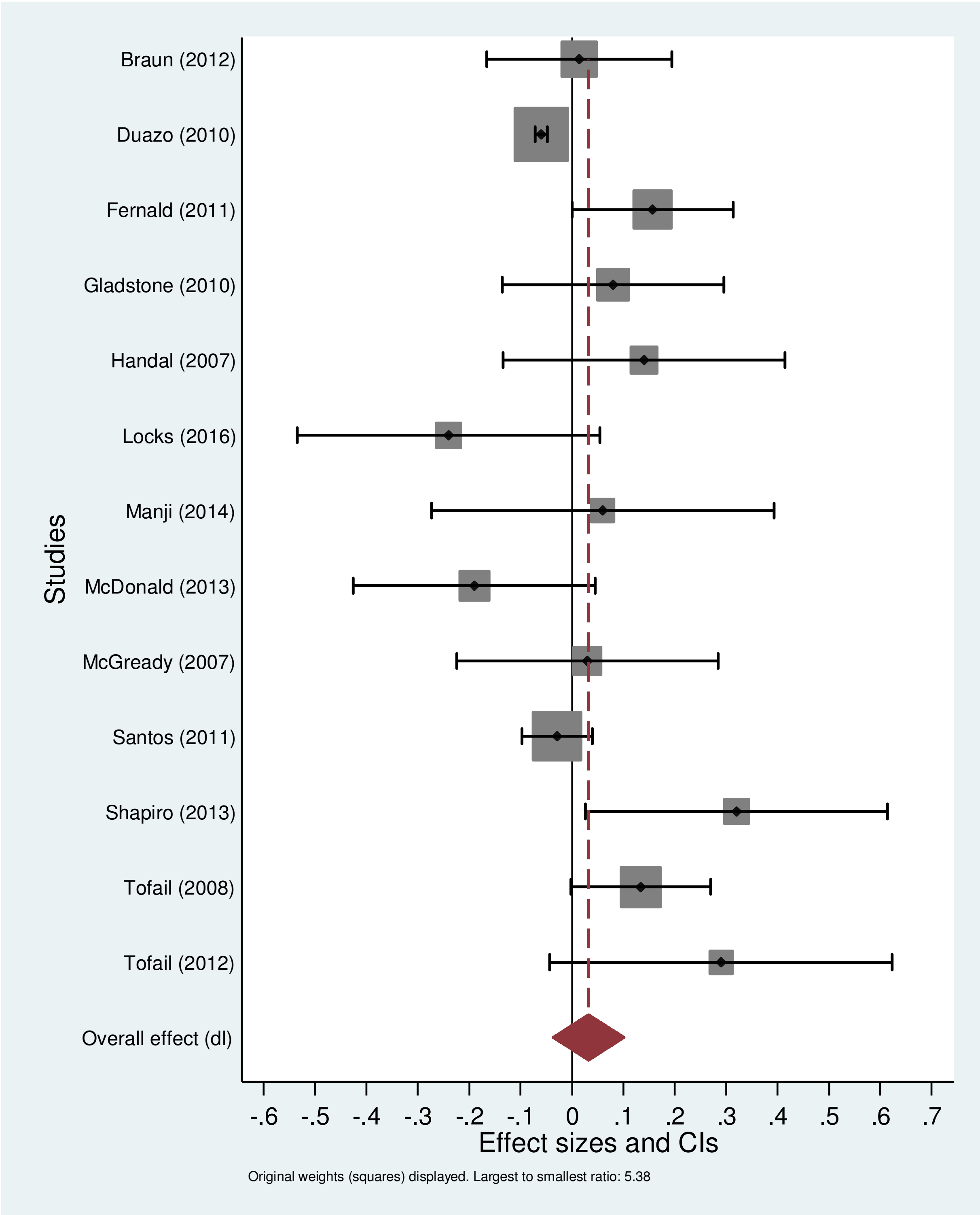

Figure 70: Association between maternal BMI <25-30 kg/m² (reference: 18.5-25) and motor development.

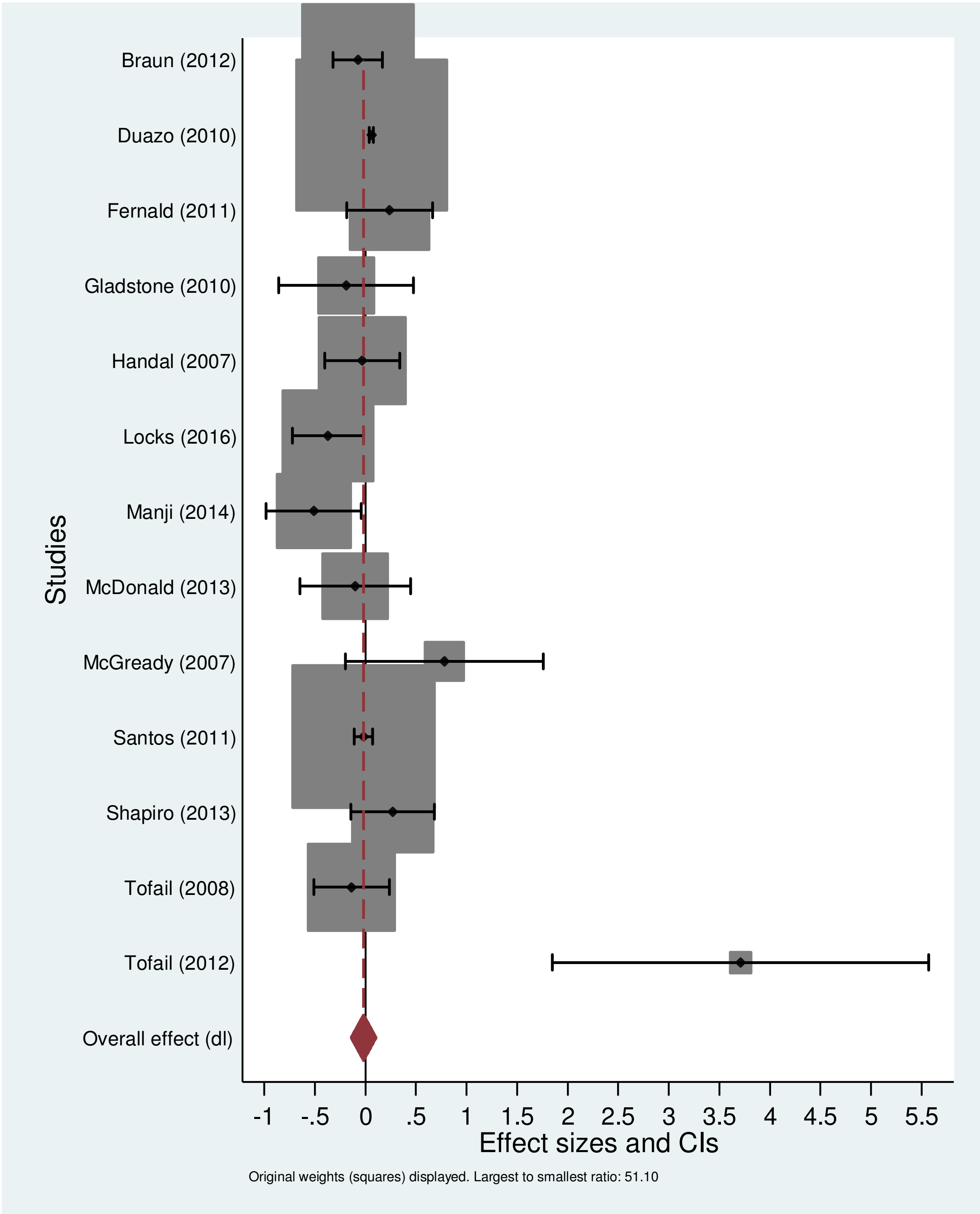

Figure 71: Association between maternal BMI >30 kg/m² (reference: 18.5-25) and motor development.

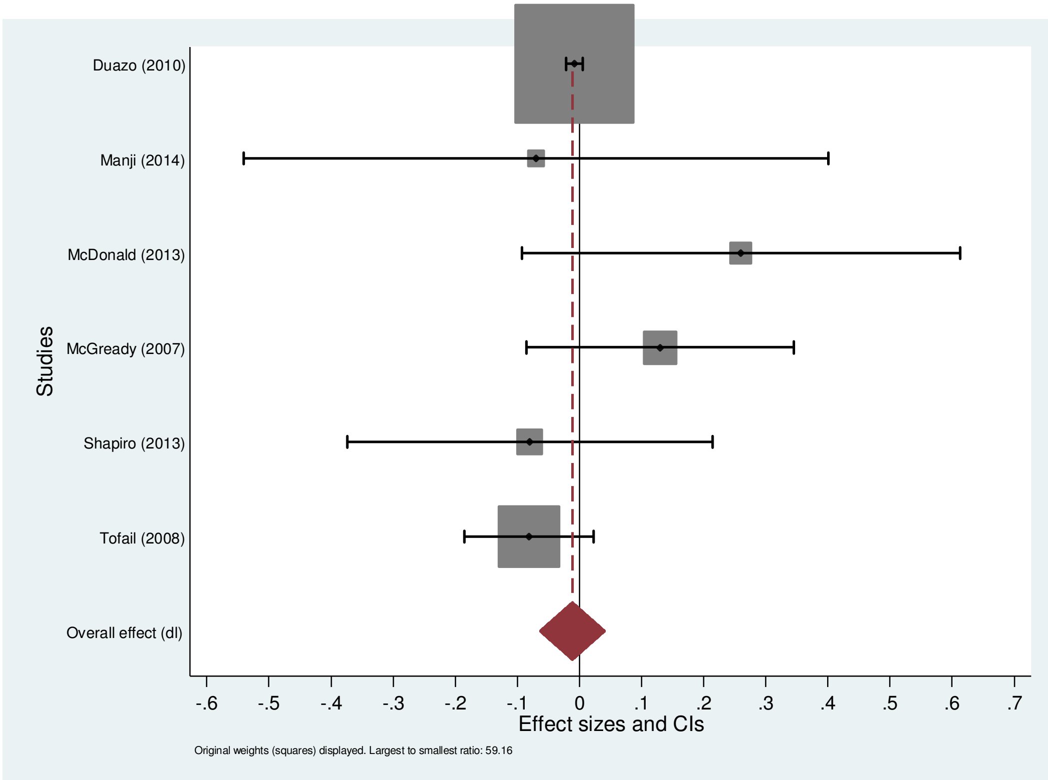

Figure 72: Association between maternal mild anemia (reference: no anemia) and motor development.

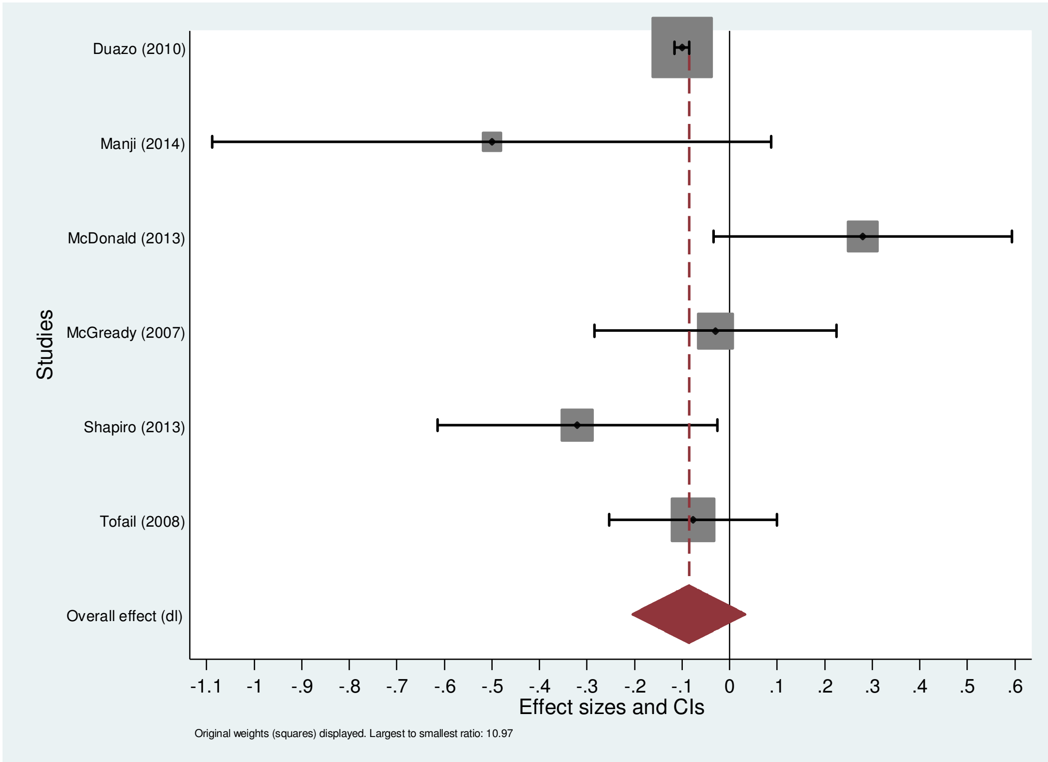

Figure 73: Association between maternal moderate anemia (reference: no anemia) and motor development.

6. Parental Risk Factors on Child's Language Development

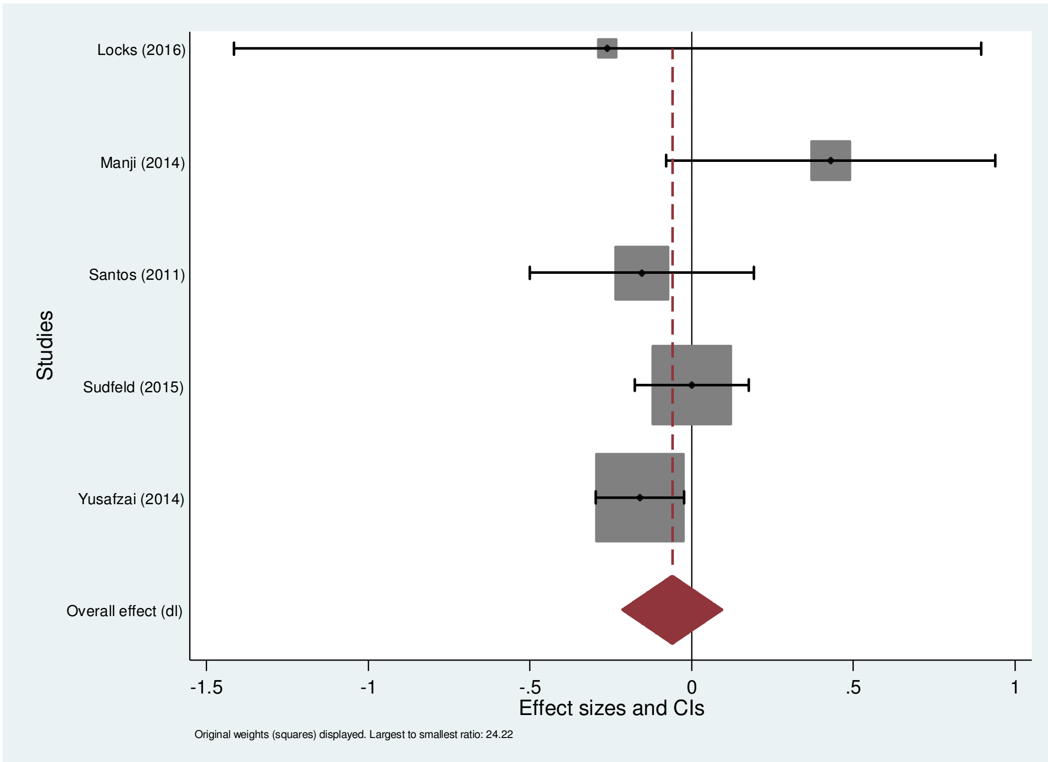

Figure 74: Association between no maternal education (reference: primary education) and language development.

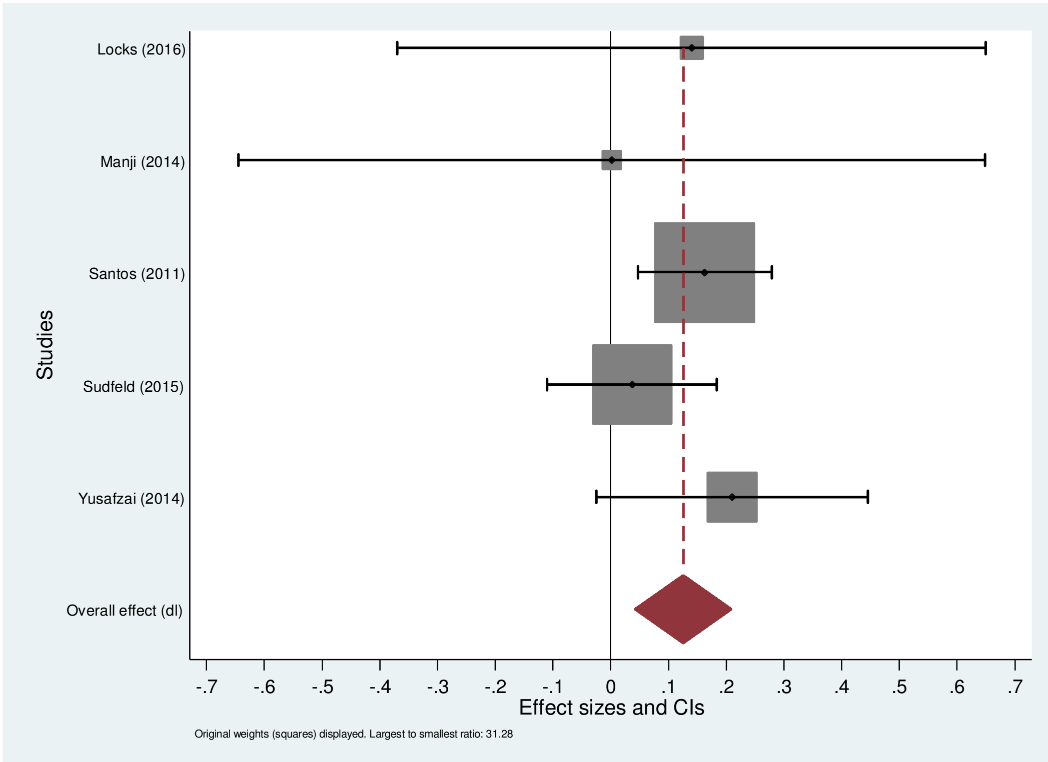

Figure 75: Association between maternal secondary education (reference: primary education) and language development.

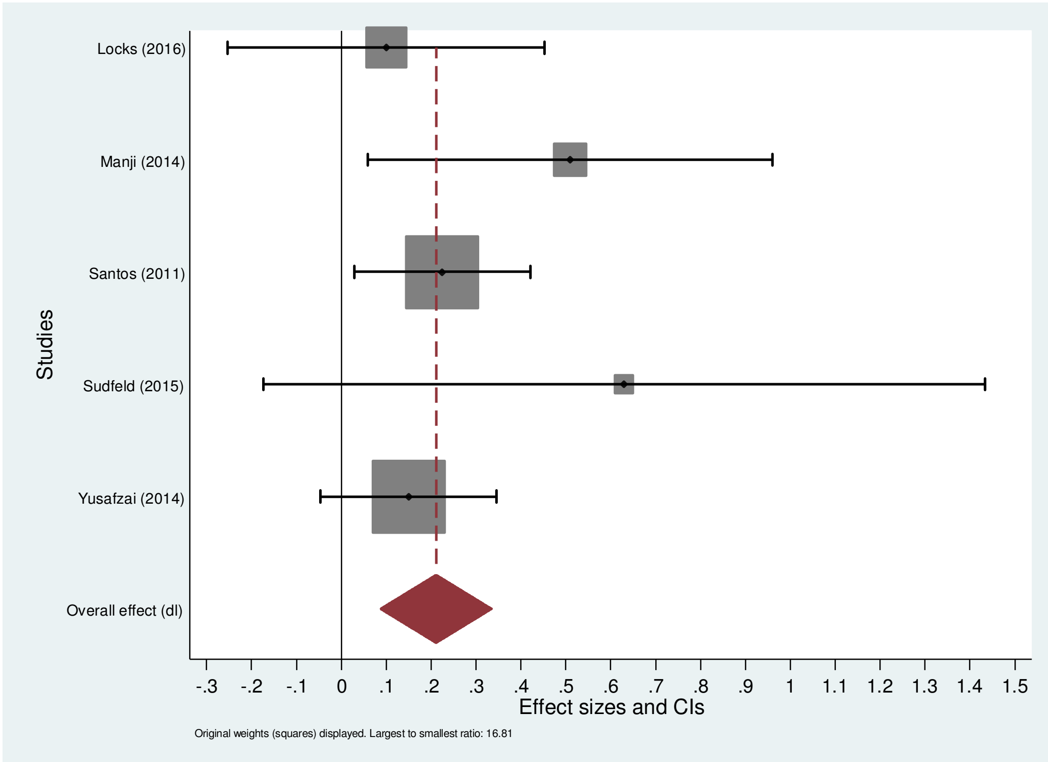

Figure 76: Association between maternal higher education (reference: primary education) and language development.

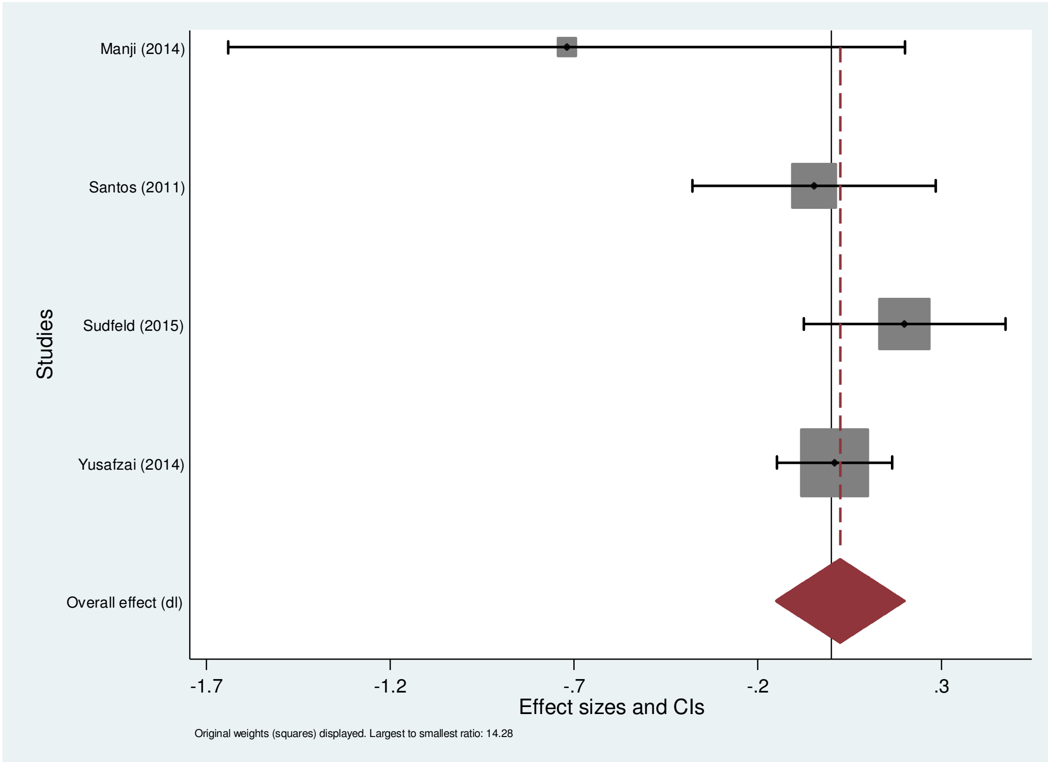

Figure 77: Association between no paternal education (reference: primary education) and language development.

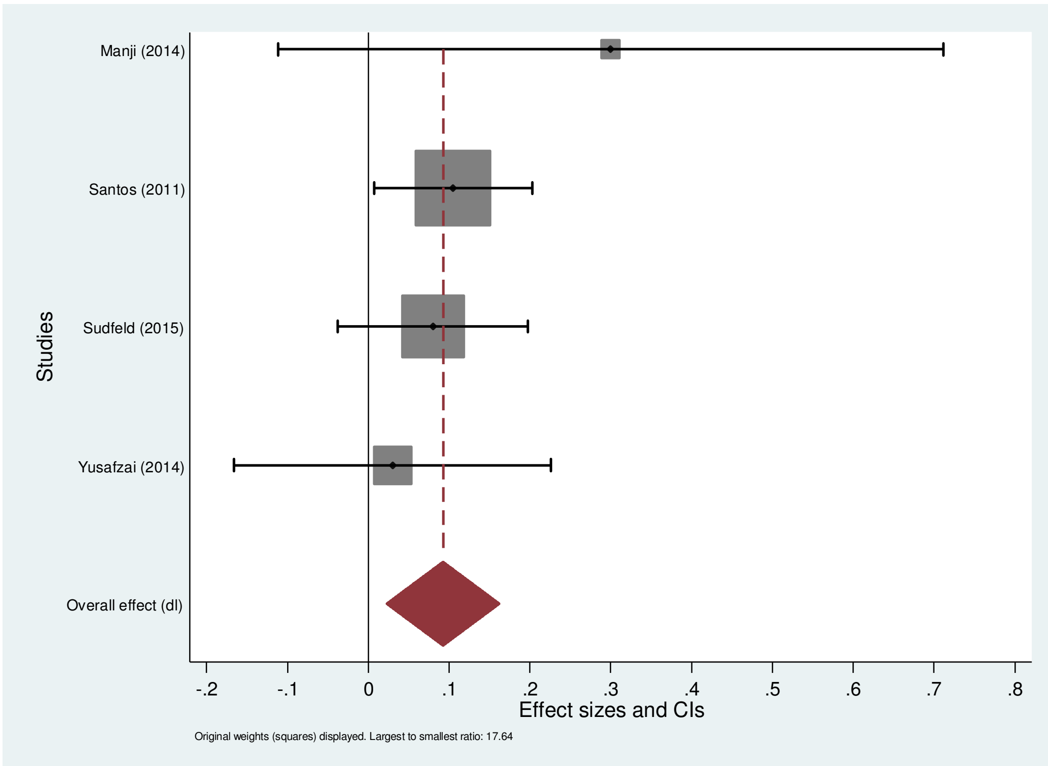

Figure 78: Association between paternal secondary education (reference: primary education) and language development.

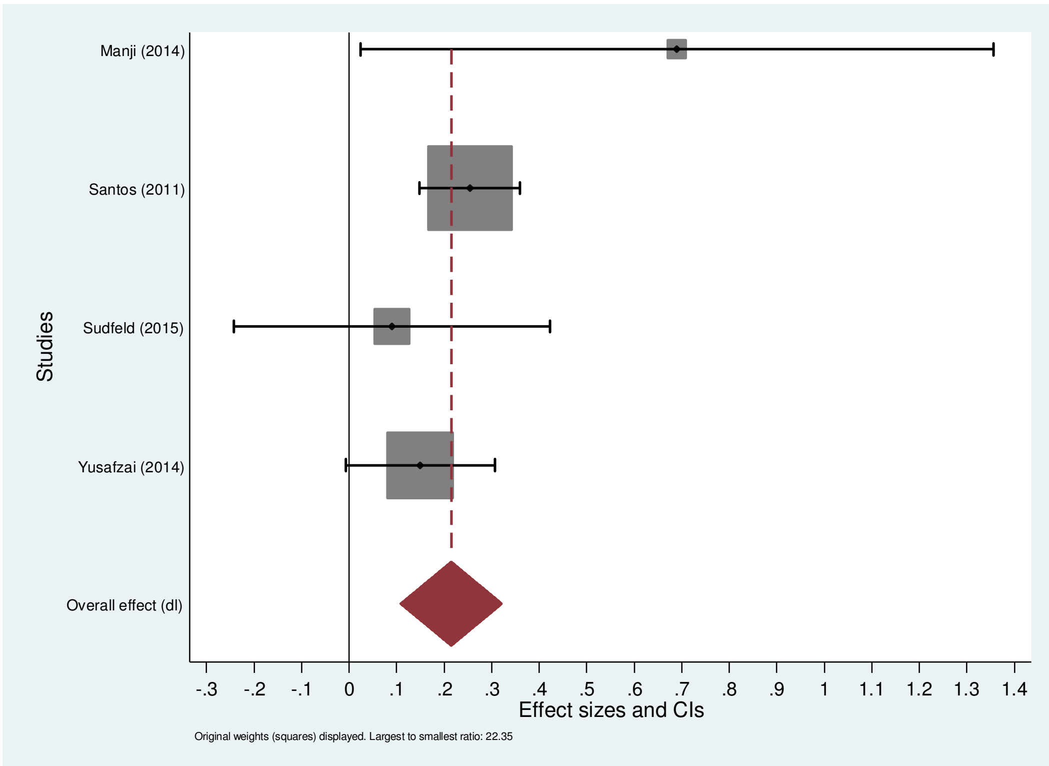

Figure 79: Association between paternal higher education (reference: primary education) and language development.

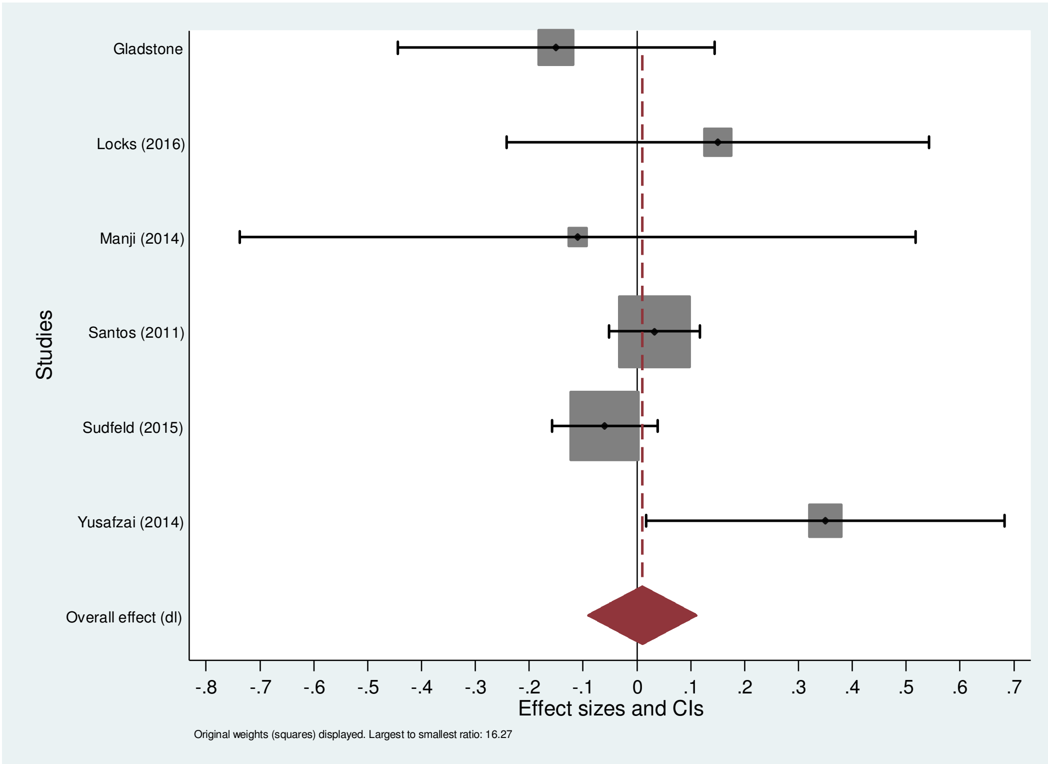

Figure 80: Association between maternal ages 15-20 (reference: ages 20-34) and language development.

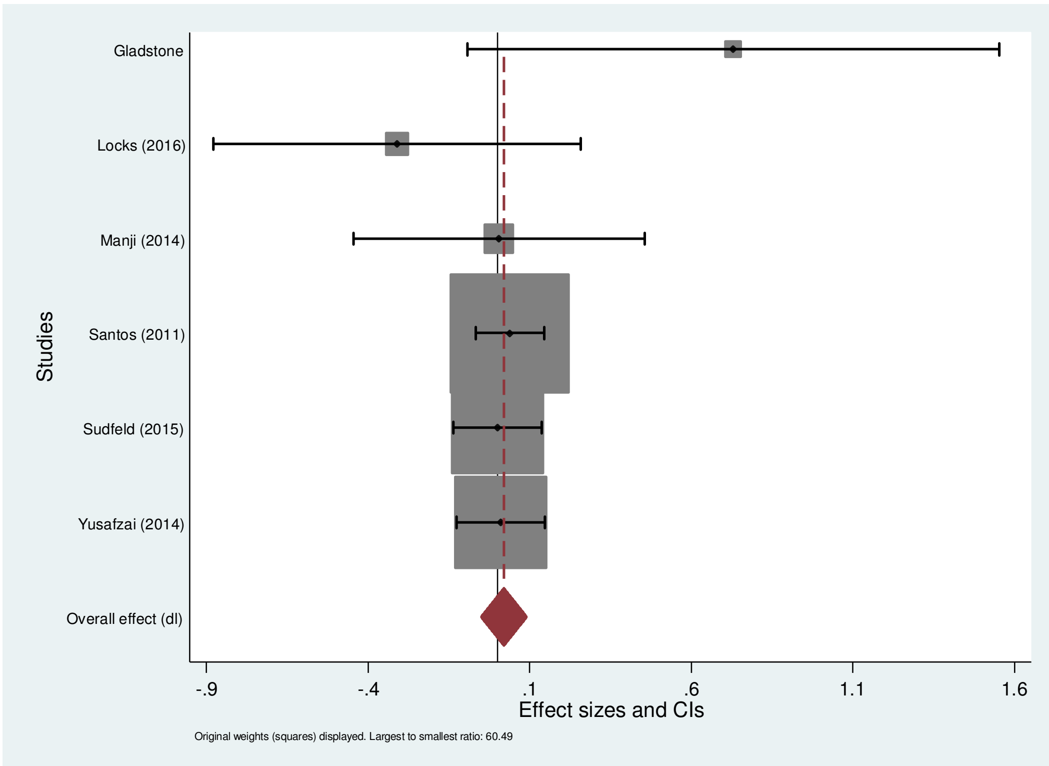

Figure 81: Association between maternal ages >35 (reference: ages 20-34) and language development.

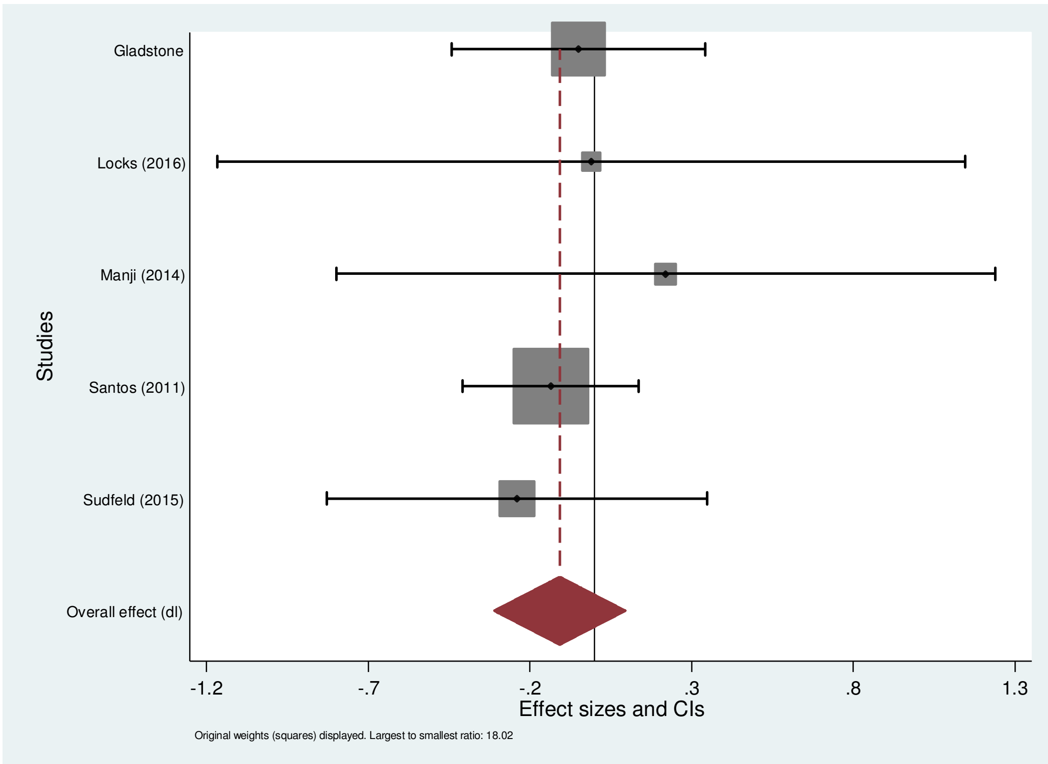

Figure 82: Association between maternal height <145 cm (reference: >155 cm) and language development.

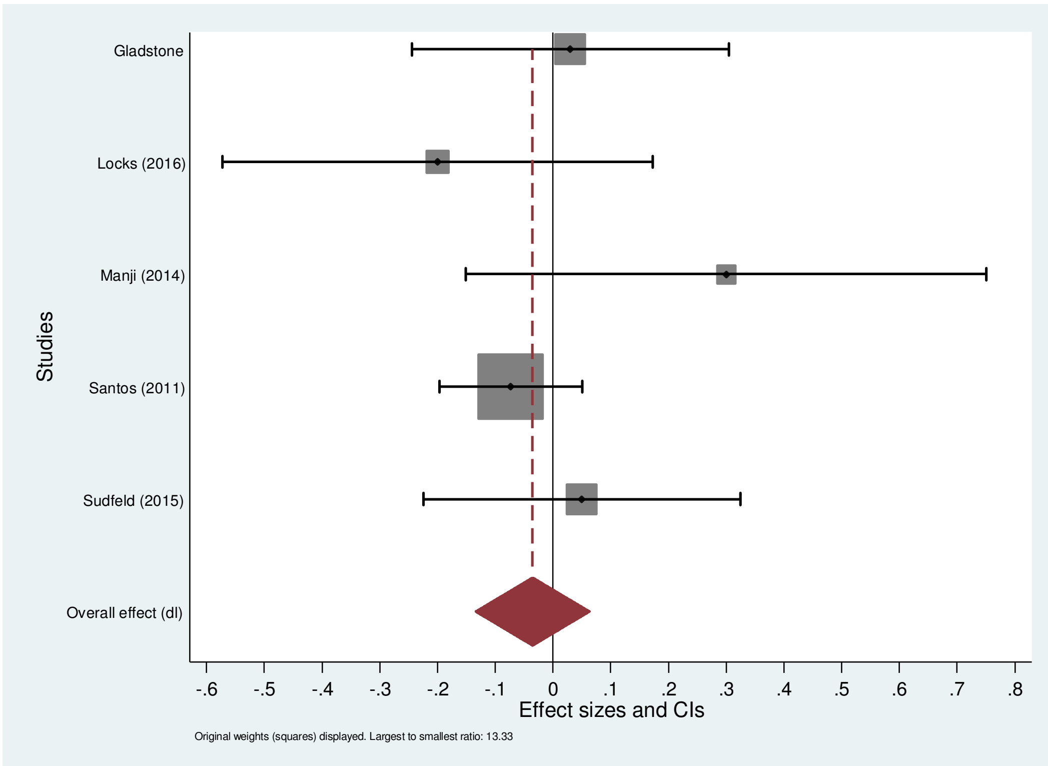

Figure 83: Association between maternal height 145-150cm (reference: >155 cm) and language development.

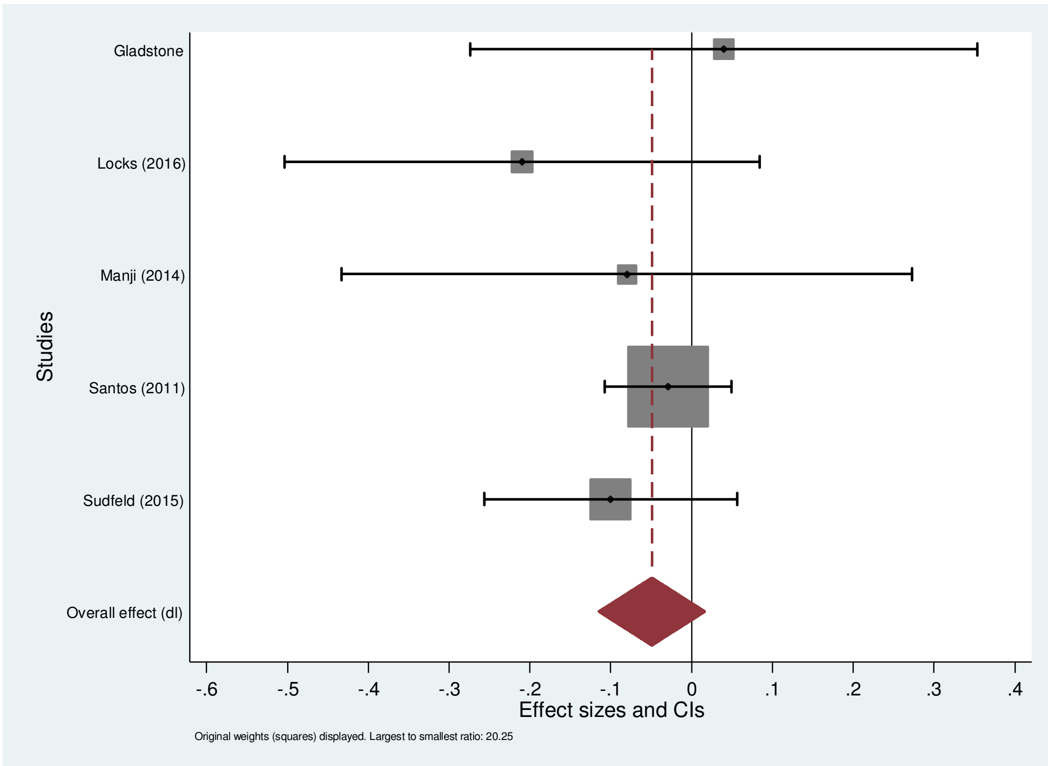

Figure 84: Association between maternal height 150-155 cm (reference: >155 cm) and language development.

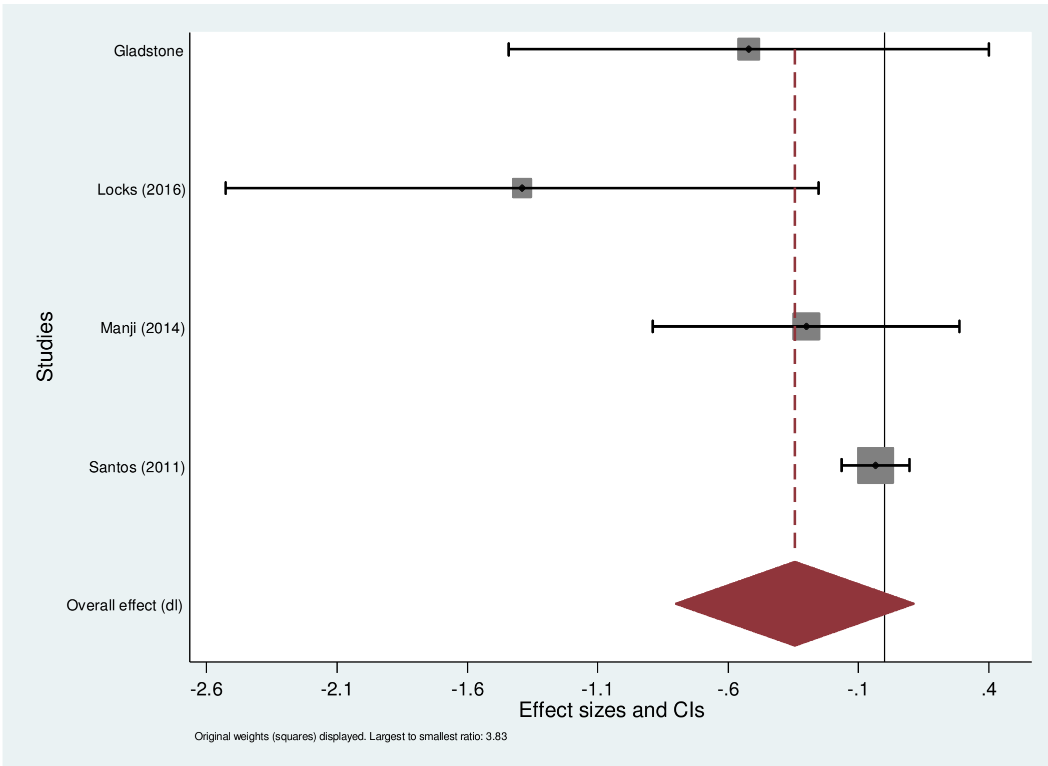

Figure 85: Association between maternal BMI 25-30 kg/m² (reference: 18.5-25) and language development.

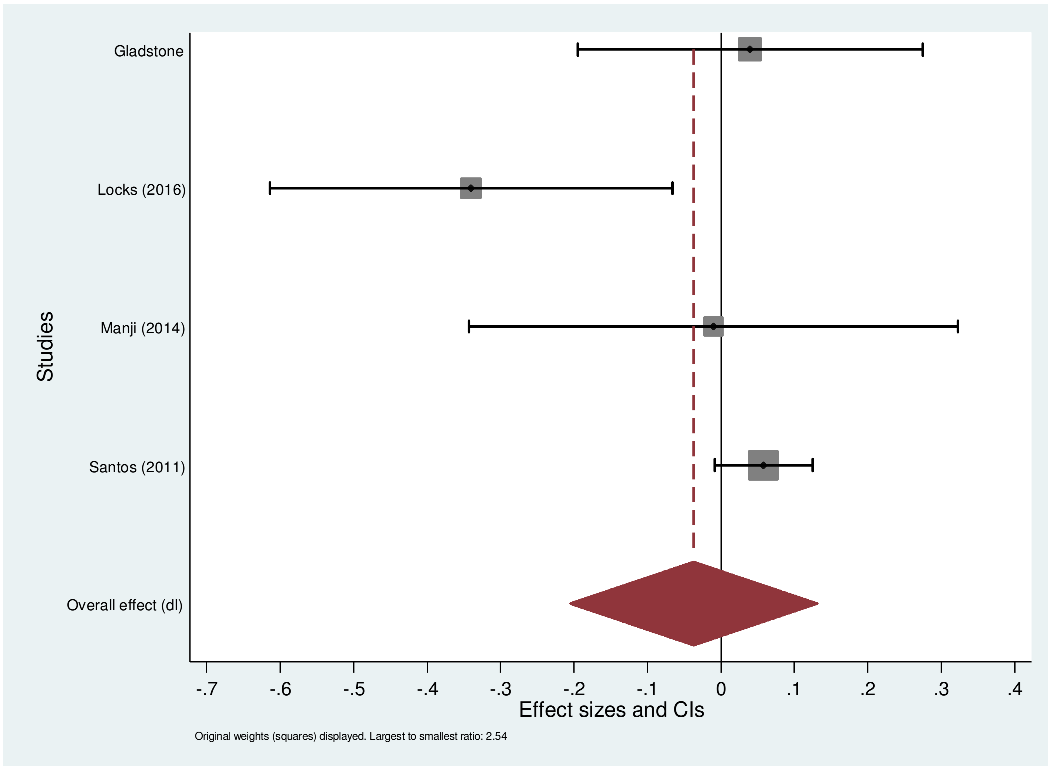

Figure 86: Association between maternal BMI >30 kg/m² (reference: 18.5-25) and language development.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	No
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6-7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration numbers.	yes
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8 & 10
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	N/A[a]
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A[b]
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A[b]
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Appendix 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Tables 2 and 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A[b]
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11-13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18 &19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	3

a. Same analyses were conducted in all individual studies by the authors and then estimates from individual studies were combined in pooled estimates. Therefore, assessment of quality of individual studies were not done.
b. Selection of studies were not based on published literature only, a large number of the studies were unpublished

PRISMA 2009 Checklist

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

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BMJ Open

Early life risk factors of motor, cognitive, and language development: a pooled analysis of studies from low-and middle-income countries

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Primary Subject Heading:	Global health
Secondary Subject Heading:	Epidemiology, Paediatrics, Public health
Keywords:	Community child health < PAEDIATRICS, Developmental neurology & neurodisability < PAEDIATRICS, PUBLIC HEALTH

Early life risk factors of motor, cognitive, and language development: a pooled analysis of studies from low-and middle-income countries

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Short title: Risk factors of child development in LMIC

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Potential Conflicts of Interest: The authors have no conflicts of interest relevant to this article to disclose

Ethics committee approval: The pooled study was approved by the Harvard T.H. Chan School of Public Health (IRB16-0256).

Abbreviations:
AGA= Appropriate for gestational age
BSID=Bayley Scales of Infant and Toddler Development
IUGR= intra-uterine growth restriction
LBW= Low birth weight, <2500 grams
LMIC= Low-and-middle income countries
LMP= last menstrual period
ECD=Early childhood development
SDGs=Sustainable Development Goals
SMDs=standardized mean differences
SGA=Small-for-gestational age

Data availability:

Data included in the study may be available upon request. This study contains deidentified data from 21 studies. Of them, 14 investigators have shared their data with researchers at Harvard School of Public Health and seven shared results of analyses. Therefore, permission from investigators of individual studies needs to be obtained before data sharing.
All forest plots of the metanalyses of each risk factors have been uploaded as supplementary document and will be publicly available.

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Authors' contributions:

Ayesha Sania conceptualized the study, conducted the literature review, data analysis and drafted the manuscript. Christopher Sudfeld, and Wafaie Fawzi conceptualized the study and drafted the manuscript. Goodarz Danaei, Günther Fink, Dana Charles McCoy, Mary C. Smith Fawzi and Majid Ezzati provided critical input in the study design, interpretation of results and reviewed the manuscript. Zhaozhong Zhu participated in literature review and data analysis for the study. Mehmet Akman, Shams Arifeen, Aluísio J. D. Barros, David Bellinger, Maureen Black, Alemtsehay Bogale, Joseph Braun, Nynke van den Broek, Verena Ilona Carrara, Paulita Duazo, Christopher P. Duggan, Lia Fernald, Melissa Gladstone, Jena Hamadani, Alexis J. Handal, Siobán Harlow, Melissa Hidrobo, Christopher W. Kuzawa, Ingrid Kvestad, Lindsey Locks, Karim Manji, Honorati Masanja, Alicia Matijasevich, Christine McDonald, Rose McGready, Arjumand Rizvi, Darci Santos, Leticia Santos, Dilsad Save, Roger Shapiro, Barbara J. Stoecker, Tor A. Strand, Sunita Taneja, Martha-Maria Tellez-Rojo, Fahmida Tofail, and Aisha K.Yousafzai contributed data to the study, analyzed data and reviewed the manuscript. All authors had full access to their respective study data and to all statistical reports and tables of the pooled analyses and can take responsibility for the integrity of the data and accuracy of data analyses. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Abstract:

Objective: To determine the magnitude of relationships of early life factors with child development in LMICs.

Design: Meta-analyses of standardized mean differences (SMD) estimated from published and unpublished data.

Data sources: We searched Medline, bibliographies of key articles and reviews, and grey literature to identify studies from LMICs that collected data on early life exposures and child development. The most recent search was done on November 4, 2014. We then invited the first authors of the publications and investigators of unpublished studies to participate in the study.

Eligibility criteria for selecting studies: Studies that assessed at least one domain of child development in at least 100 children under 7 years of age and collected at least one early life factor of interest were included in the study.

Analyses: Linear regression models were used to assess SMDs in child development by parental and child factors within each study. We then produced pooled estimates across studies using random effects meta-analyses.

Results: We retrieved data from 21 studies including 20,882 children across 13 LMICs, to assess the associations of exposure to 14 major risk factors with child development. Children of mothers with secondary schooling had 0.14 SD (95% Confidence Interval, CI: 0.05, 0.25) higher cognitive scores compared to children whose mothers had primary education. Preterm birth was associated with 0.14 SD (-0.24, -0.05) and 0.23 SD (-0.42, -0.03) reductions in cognitive and motor scores, respectively. Maternal short stature, anemia in infancy, and lack of access to clean water and sanitation had significant negative associations with cognitive and motor development with effects ranging from -0.18 to -0.10 SDs.

Conclusions: Differential parental, environmental, and nutritional factors contribute to disparities in child development across LMICs. Targeting these factors from pre-pregnancy through childhood may improve health and development of children.

Funding: Grand Challenges Canada under the Saving Brains program (grant # 0073-03), National Institute of Health (grant # T32AI114398).

Strengths and Limitations of this study:

- Pooling data from 21 studies, this study provides the most comprehensive analysis of early life risk factors of child development in low-and middle-income countries
- The study cohorts were selected from 13 countries across the globe
- Uniform classifications of early life exposures and statistical analyses applied across studies
- 14 major risk factors, - parental, environmental and nutritional factors are included
- Data on important risk factors such as exposure to environmental neurotoxicants, responsive parenting behaviors, and child stimulation were not available

Introduction:

More than 250 million children under age 5 years in low-and middle-income countries (LMICs) are at risk of not attaining their full development potential.[1-3] The first 1000 days (from conception through 24 months of age) is critical for children's development, as the plasticity of the rapidly developing brain makes it vulnerable to harmful exposures as well as receptive to positive stimuli during this period.[4 5] Suboptimal development in early childhood may have long-term detrimental effects on education[6] and income attainment,[7] which in turn contribute to poverty and inequality across the lifecycle, and possibly also across generations.[8] Disadvantaged children with developmental deficits lose an estimated 19.8% of adult income yearly,[9] with an estimated global cost of US$ 177 billion for physical growth delays alone.[10] In recognition of the high burden and cost associated with early life disadvantage, the 2030 Sustainable Development Goals (SDGs) directly target early childhood development under SDG 4,[11] which calls for ensuring access to quality early childhood development care and pre-primary education for all children.

The relative importance of exposures to nutritional, socioeconomic and environmental risk factors in early life on different domains of child development in LMICs is poorly understood. Studies systematically reviewing the evidence linking early life risk factors to child outcomes primarily focused on growth (e.g., stunting),[9 12] identifying iodine deficiency, iron deficiency anemia, intrauterine growth restriction, maternal depression, exposure to violence, HIV infection as risk factors, and cognitive stimulation, maternal education, breastfeeding as protective factors.[13 14] However, the independent pathways from these risks to cognitive, motor and language development are not fully elucidated yet.[15 16] Consequently, priority risk factors and

interventions for improving cognitive, language, and motor development may differ from those designed to improve physical development in LMICs.

To determine the magnitude of the relationships linking early life exposures with child development in LMICs, we pooled data from 21 studies conducted in LMICs. We then examined the associations of early life risk factors on cognitive, motor and language development among children aged less than 7 years across studies. These pooled observational estimates are intended to inform the design of individual and packaged intervention studies to promote early child development in LMICs.

Methods

Study identification:

We searched Medline, bibliographies of key articles and reviews, and grey literature to identify datasets from low-income and middle-income countries (LMICs) that collected data on early life exposures and child development. Search terms included a list of risk factors, terms related to motor, cognitive, language and socioemotional development, and a list of low and middle income countries (list of search terms, appendix 1). The most recent search was done on November 4, 2014. We also identified additional datasets via communication with researchers of published studies that were not retrieved in our search. The primary criterion for inclusion of the datasets was the assessment of at least one domain of child development (cognitive, motor, language and socioemotional) using a standard child development assessment instrument in at least 100 children before 7 years of age, as well as the collection of at least one early life factor of interest as part of the study.

Following identification of the potential datasets, we contacted 50 first authors of the publications and investigators of unpublished studies, of whom 33 (66%) responded to participate in the present study (figure 1). We asked researchers to complete a survey that included questions about child development assessment tools used, age of developmental assessment and details on the early life factors measured in their study. Following the survey, 10 investigators declined to participate, 2 studies were excluded as the eligible sample size was less than 100 and 1 study was excluded as development was assessed after age 7 years. The investigators then shared results of pre-defined analyses on their data or shared data with researchers at the Harvard T.H. Chan School of Public Health to complete the analyses of individual studies and the meta-analyses.

Early life factors

We created a list of early life risk factors based on the review of the current literature[13 14]. These risk factors are represented in the 'Good Health' and 'Adequate Nutrition' components of nurturing care framework for early childhood development proposed by the WHO[17]. We enquired about the availability of data on a list of risk factors in the preliminary survey sent to the investigators. Based on the survey responses, we then selected 14 early life factors that were available in at least four datasets to include in the pooled analyses. Following the standard definitions of categories used in published studies and the survey responses on how individual studies recorded data on each risk factors, we used uniform categorization of the risk factors applicable to all datasets. Risk factors were grouped into parental factors: father's education and mother's education (categories for each variable: none <1 year; primary 1 - <6 years; secondary 6-<10 years; higher ≥10 years), maternal age (<15 years, 15-<20 years, 20-<35 years; ≥35 years), maternal height (<145 cm, 145-<150 cm, 150-<155 cm, >155 cm) maternal body mass index (BMI; <18.5 kg/m^2, 18.5-<25 kg/m^2, 25-<30 kg/m^2, ≥30 kg/m^2), hemoglobin level during pregnancy (normal ≥110 g/L; mild anemia 100-109 g/L ; moderate anemia 70-99 g/L) and child factors: birth weight (low birth weight <2500g; moderate low 2000-2500g; very low birth weight <2000g), preterm birth (preterm<37 weeks; late preterm 34-37 weeks; early preterm <34 weeks), small-for-gestational-age (SGA; <10 percentile; moderate SGA 3-<10 percentile; severe SGA <3 percentile) as determined by Alexander and Oken standards, exclusive breastfeeding until 6 months of age, hemoglobin levels in infancy (normal ≥110 g/L; mild anemia 100-109 g/L ; moderate anemia 70-99 g/L), access to clean water (yes, no), access to sanitation (yes, no) and diarrhea preceding the 6 months before development assessment (yes, no). Details on the definition and categories of the risk factors are included in appendix 2. We also enquired about data on birth spacing, maternal HIV infection, malaria, intimate partner violence and depression, but a limited number of studies had data on these factors.

Outcomes:

We included cognitive, motor and language outcomes in the analyses, socioemotional outcomes were not measured in a sufficient number of studies. If a study measured child development on multiple occasions, we included the measurement obtained at the age closest to 24 months. Since different tools were used for development assessment across studies, all development scores were standardized (z-scored) to ensure comparability between the measurements in different studies.

Analyses of individual studies:

Within each study, linear regression models were used to assess standardized mean differences (SMDs) in cognitive, motor, and language scores for the selected risk factors. Multivariable models were adjusted for child's age and sex, maternal education and a measure of socioeconomic status (e.g. household income or wealth index). Maternal education was adjusted as a confounder in all models except for the model that estimated the effects of maternal education. If a study was a randomized trial, intervention assignment was also included in the adjusted model. In addition, estimates for preterm birth and gestation-specific birth weight category (SGA and appropriate-for-gestational-age) were adjusted for each other. The missing indicator method was used for covariates when <10% of the data were missing; if more than 10% were missing the covariate was excluded from the analyses.

Meta-analysis:

Meta-analysis for a given risk factor was conducted if estimates from at least four studies were available. To account for the variation in tools used for measuring development we only pooled the means and standard errors of the standardized outcomes scores. As multivariable adjustment substantially changed the effect estimates, we used the adjusted effect estimates for meta-analysis. Given that heterogeneous effects seemed likely across the large variety of contexts studied, random effects meta-analysis was conducted using the DerSimonian and Larid method.[18] Heterogeneity was assessed using I^2 statistics. All analyses were conducted using the metaan commands in Stata 12.0 (StataCorp, College Station, TX)

Ethical consideration:

The pooled study was approved by the Harvard T.H. Chan School of Public Health (IRB16-0256).

Patient and Public Involvement:

Patients and or public were not involved**.**

Results:

Table 1 shows the characteristics of the studies included in the analyses. We included 21 data sets with developmental measurements on 20,882 children of which 8 were from Asia,[19-26] 7 were from sub-Saharan Africa,[27-33] 5 were from Latin America and 1 from Europe.[34-39] The majority of studies (n=18), including 12 randomized trials,[19-23 26 27 30-33 39] followed up the participants prospectively. The Bayley Scales of Infant and Toddler Development (BSID) was used to assess child development in most of the studies with, BSID-III administered in 5 studies,[24 27 31-33] BSID-II in 5 studies,[19-22 30] and BSID I in 1 study.[39] The Ages and Stages questionnaire was used in 2 studies,[23 37] and a few studies used local adaptations of standard tools.[29 36] The majority of the studies had data on both motor and cognitive development,[19-25 27-39] 1 study had data on motor development only[26] and 6 studies provided data on language development.[29 31-34] Development was assessed before age 2 years in most studies,[19-27 29-35 38 39] except for 3 studies that assessed development at ages between 3-6 years. [28 36 37]

Parental factors:

Pooled estimates for the association of parental factors with child cognitive, motor, and language development are presented in Table 2. Higher attained maternal education was associated with improved cognitive, motor, and language development scores. Children whose mothers attended or completed secondary school had 0.14 SD (95% CI: 0.05, 0.25), 0.12 SD (95% CI: 0.06, 0.18), and 0.13 SD (95% CI: 0.04, 0.21) higher cognitive, motor and language scores, respectively, as compared to children whose mothers only had primary school education. Compared to children of mothers with primary education, children of mothers with ≥ ten years of education scored 0.36 SD (95% CI: 0.19, 0.48), 0.26 SD (95% CI: 0.14, 0.38) and 0.21 SD (95% CI 0.09, 0.33) higher

in cognitive, motor and language scores, respectively. Children of mothers with no formal schooling scored lowest in cognitive, motor and language scores. There was a significant positive association between father's education and cognitive and motor development after adjusting for maternal education, although the magnitude of the effect sizes was smaller than for those of maternal education. We found no significant relationships between maternal age at birth and cognitive, motor, or language development.

Children of mothers with short stature (height <155 cm) tended to have lower cognitive, motor, and language scores as compared with a maternal height >155cm. Children whose mothers were <145cm scored 0.10 SD (95% CI -0.20, -0.004), 0.11 SD (95% CI: -0.19, -0.03), and 0.11 SD (95% CI: -0.31, 0.09) lower on cognitive, motor, and language development, respectively. Low maternal BMI (<18.5 kg/m^2) was significantly associated with lower cognitive development scores (SD: -0.10; 95% CI -0.19, -0.02), but not motor or language development. There was no significant association of maternal hemoglobin with child cognition.

Child factors:

Pooled estimates for the association of child factors with development are presented in Table 3. Compared to children born with normal birth weight, children born with low birth weight (<2500g) had significantly poorer cognitive and motor scores. Children with birthweights <2000g had on average 0.27 SD (95% CI: -0.49, -0.07) lower cognitive, 0.26 SD (95% CI: -0.40, -0.12) lower motor and 0.28 SD (95% CI: -0.60, 0.05) lower language scores, compared with normal birthweight children (≥2500 g). Compared to term and appropriate for gestational age (AGA) infants, preterm-AGA infants had 0.14 SD (95% CI: -0.24, -0.05) and 0.23 SD (95% CI:

-0.42, -0.03) lower cognitive and motor scores, respectively. Term-SGA infants had poorer developmental scores in some studies, but the pooled effect estimates for term-SGA, adjusted for preterm birth, were not statistically significant.

Anemia in infancy was significantly and negatively associated with both motor and cognitive development scores. Combined effect sizes of moderate anemia were -0.18 SD (95% CI -0.27, -0.09) for motor and -0.11 SD (95% CI -0.12, - 0.10) for cognitive scores. Compared to children residing in households with access to clean water, children without access had 0.10 SD (95% CI: -0.12, -0.09) lower cognitive and 0.07 SD (95% CI: -0.16, 0.01) lower motor and 0.15 SD (95% CI: -0.35, -0.05) lower language scores. Children without access to clean sanitation had 0.13 SD (95% CI: -0.18, -0.07) lower cognitive and 0.10 SD (95% CI: -0.19, -0.01) lower motor scores. In the pooled analyses, exclusive breastfeeding until 6 months of age and diarrhea during the preceding 6-month of development assessment did not have significant associations with either cognitive or motor development.

Figures 2 and 3 present effect sizes of all risk factors included in the analyses. Forests plots of metanalysis of individual risk factors are included in appendix 2, Figures 1-86.

Discussion:

This pooled analysis of development assessment of 20,882 children from 21 LMIC studies determined that low maternal and paternal education, short maternal stature, low birth weight, preterm birth, anemia in infancy, and lack of access to clean water and sanitation were associated with lower child development scores among children < 7 years of age. We did not find significant associations of maternal anemia, fetal growth restriction, exclusive breastfeeding, or childhood diarrhea with development scores.

We observed a dose-response relationship between parental education and child development. While a large body of literature supports the consistent role of maternal education in promoting children's language and cognitive developments, evidence on the role of paternal education is more limited.[35 40 41] Recent reports suggest advanced language and cognitive development among children of more educated fathers that persisted after adjustment for family income and mothers' education.[42] Maternal education is associated with more warm, responsive, and stimulating home environments, which in turn are predictive of more positive developmental outcomes for children.[43] High maternal education is also linked with protective factors like good feeding and hygiene practices and frequent utilization of antenatal care and child immunization.[44 45] In addition, low maternal education is associated with known risk factors of poor child development such as malnutrition in children, and depression and stress in mothers.[46 47] Although prior work suggests that less educated mothers tend to be less receptive to early childhood development (ECD) messages, research also shows that their children may benefit more from ECD interventions.[48] Therefore, adopting a 2-generational intervention approach to empower parents and improve parenting capacity are likely to generate long-term benefits for child development.

Due to the availability of maternal education data, low maternal education can serve as a simple risk marker to target children in need of ECD intervention.[49]

We found significant negative associations of preterm birth with cognitive and motor development but not with language development. Meta-analyses of studies conducted in developed countries reported lower IQ scores and cognitive functioning, [50-52] along with deficits in motor [53], language [54], and visual-spatial abilities[55] in preterm infants. Reduction of the intrauterine period interrupts the trajectory of neurodevelopmental processes such as synapse formation and myelination, which often leads to neurocognitive deficits.[56] Although most preterm infants catch up in physical growth[57], this deficit in neurocognitive development often persists into childhood and adolescence.[58 59] Given the high incidence of preterm delivery in LMIC[60] and the increased survival of preterm infants with medical advances, the burden of the developmental deficits caused by preterm birth in LMIC may be increasing. There are currently few interventions to prevent preterm birth[61]; however, a variety of psychosocial interventions to alleviate the adverse neurodevelopmental effects of preterm birth implemented at different points in early childhood have shown modest short-term benefits.[62]

We found that fetal growth restriction, assessed via SGA, was not significantly associated with child development. This agrees with several reports from developed countries[63-65] whereas others have reported adverse effects of SGA on cognitive and motor functioning[32 66 67]. These disparate findings could be caused by different definitions of SGA and/or timing of the developmental assessment. Most studies from LMICs used LBW (as marker of SGA), which is also caused by prematurity, a major risk predictor of child development. There is some evidence that with

adequate nutrition, the developmental deficit in SGA infants is often compensated with age, although the gap in physical growth remains[68]. This finding underscores the potentially differential roles and separate causal mechanisms of effects of early life risk factors for physical and mental development. It is important to note that the effect size for SGA may be biased downwards considering the heterogeneity in outcome and the measurement error due to the use of last menstrual period (LMP) date for the estimation of gestational age in most the studies. We found significant negative associations between short maternal stature (<145 cm) and low BMI (<18.5 kg/m2)[69] on cognitive function, which may indicate the role of chronic malnutrition of mothers over their life course on pregnancy health and development of fetus. These are also known risk factors of SGA,[69] suggesting that adverse effects of fetal growth restriction on child development are possible. Further research is needed to quantify the effects of fetal growth restriction on children's development and evaluate the effects of interventions to alleviate the negative impacts of SGA on development.

We found an adverse role of anemia in infancy with motor and cognitive development. Prior studies reported significant effects of anemia on cognitive, motor and socioemotional development that persisted into middle childhood during longitudinal follow-up[70]. Worldwide, the predominant cause of anemia for infants and children is iron deficiency[71], which can interfere with myelination, synapse formation and protein expression during sensitive periods of neurodevelopment[72]. Meta-analyses of randomized trials of infant iron supplementation have not established an effect on child development; however statistical power to detect effect sizes of < 0.2 SD as our analysis predicts is limited due to few trials with large enough sample sizes.[73 74] In our pooled analyses, maternal anemia during pregnancy, an important determinant of anemia in

infancy[75], was not significantly associated with children's development. We also did not find a significant association between exclusive breastfeeding until 6 months of age and children's development. Nevertheless, few studies included in our pooled analyses had a sufficient number of infants who were exclusively breastfed until six months to allow for a well-powered analysis. Because of the multidimensional benefits of breastfeeding from infection prevention to fostering mother-infant bonding and infant attachment, significant positive effects of exclusive breastfeeding on child development are plausible. Meta-analyses of studies of effects of breastfeeding on children's development reported significant increases in intelligence and cognitive scores[76 77]; however some studies have attributed these associations entirely to the presence of confounding by socioeconomic status and stimulation at home.[78]

This study is among the first to report on the associations between lack of access to safe water and sanitation and child cognitive development. The burden of developmental deficit attributed to these risk factors is likely very high as a large proportion of the population in LMICs reside in unhygienic environments with limited access to safe water. The effects of poor sanitation and unsafe water on child cognitive development are potentially mediated through childhood anemia, inflammation and undernutrition resulting from frequent enteric infections[79]. However, in the pooled analyses, we did not find any significant adverse associations between diarrhea and development, which is different from previously published evidence[23 80 81]. One potential explanation for the lack of association found in this study may be measurement error: diarrhea is inherently complex and hard to measure; variations in the definitions of episodes as well as parental inability to correctly report diarrhea may have led to the failure to detect potential effects of diarrhea on cognitive, motor and language development in this study.

The strengths of this pooled study include the global coverage of the cohorts, the large sample size, and uniform classifications of early life exposures and statistical analyses across studies. Nevertheless, there are also several limitations, including the lack of data on exposure to environmental neurotoxicants, maternal depression, responsive parenting behaviors, and child stimulation and early education. A recent meta-analysis determined that the potential effect of responsive stimulation on cognitive development at 2 years of age was +0.42SD (95% CI: 0.36, 0.48)[82], which is larger than all risk factors examined in our analysis. Thus, comprehensive packages of environmental, nutrition, and stimulation interventions may produce larger effect sizes than interventions targeting single risks. In addition, due to the observational nature of the studies included in this analysis, we are unable to determine a causal relationship between parental and child factors with child development. Although we have adjusted for major confounders the potential for residual confounding remains. Another limitation is that we did not perform any risk of bias assessments for observational studies. Nevertheless, each study adjusted for the same set of factors in the pooled analyses and thereby likely minimized differences in control of confounding between studies. Last, there was moderate to high levels of heterogeneity, as indicated by the I^2 values, in some of our pooled estimates. The magnitude of the relationship for maternal education, prematurity, birthweight, SGA, and access to water and sanitation appeared to vary by study cohort. As a result, cultural and other contextual factors may be important in determining the strength of the relationship between health and nutrition exposures with child development outcomes. Accordingly, future intervention studies should be conducted among diverse study populations as their effect may importantly differ by setting.

In summary, in a pooled study of 21 studies in LMICs, we determined that multiple risk factors classically associated with child morbidity and mortality also appear to have negative associations with cognitive, motor, and language development. As a result, our study suggests that interventions that span pre-pregnancy through early and middle childhood may be necessary to provide optimal child development in LMICs. Future research should focus on determining the effectiveness of, and delivery strategies for comprehensive intervention packages to promote child development.

Key Words:

Motor development
cognitive development
Language development
Early life risk factors
Preterm
SGA
Maternal education
Paternal education
Maternal short stature
Maternal anemia
anemia in infancy,
Access to clean water
Access to sanitation
Breastfeeding
Diarrhea

Figure Legends

Figure 1: Flow chart of study selection

Figure 2: Pooled estimates of association between maternal factors and development

Figure 3: Pooled estimates of association between child factors and development

Table 1: Characteristics of the included studies

	Study	Setting	Primary study design	Study population	N (data on child development)	Child development tool used	Child age in years at assessment (mean±SD)
Asia							
1	Black (2004)[19]	Bangladesh	randomized controlled trial	birth cohort	221	Bayley Scales of Infant and Toddler Development, 2nd edition (BSID-II) and the Home Observation for Measurement of the Environment (HOME) Inventory	1.06±0.03
2	Tofail (2008)[20]	Bangladesh	randomized controlled trial	birth cohort	2853 total (2116 tested)	2 problem-solving tests, motor index of Bayley Scales of Infant and Toddler Development, 2nd edition (BSID-II) and Wolke's behavior ratings	0.61±0.02
3	Tofail (2012)[21]	Bangladesh	randomized controlled trial	prospective, community-based cohort	249	Bayley Scales of Infant and Toddler Development, 2nd edition (BSID-II)	0.84±0.01
4	Taneja (2005)[22]	India	randomized placebo-controlled trial	Prospective, community-based cohort	571	Bayley Scales of Infant and Toddler Development, 2nd edition (BSID-II)	1.25±0.16
5	Kvestad (2015)[23]	India	randomized placebo-controlled trial	prospective, community-based cohort	422	Ages and Stages Questionnaire, 3rd edition (ASQ-3)	1.37±0.60
6	Yousafzai (2014)[24]	Pakistan	community-based cluster-randomized effectiveness trial	prospective, community-based cohort	1357	Bayley Scales of Infant and Toddler Development, 3rd edition (BSID-III)	11.6 ±0.83
7	Duazo (2010)[25]	Philippines	longitudinal program evaluation	birth cohort	4904	Philippines Revised Early Childhood Development Checklist (REC)	1.62±0.88
8	McGready (2007)[26]	Thailand	randomized controlled trial	prospective, facility-based cohort	503	Shoklo Developmental Test	1.62±0.02
Sub-Saharan Africa							
9	Shapiro (2013)[27]	Botswana	randomized controlled trial	prospective, community-based cohort	224	Bayley Scales of Infant and Toddler Development, 3rd edition (BSID-III)	2.03±0.08
10	Alemtsehay (2009)[28]	Ethiopia	cross-sectional study	cross-sectional, community-based cohort	100	Raven's Colored Progressive Matrices (CPM) and Kaufman Assessment Battery for Children-II (KABC-II)	5.11±0.24
11	Gladstone (2011)[29]	Malawi	cross-sectional community-based cohort study	community-based cohort	840	Ten Question Questionnaire [TQQ] and Malawi Developmental Assessment Tool [MDAT]	1.74±0.33
12	McDonald (2013)[30]	Tanzania	randomized placebo-controlled trial	birth cohort	305	Bayley Scales of Infant and Toddler Development, 2nd edition (BSID-II)	1.28±0.04
13	Manji (2014)[31]	Tanzania	randomized placebo-controlled trial	birth cohort	206	Bayley Scales of Infant and Toddler Development, 3rd edition (BSID-III)	1.28±0.04
14	Sudfeld (2015)[32]	Tanzania	randomized placebo-controlled trial	birth cohort	958	Bayley Scales of Infant and Toddler Development, 3rd edition (BSID-III)	2.25±0.52

	Study	Setting	Primary study design	Study population	N (data on child development)	Child development tool used	Child age in years at assessment (mean±SD)
15	Locks (2016)[33]	Tanzania	randomized placebo-controlled trial	birth cohort	248	Bayley Scales of Infant and Toddler Development, 3rd edition (BSID-III)	1.21±0.03
Latin America							
16	Santos IS (2011)[34]	Brazil	longitudinal birth cohort survey	2004 Pelotas birth cohort	3868	Battelle Screening Developmental Inventory (BSDI)	1.99 ± 0.05
17	Santos (2008)[35]	Brazil	longitudinal birth cohort survey	Longitudinal, community-based cohort	365	Wechsler Pre-School and Primary Scale of Intelligence-Revised (WPPSI-R)	5.80±3.02
18	Fernald (2011)[36]	Ecuador	randomized effectiveness trial	Prospective, community-based cohort	1265	MacArthur-Bates Communicative Development Inventory, short form, Spanish version	4.59±0.87
19	Handal (2008)[37]	Ecuador	cross-sectional	Community based, selected using door-to-door survey	283	Ages and Stages Questionnaire (ASQ)	2.46±1.46
20	Braun (2012)[38]	Mexico	prospective cohort study	prospective, facility-based cohort	1032	Bayley Scales of Infant and Toddler Development, 2nd edition (BSID-II) McCarthy Scales of Children's Abilities (MSCA)	2.02±0.03
Europe							
21	Akman (2004)[39]	Europe-Turkey	randomized clinical trial	facility-based hospital	108	Bayley Scales of Infant and Toddler Development, 1st edition (BSID-I)	1.42±0.59

Table 2: Summary results of meta-analysis of associations of parental factors and cognitive, motor and language developments

Risk Factor	Cognitive				Motor				Language			
	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)
Mother's education												
No education (<1 years)	15	-0.12 (-0.24, -0.008)	0.05	50.8	18	-0.07 (-0.13, -0.01)	0.03	18.2	5	-0.06 (-0.21, -0.09)	0.49	35.5
Primary (1- <6 years)		Reference				Reference				Reference		
Secondary (6- <10 years)	17	0.14 (0.05, 0.24)	< 0.01	59.7	19	0.12 (0.06, 0.18)	< 0.01	51.8	5	0.13 (0.04, 0.21)	0.04	0.0
Higher (≥10 years)	17	0.36 (0.19, 0.48)	< 0.01	65.8	19	0.26 (0.14, 0.38)	< 0.01	70.6	5	0.21 (0.09, 0.33)	0.03	0.0
Father's education												
No education (<1 years)	13	-0.005 (-0.08, 0.07)	0.91	0.0	17	-0.08 (-0.11, -0.04)	< 0.01	0.0	4	0.02 (-0.15, 0.20)	0.80	30.0
Primary (1- <6 years)		Reference				Reference				Reference		
Secondary (6- <10 years)	15	0.06 (0.015, 0.11)	0.02	0.0	17	0.08 (0.03, 0.13)	< 0.01	30.3	4	0.09 (0.02, 0.16)	0.08	0.0
Higher (≥10 years)	15	0.15 (0.08, 0.21)	< 0.01	0.0	17	0.18 (0.10, 0.26)	< 0.01	42.3	4	0.22 (0.11, 0.32)	0.03	17.9
Mother's age												
<15 years	5	-0.06 (-0.13, 0.25)	0.57	0.0	5	0.12 (-0.06, 0.30)	0.25	0.0	2	n/a	n/a	n/a
15-<20 years	18	-0.007 (-0.06, 0.05)	0.80	10.7	20	-0.02 (-0.11, 0.08)	0.75	83.6	6	0.01 (-0.09, 0.11)	0.85	37.0
20-34 years		Reference				Reference				Reference		
≥35 years	18	-0.01 (-0.06, 0.04)	0.58	0.0	20	-0.006 (-0.07, 0.05)	0.85	50.1	6	0.02 (-0.05, 0.09)	0.59	0.0
Mother's height												
<145 cm	11	-0.10 (-0.20, -0.004)	0.07	0.0	13	-0.11 (-0.19, -0.03)	0.02	21.5	5	-0.11 (-0.31, 0.09)	0.35	0.0
145 -<150 cm	13	-0.11 (-0.19, -0.02)	0.03	27.1	15	-0.07 (-0.16, 0.03)	0.17	71.1	5	-0.06 (-0.13, 0.06)	0.52	0.0
150- <155 cm	13	-0.09 (-0.14, -0.04)	< 0.01	3.3	15	-0.04 (-0.09, 0.009)	0.14	31.5	5	-0.05 (-0.12, 0.02)	0.22	0.0
>155 cm		Reference				Reference				Reference		
Mother's BMI (kg/m^2)												

Risk Factor	Cognitive				Motor				Language			
	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)
<18.5	11	-0.11 (-0.20, -0.02)	0.03	12.7	13	-0.02 (-0.11, 0.07)	0.69	51.4	3	n/a	n/a	n/a
18.5 -<25		Reference				Reference				Reference		
25-<30	12	0.03 (-0.04, 0.09)	0.44	23.3	14	0.04 (-0.03, 0.11)	0.31	64.6	4	-0.04 (-0.21, 0.13)	0.70	61.0
≥30	12	-0.02 (-0.17, 0.14)	0.82	46.3	14	-0.02 (-0.14, 0.10)	0.77	63.6	4	-0.14 (-0.34, 0.06)	0.26	35.9
Mother's hemoglobin level (g/L)												
Normal (≥110 g/L))		Reference				Reference				Reference		
Mild anemia (100-109 g/L)	4	-0.06 (-0.15, 0.03)	0.28	0.0	11	0.06 (0.008, 0.11)	0.04	29.7	1	n/a	n/a	n/a
Moderate anemia (70-99 g/L)	4	-0.06 (-0.19, 0.06)	0.39	0.0	6	-0.01 (-0.06, 0.04)	0.68	16.3	1	n/a	n/a	n/a

[1]Adjusted for child's gender and age, mother's education and household wealth

Table 3: Summary results of meta-analysis of associations of child factors and cognitive, motor and language developments, standardized scores

Risk Factor	Cognitive				Motor				Language			
	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)
Birth weight (g)												
Normal (≥2500 g)		Reference				Reference				Reference		
Low (<2500 g)	14	-0.13 (-0.20, -0.07)	< 0.01	51.0	15	-0.14 (-0.23, -0.06)	< 0.01	66.5	5	-0.11 (-0.22, 0.00)	0.12	74.6
Moderate low (2000-2500 g)	14	-0.07 (-0.12, -0.03)	< 0.01	17.2	15	-0.11 (-0.20, -0.02)	0.03	64.0	5	-0.05 (-0.10, 0.01)	0.20	29.6
Very low (<2000 g)	14	-0.27 (-0.49, -0.07)	0.02	74.0	13	-0.26 (-0.40, -0.12)	< 0.01	74.9	5	-0.28 (-0.60, 0.05)	0.17	81.1
Gestational age (g)[2]												
Term (≥37 weeks)		Reference				Reference				Reference		
Late preterm (34-37 weeks)	8	-0.21 (-0.39, -0.04)	0.04	69.8	8	-0.14 (-0.33, 0.04)	0.17	74.5	5	-0.05 (-0.23, 0.13)	0.64	72.1
Early preterm (<34 weeks)	8	-0.16 (-0.34, 0.31)	0.15	53.5	7	-0.26 (-0.53, 0.006)	0.10	65.0	4	-0.20 (-0.55, 0.15)	0.35	75.4
Size for gestational age[3]												
AGA (≥10 percentile)		Reference				Reference				Reference		
Moderate SGA (3-<10 percentile)	8	-0.05 (-0.11, 0.12)	0.16	0.0	9	-0.01 (-0.10, 0.07)	0.77	36.6	4	-0.06 (-0.18, 0.06)	0.40	29.4
Severe SGA (<3 percentile)	8	-0.09 (-0.24, 0.07)	0.30	72.0	9	0.02 (-0.09, 0.12)	0.78	37.4	4	0.03 (-0.13, 0.19)	0.73	37.7
Gestational age and Size-for-gestational age												
Term-AGA		Reference				Reference				Reference		
Preterm-AGA	8	-0.14 (-0.24, -0.05)	0.02	17.0	9	-0.23 (-0.42, -0.03)	0.05	76.5	4	-0.02 (-0.23, 0.19)	0.87	78.0
Term-SGA	8	-0.02 (-0.10, 0.06)	0.66	44.6	9	-0.007 (-0.08, 0.06)	0.84	31.4	4	-0.03 (-0.12, 0.06)	0.55	9.3
Preterm-SGA	5	-0.17 (-0.29, -0.05)	0.05	0.0	5	-0.15 (-0.40, 0.09)	0.29	53.1	3	n/a	n/a	n/a
Exclusive breastfeeding												
Yes		Reference				Reference				Reference		
No	4	-0.02 (-0.08, 0.04)	0.60	0.0	4	-0.05 (-0.13, 0.04)	0.36	16.4	3	n/a	n/a	n/a

Risk Factor	Cognitive				Motor				Language			
	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)	No. of studies	Adjusted[1] SMD (95% CI)	*p*-value	I^2 (%)
Child hemoglobin level (g/L)												
Normal (≥110 g/L)		Reference				Reference				Reference		
Mild anemia (100-109 g/L)	9	-0.06 (-0.13, 0.01)	0.14	27.7	9	-0.03 (-0.13, 0.07)	0.54	51.2	3	n/a	n/a	n/a
Moderate anemia (70-99 g/L)	9	-0.11 (-0.12, -0.10)	< 0.01	0.0	9	-0.18 (-0.28, -0.09)	< 0.01	49.0	3	n/a	n/a	n/a
Access to clean water												
Yes		Reference				Reference				Reference		
No	8	-0.10 (-0.12, -0.09)	< 0.01	0.0	8	-0.07 (-0.16, 0.01)	0.14	71.0	4	-0.15 (-0.35, 0.05)	0.23	82.5
Access to sanitation												
Yes		Reference				Reference				Reference		
No	8	-0.13 (-0.18, -0.07)	< 0.01	47.5	8	-0.10 (-0.19, -0.01)	0.05	82.8	4	-0.12 (-0.27, 0.03)	0.21	92.4
Diarrhoea												
Yes	5	-0.02 (-0.16, 0.13)	0.84	66.8	5	-0.02 (-0.14, 0.09)	0.71	62.8	2	n/a	n/a	n/a
No		Reference				Reference				Reference		

[1]Adjusted for child's gender and age, mother's education and household wealth
[2]Adjusted for small for gestational age
[3]Adjusted for gestational age

AGA: Appropriate for Gestational Age
SGA: Small for Gestational Age

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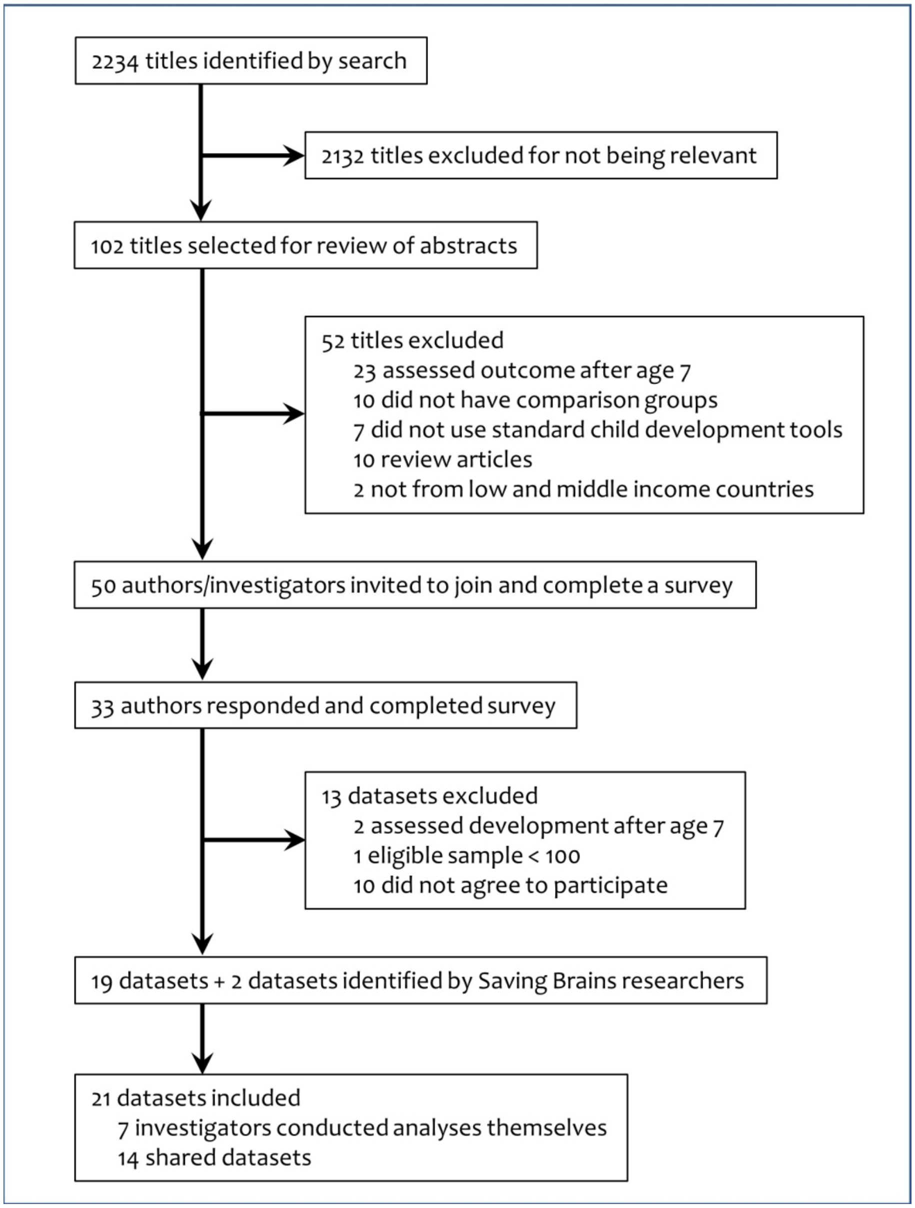

Figure 1: flow chart of study selection

142x187mm (300 x 300 DPI)

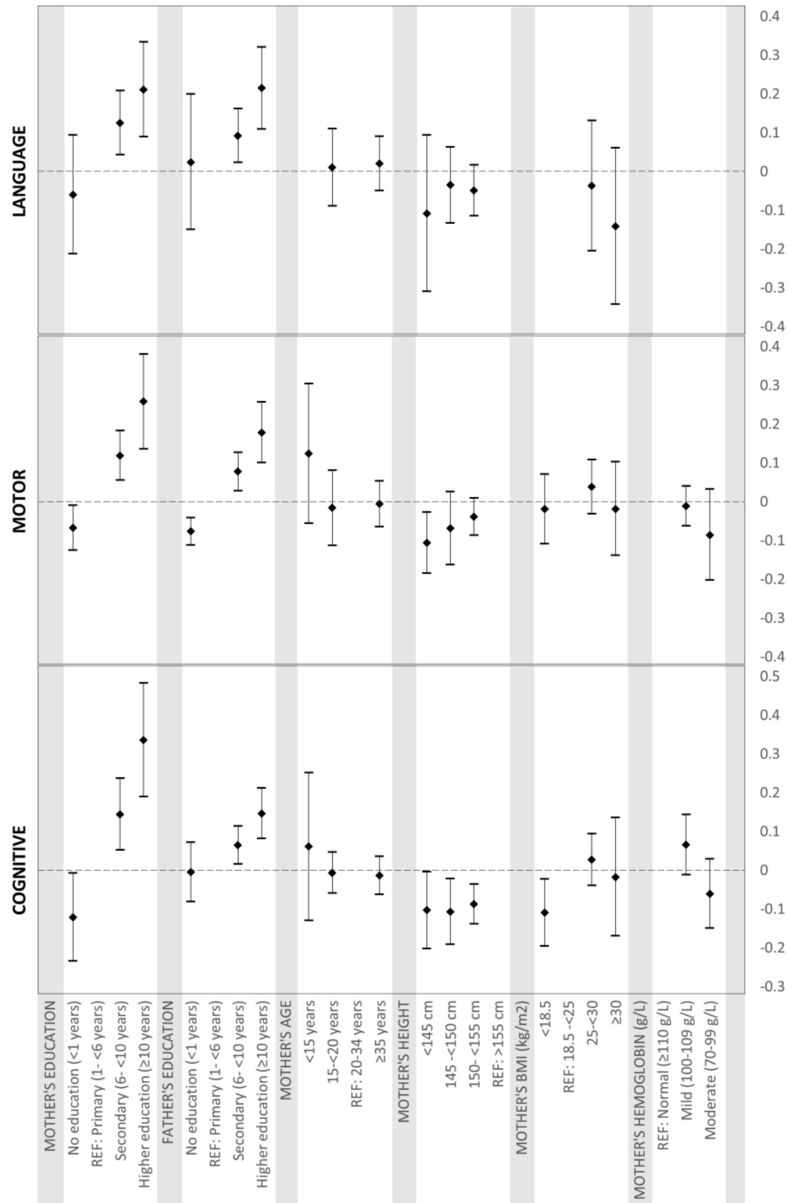

Figure 2: Pooled estimates of association between maternal factors and development

157x237mm (300 x 300 DPI)

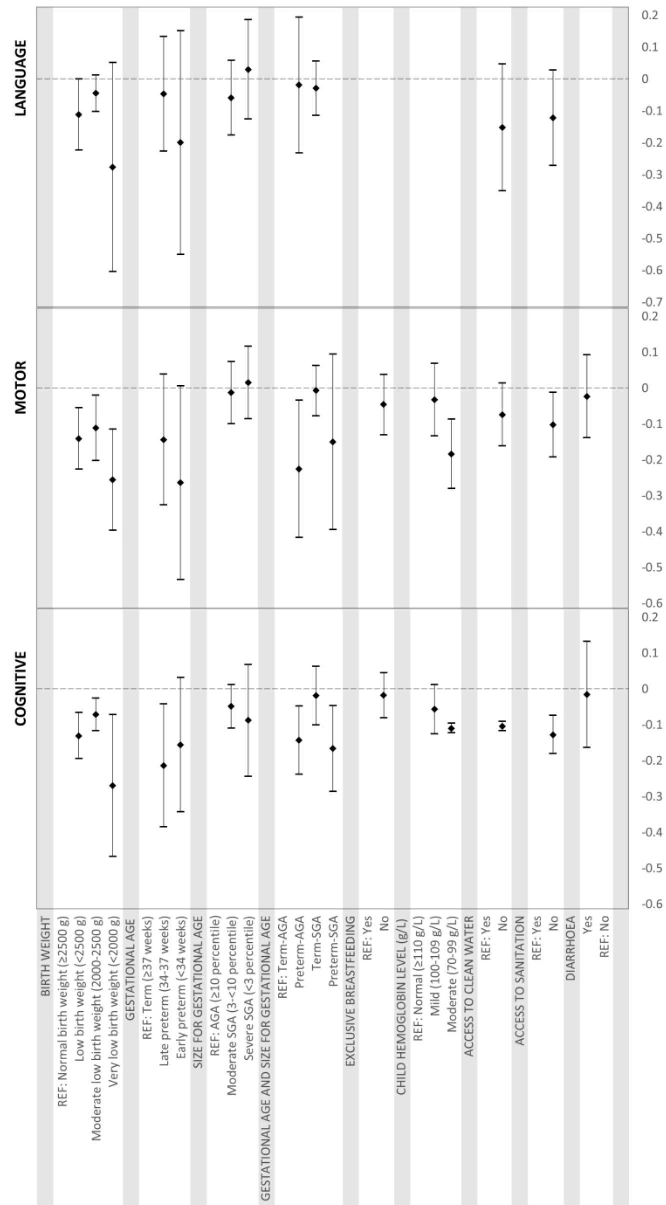

Figure 3: Pooled estimates of association between child factors and development.

157x284mm (300 x 300 DPI)

Appendix 1: Search terms

("child"[MeSH] OR "infant"[MeSH]) AND ("child development"[MeSH] OR "cognition"[MeSH] OR "psychomotor disorders"[MeSH] OR "psychomotor performance"[MeSH] OR "motor skills"[MeSH] OR "intelligence"[MeSH] OR "IQ"[All Fields] OR "executive function"[MeSH] OR "attention"[MeSH] OR "memory"[MeSH] OR "learning"[MeSH] OR "education"[MeSH] OR "reading"[MeSH] OR "mathematics"[MeSH] OR "learning disorders"[MeSH] OR "aptitude tests"[MeSH] OR "language tests"[MeSH] OR "mental health"[MeSH] OR "child behavior"[MeSH] OR "emotional intelligence"[MeSH] OR "emotions"[MeSH] OR "temperament"[MeSH] OR "self concept"[MeSH] OR "self efficacy"[MeSH] OR "mental competency"[MeSH] OR "aggression"[MeSH]) AND ("preterm"[All Fields] OR "low birth weight"[All Fields] OR “maternal height” OR “maternal underweight” OR “malaria” OR “birth spacing” OR “Teen pregnancy” OR “anemia” or “hemoglobin” OR “HIV” OR “iron supplement” OR “iron deficiency” OR “childhood diarrhea” OR “HIV” OR “zinc” OR “iodine” OR “sanitation” OR “clean water” OR “breastfeeding” OR “hookworms”) AND ("Armenia"[All Fields] OR "Azerbaijan"[All Fields] OR "Georgia"[All Fields] OR "Kazakhstan"[All Fields] OR "Kyrgyzstan"[All Fields] OR "Mongolia"[All Fields] OR "Tajikistan"[All Fields] OR "Turkmenistan"[All Fields] OR "Uzbekistan"[All Fields] OR "Afghanistan"[All Fields] OR "Bangladesh"[All Fields] OR "Bhutan"[All Fields] OR "India"[All Fields] OR "Nepal"[All Fields] OR "Pakistan"[All Fields] OR "Cambodia"[All Fields] OR "Indonesia"[All Fields] OR "Lao People's Democratic Republic"[All Fields] OR "Malaysia"[All Fields] OR "Maldives"[All Fields] OR "Mauritius"[All Fields] OR "Mayotte"[All Fields] OR "Myanmar"[All Fields] OR "Philippines"[All Fields] OR "Seychelles"[All Fields] OR "Sri Lanka"[All Fields] OR "Thailand"[All Fields] OR "Viet Nam"[All Fields] OR "Anguilla"[All Fields] OR "Antigua and Barbuda"[All Fields] OR "Aruba"[All Fields] OR "Bahamas"[All Fields] OR "Barbados"[All Fields] OR "Belize"[All Fields] OR "Bermuda"[All Fields] OR "British Virgin Islands"[All Fields] OR "Cayman Islands"[All Fields] OR "Cuba"[All Fields] OR "Turks and Caicos Islands"[All Fields] OR "Bolivia"[All Fields] OR "Ecuador"[All Fields] OR "Peru"[All Fields] OR "Colombia"[All Fields] OR "Costa Rica"[All Fields] OR "El Salvador"[All Fields] OR "Guatemala"[All Fields] OR "Honduras"[All Fields] OR "Mexico"[All Fields] OR "Nicaragua"[All Fields] OR "Panama"[All Fields] OR "Venezuela"[All Fields] OR "Argentina"[All Fields] OR "Chile"[All Fields] OR "Falkland Islands"[All Fields] OR "Malvinas"[All Fields] OR "Uruguay"[All Fields] OR "Brazil"[All Fields] OR "Paraguay"[All Fields] OR "Algeria"[All Fields] OR "Bahrain"[All Fields] OR "Egypt"[All Fields] OR "Iran"[All Fields] OR "Iraq"[All Fields] OR "Jordan"[All Fields] OR "Kuwait"[All Fields] OR "Lebanon"[All Fields] OR "Libyan Arab Jamahiriya"[All Fields] OR "Morocco"[All Fields] OR "Occupied Palestinian Territory"[All Fields] OR "Oman"[All Fields] OR "Qatar"[All Fields] OR "Saudi Arabia"[All Fields] OR "Syrian Arab Republic"[All Fields] OR "Tunisia"[All Fields] OR "Turkey"[All Fields] OR "United Arab Emirates"[All Fields] OR "Western Sahara"[All Fields] OR "Yemen"[All Fields] OR "American Samoa"[All Fields] OR "Cook Islands"[All Fields] OR "Fiji"[All Fields] OR "French Polynesia"[All Fields] OR "Guam"[All Fields] OR "Kiribati"[All Fields] OR "Marshall Islands"[All Fields] OR "Micronesia"[All Fields] OR "Nauru"[All Fields] OR "New Caledonia"[All Fields] OR "Niue"[All Fields] OR "Northern Mariana Islands"[All Fields] OR "Palau"[All Fields] OR "Papua New Guinea"[All Fields] OR "Pitcairn"[All Fields] OR "Samoa"[All Fields] OR "Solomon Islands"[All Fields] OR "Tokelau"[All Fields] OR "Tonga"[All Fields] OR "Tuvalu"[All Fields] OR "Vanuatu"[All Fields] OR "Wallis and Futuna Islands"[All Fields] OR "Angola"[All Fields] OR "Central African Republic"[All Fields] OR

"Congo"[All Fields] OR "Democratic Republic of the Congo"[All Fields] OR "Equatorial Guinea"[All Fields] OR "Gabon"[All Fields] OR "Burundi"[All Fields] OR "Comoros"[All Fields] OR "Djibouti"[All Fields] OR "Eritrea"[All Fields] OR "Ethiopia"[All Fields] OR "Kenya"[All Fields] OR "Madagascar"[All Fields] OR "Malawi"[All Fields] OR "Mozambique"[All Fields] OR "Rwanda"[All Fields] OR "Somalia"[All Fields] OR "Sudan"[All Fields] OR "Uganda"[All Fields] OR "United Republic of Tanzania"[All Fields] OR "Zambia"[All Fields] OR "Botswana"[All Fields] OR "Lesotho"[All Fields] OR "Namibia"[All Fields] OR "South Africa"[All Fields] OR "Swaziland"[All Fields] OR "Zimbabwe"[All Fields] OR "Benin"[All Fields] OR "Burkina Faso"[All Fields] OR "Cameroon"[All Fields] OR "Cape Verde"[All Fields] OR "Chad"[All Fields] OR "Cote d'Ivoire"[All Fields] OR "Gambia"[All Fields] OR "Ghana"[All Fields] OR "Guinea"[All Fields] OR "Guinea-Bissau"[All Fields] OR "Liberia"[All Fields] OR "Mali"[All Fields] OR "Mauritania"[All Fields] OR "Niger"[All Fields] OR "Nigeria"[All Fields] OR "Saint Helena"[All Fields] OR "Sao Tome and Principe"[All Fields] OR "Senegal"[All Fields] OR "Sierra Leone"[All Fields] OR "Togo"[All Fields])

Appendix 2: Forest plots

1. Child Risk Factors on Child's Cognitive Development

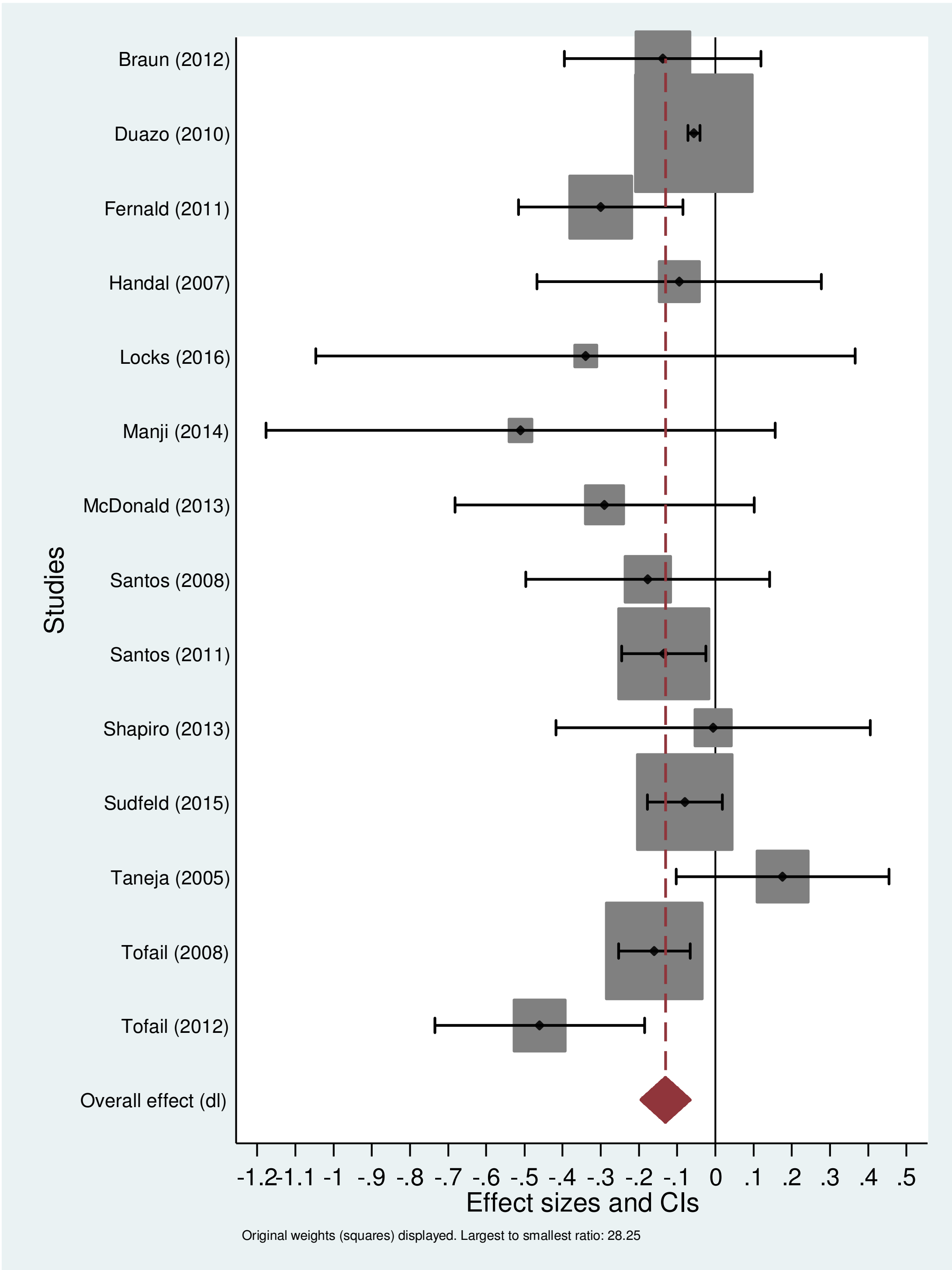

Figure 1: Association between low birth weight (LBW) and (reference: normal birth weight) and cognitive development.

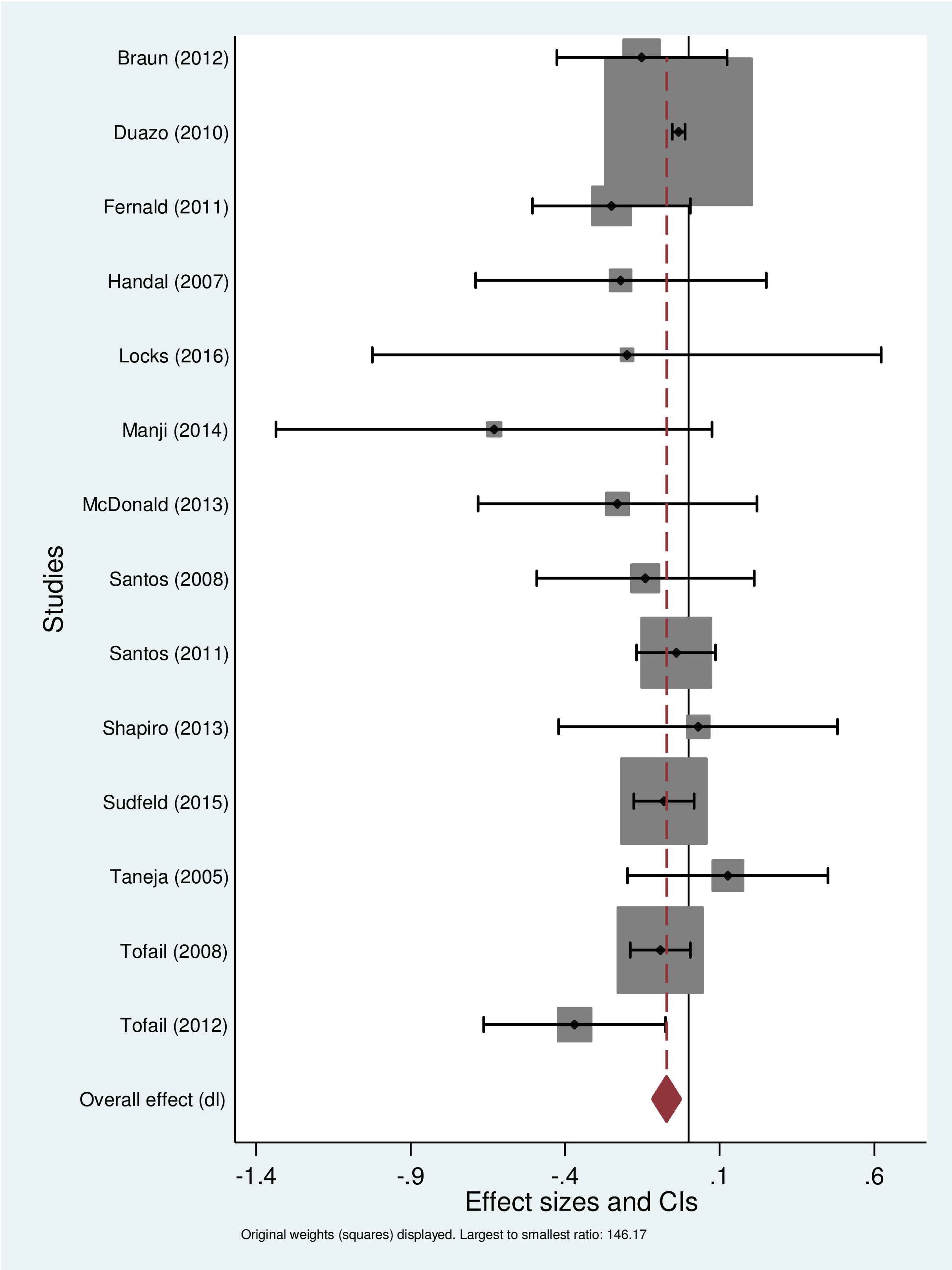

Figure 2: Association between Moderately low birth Weight (reference, normal birth weight) and cognitive development.

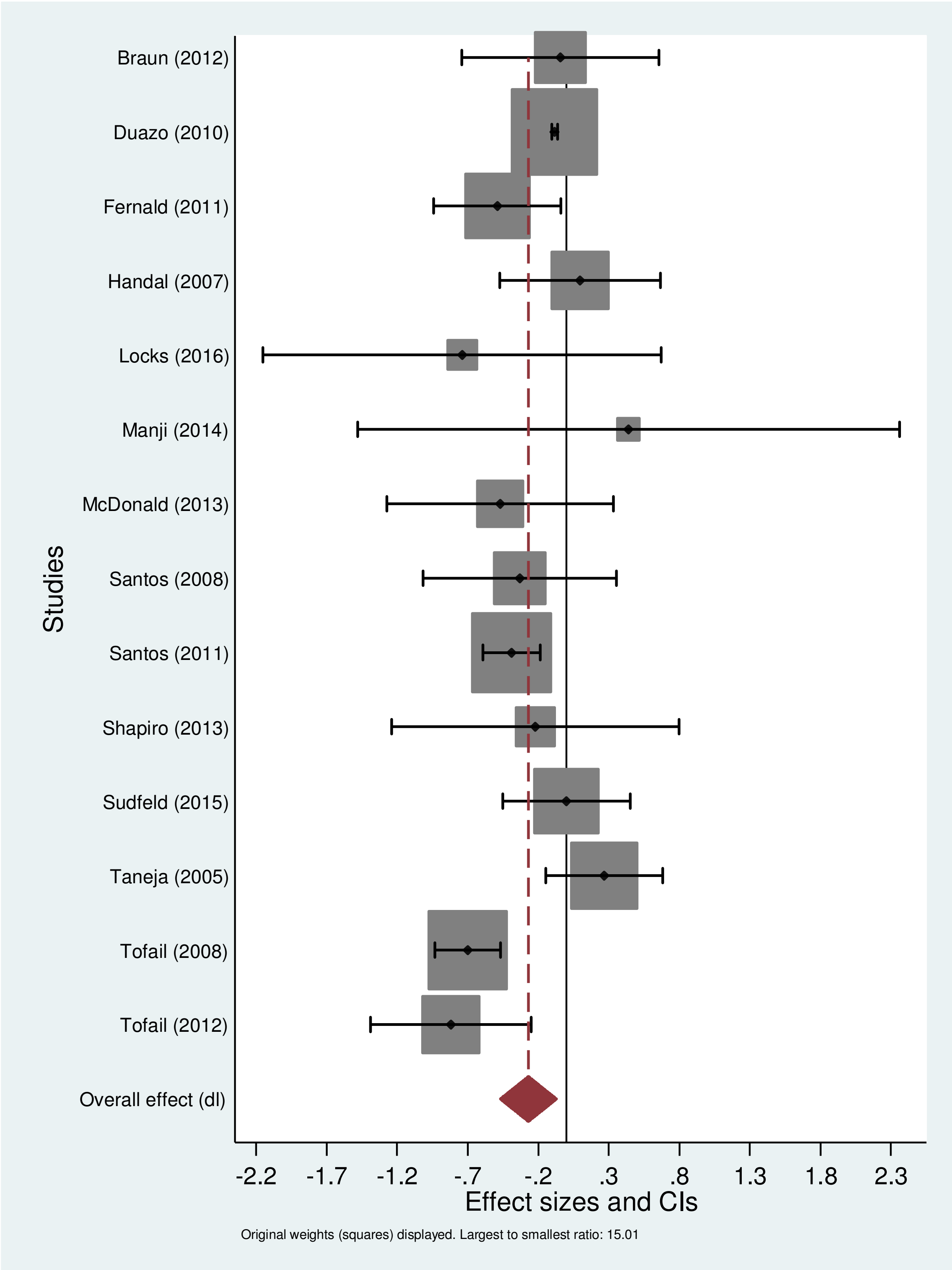

Figure 3: Association between very low Birth weight (reference: normal birth weight)) and cognitive development.

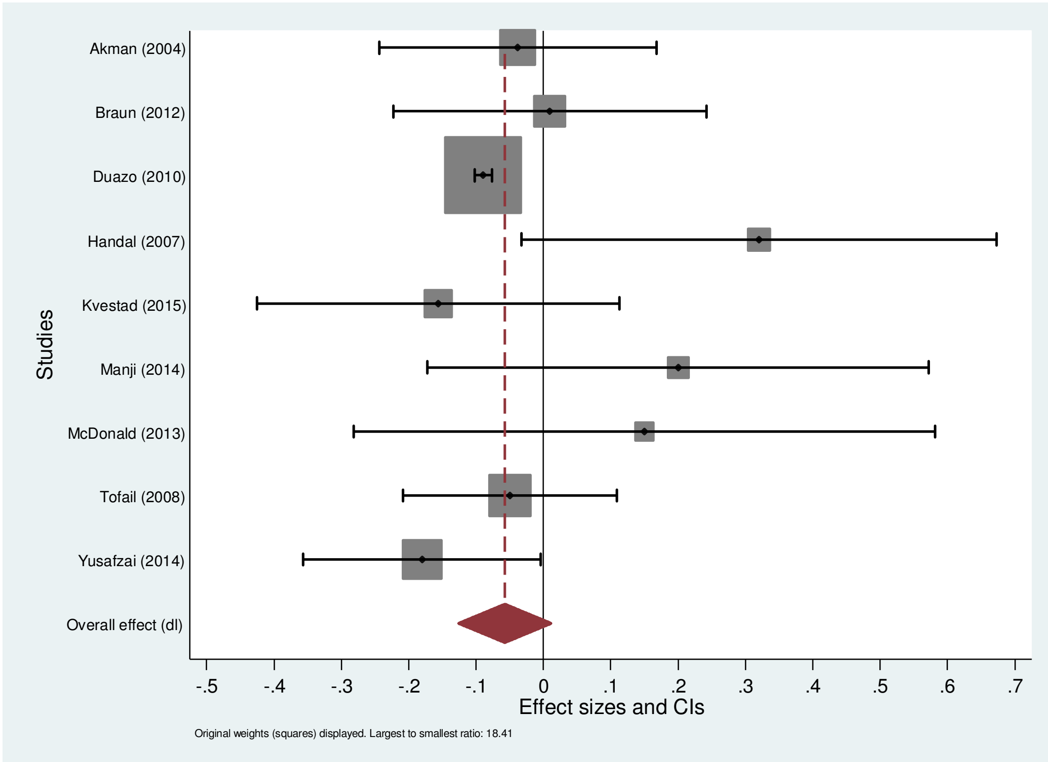

Figure 4: Association between child mild anemia (reference: no anemia) and cognitive development.

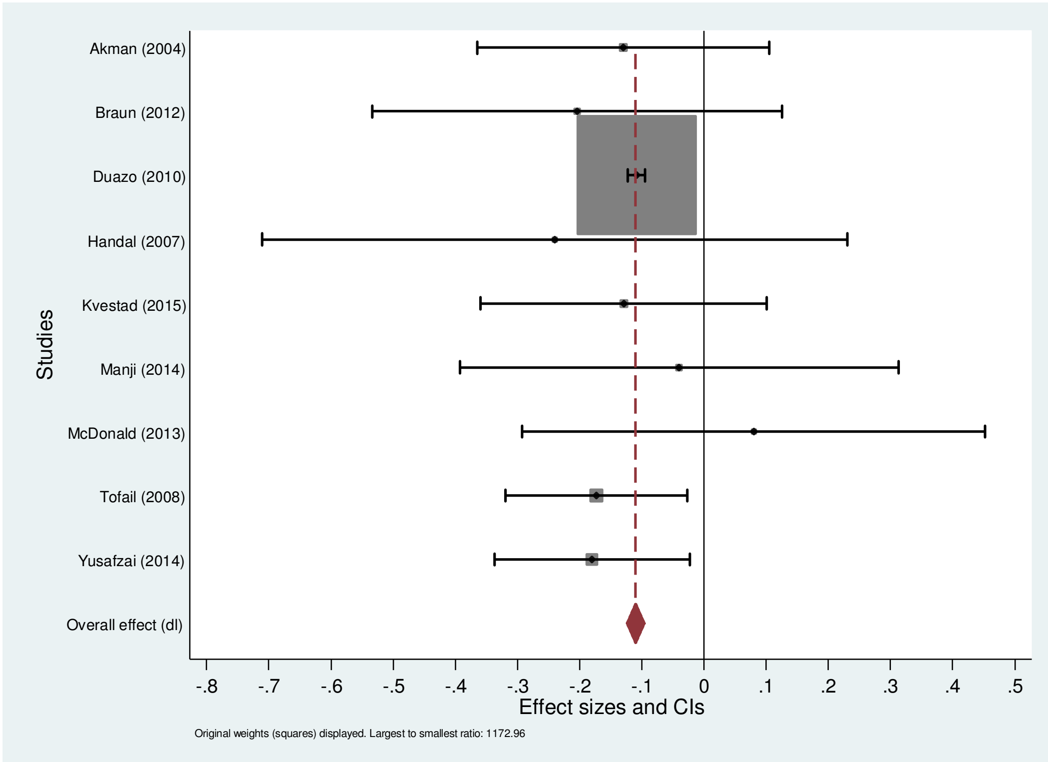

Figure 5: Association between child moderate anemia (reference: no anemia) and cognitive development.

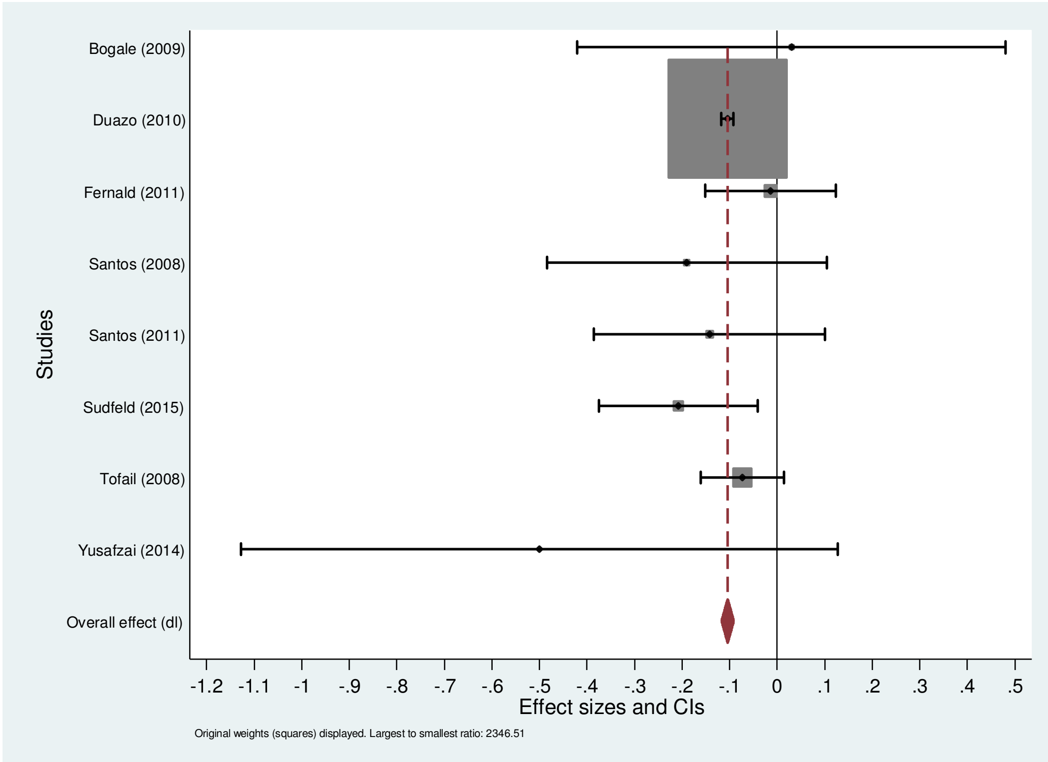

Figure 6: Association between lack of access to clean water (reference: access to clean water) and cognitive development.

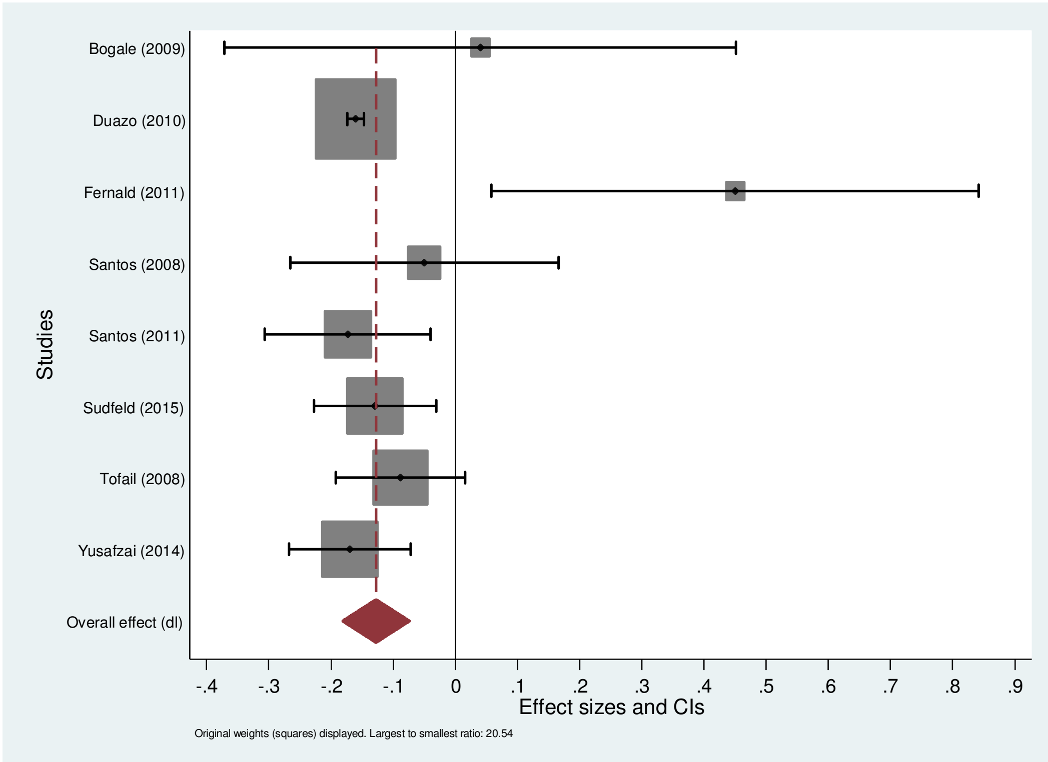

Figure 7: Association between lack of access to sanitation (reference: access to sanitation) and cognitive development.

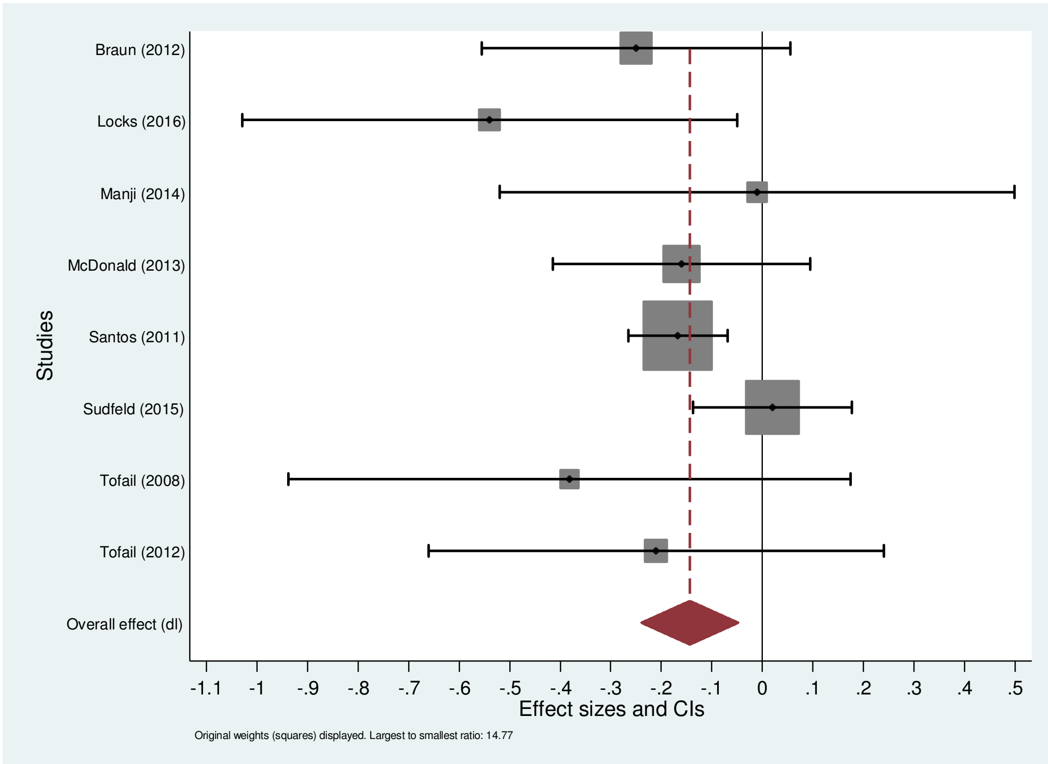

Figure 8: Association between preterm-AGA (reference: term-AGA) and cognitive development.

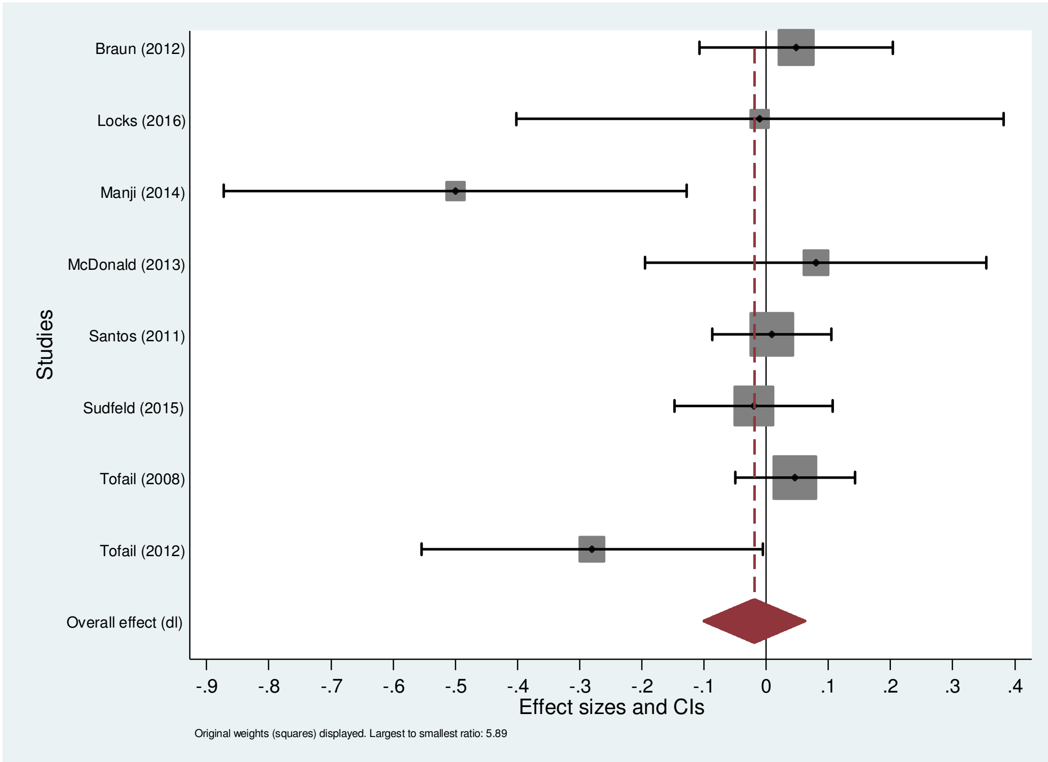

Figure 9: Association between term-SGA (reference: term-AGA) and cognitive development.

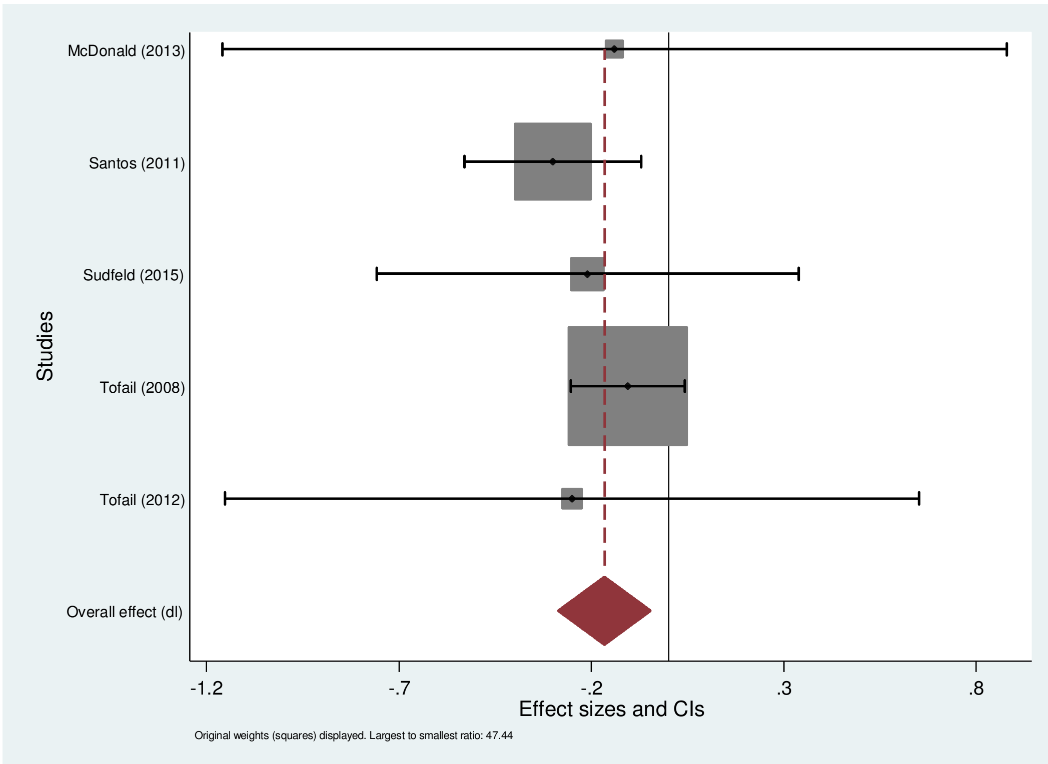

Figure 10: Association between preterm- SGA (reference: term-AGA) and cognitive development.

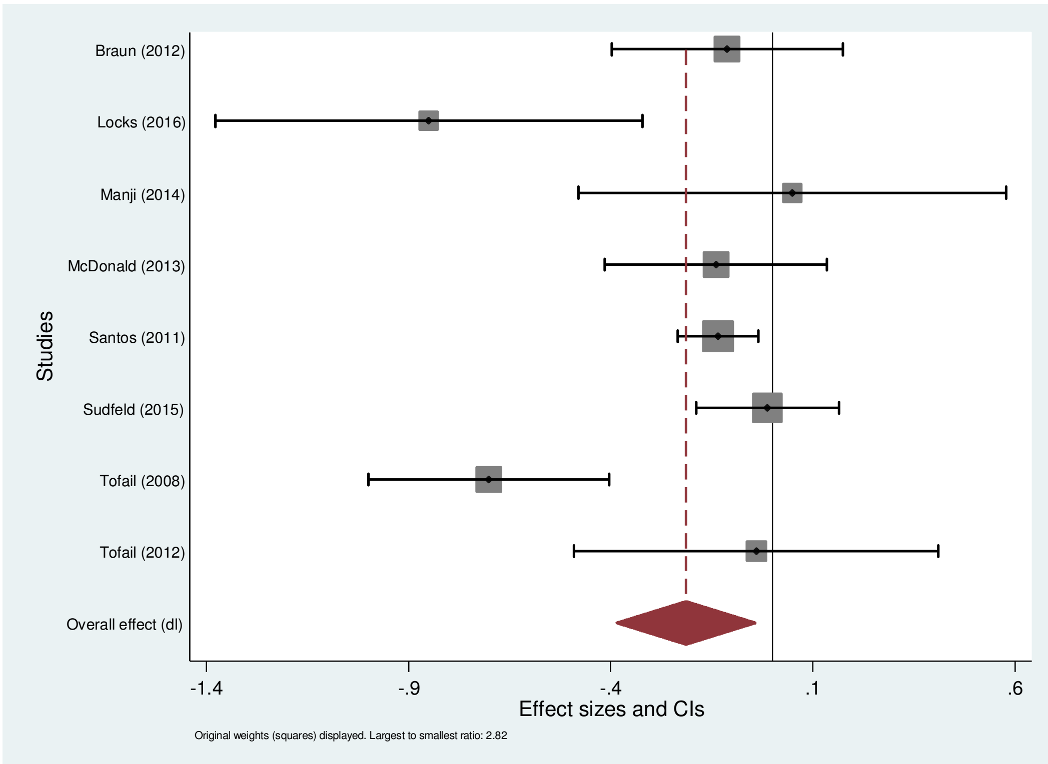

Figure 11: Association between late preterm birth, 34-37 weeks (reference: term) and cognitive development.

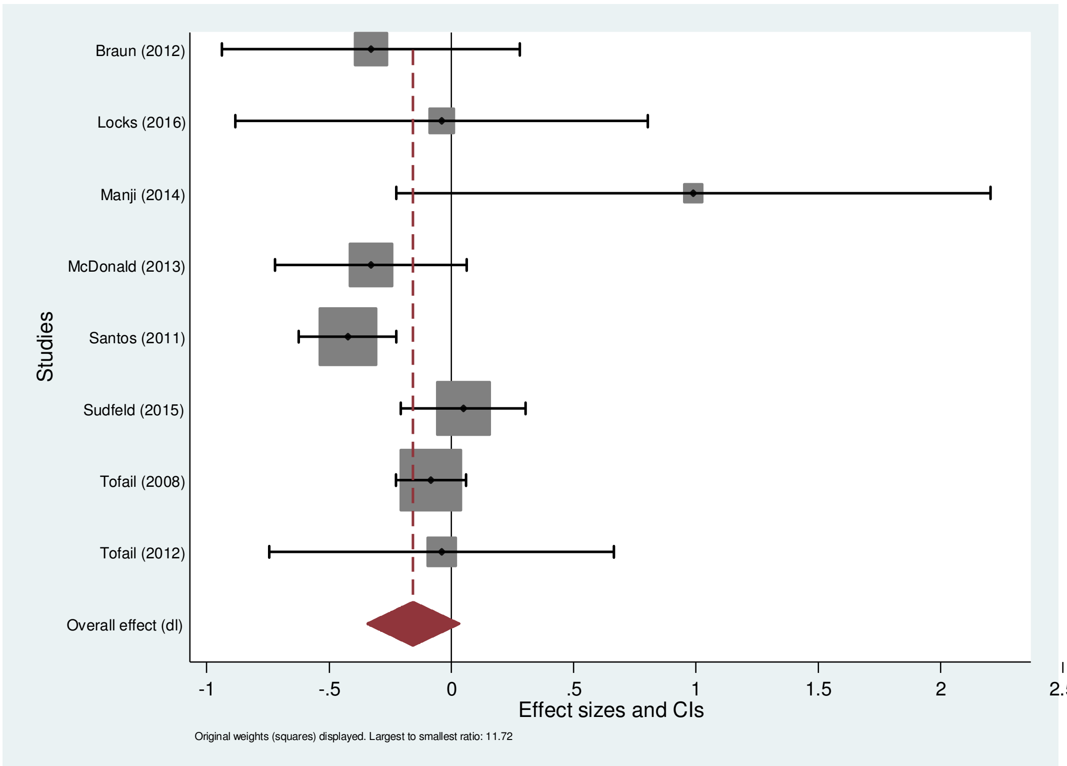

Figure 12: Association between early preterm birth, < 34 weeks (reference: term) and cognitive development.

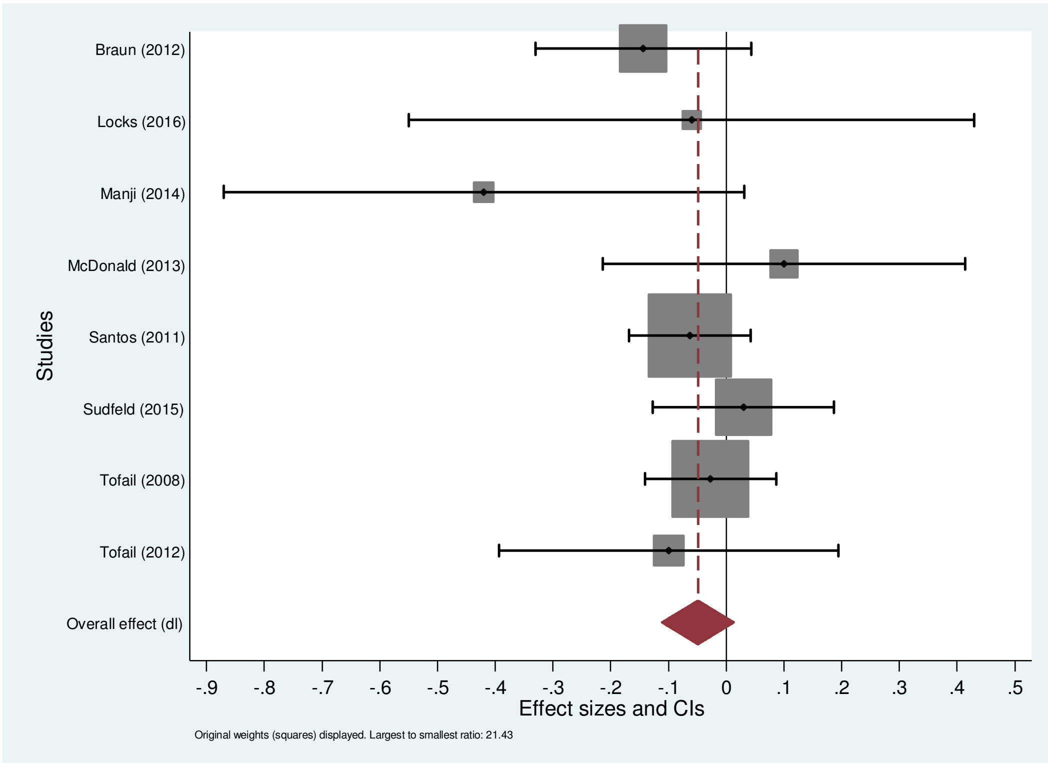

Figure 13: Association between moderate SGA (reference: AGA) and cognitive development.

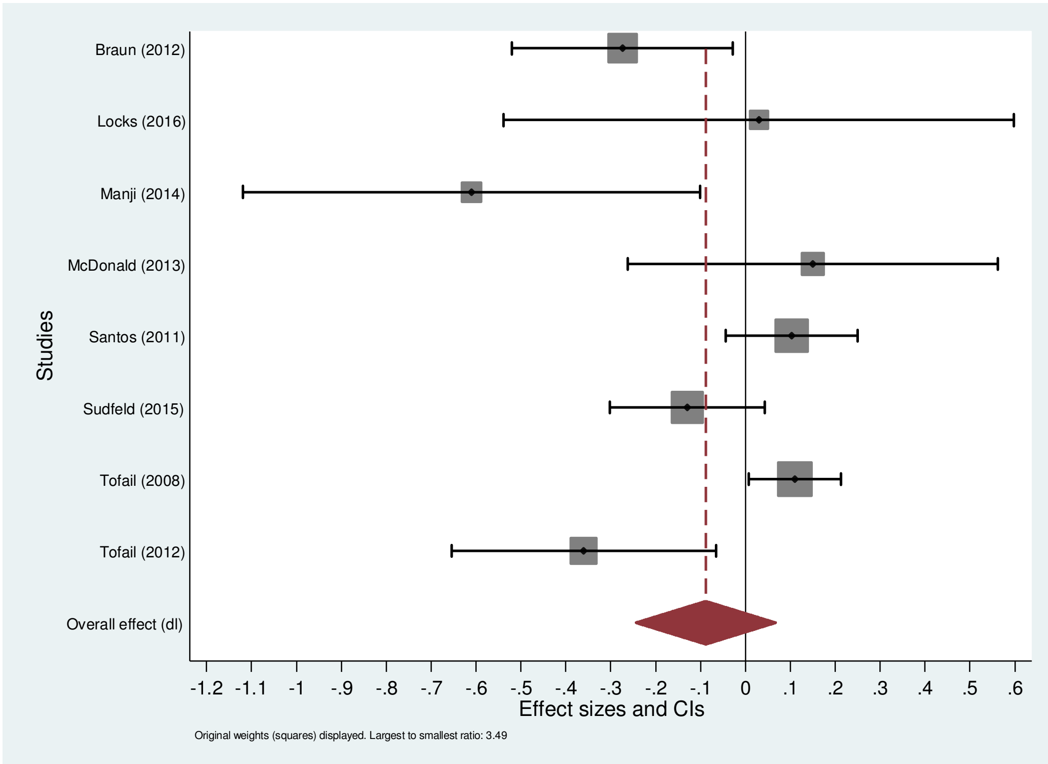

Figure 14: Association between severe SGA (reference: AGA) and cognitive development.

2. Child Risk Factors on Child's Motor Development

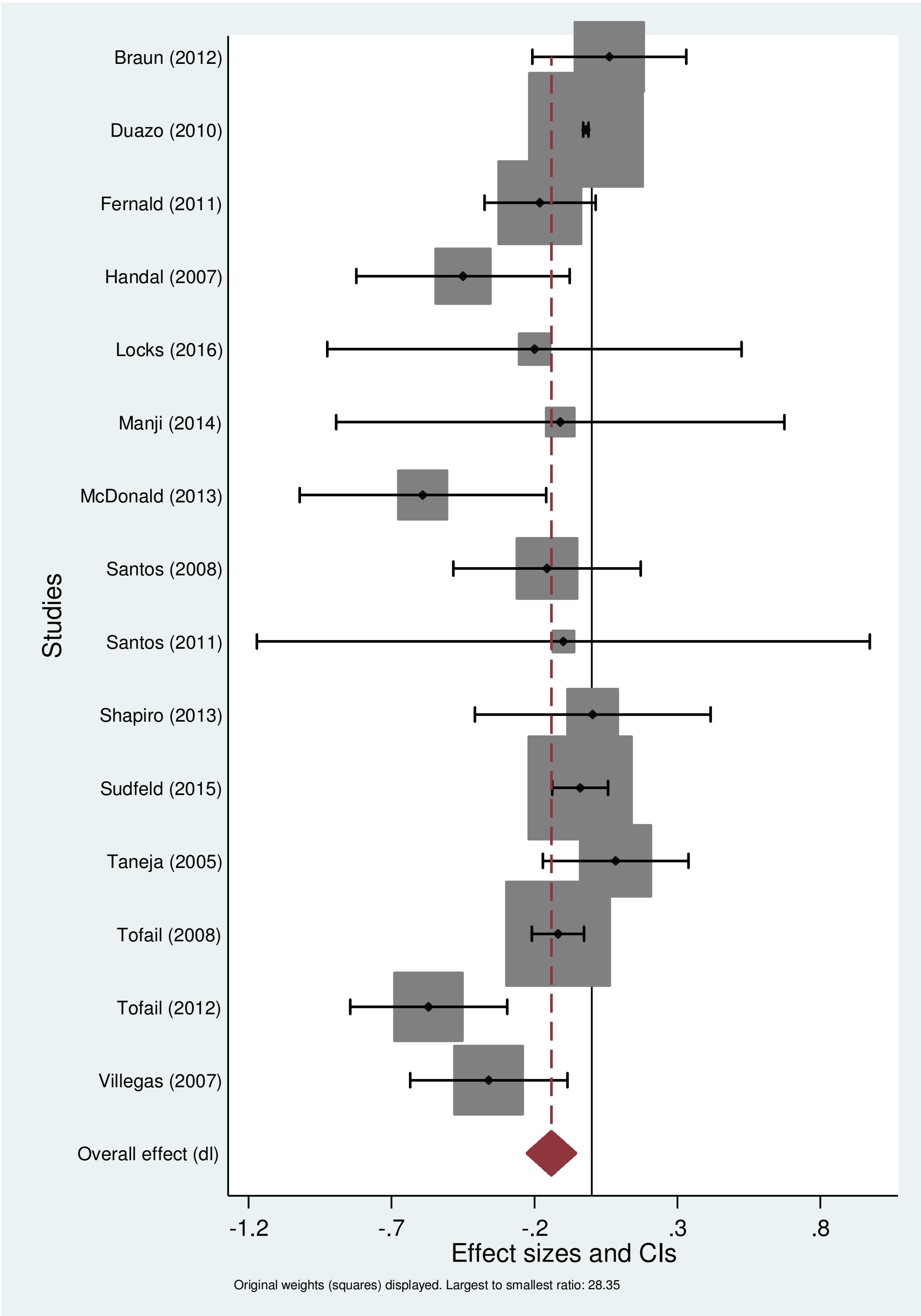

Figure 15: Association between low birth weight (reference: normal birth weight) and motor development.

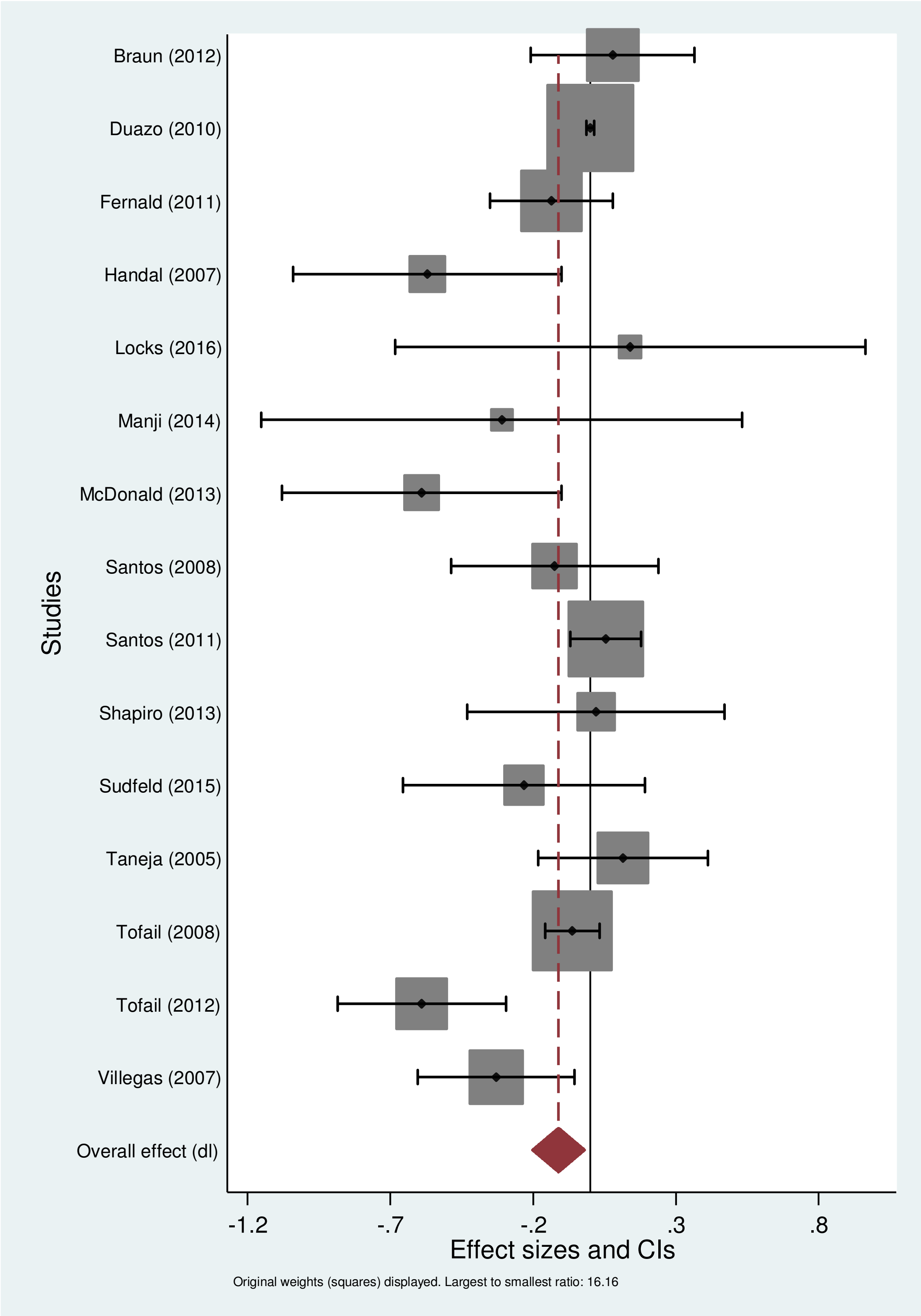

Figure 16: Association between moderately low birth weight (reference: normal birth weight) and motor development.

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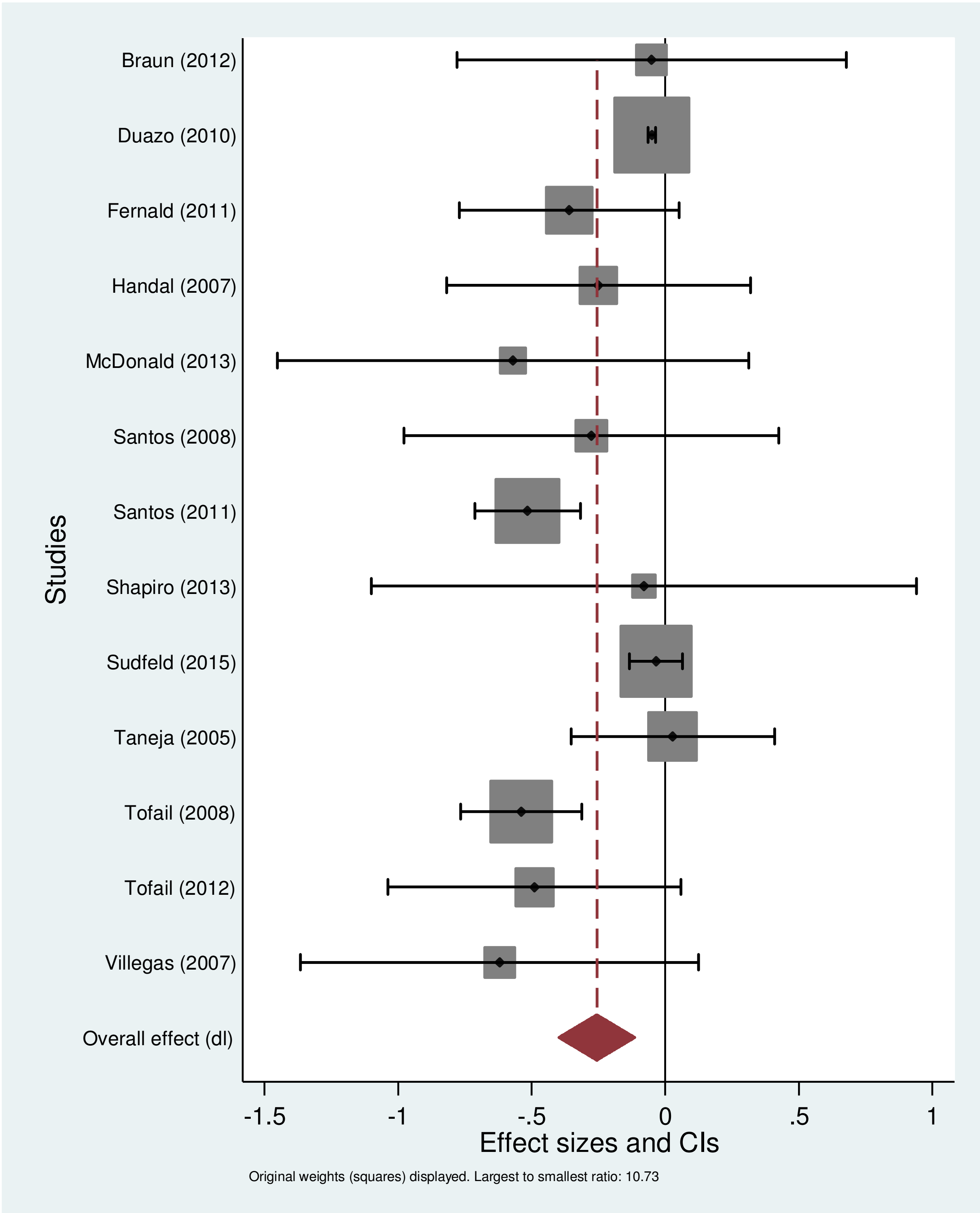

Figure 17: Association between very low birth weight (reference: normal birth weight) and motor development.

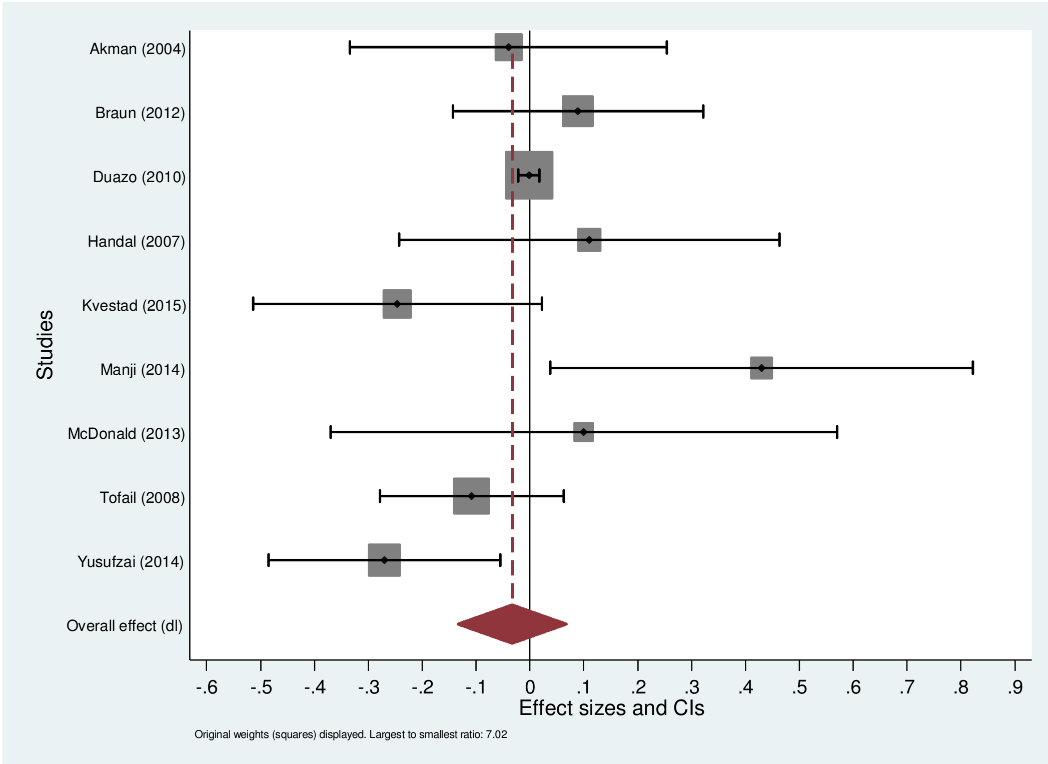

Figure 18: Association between child mild anemia (reference: no anemia) and motor development.

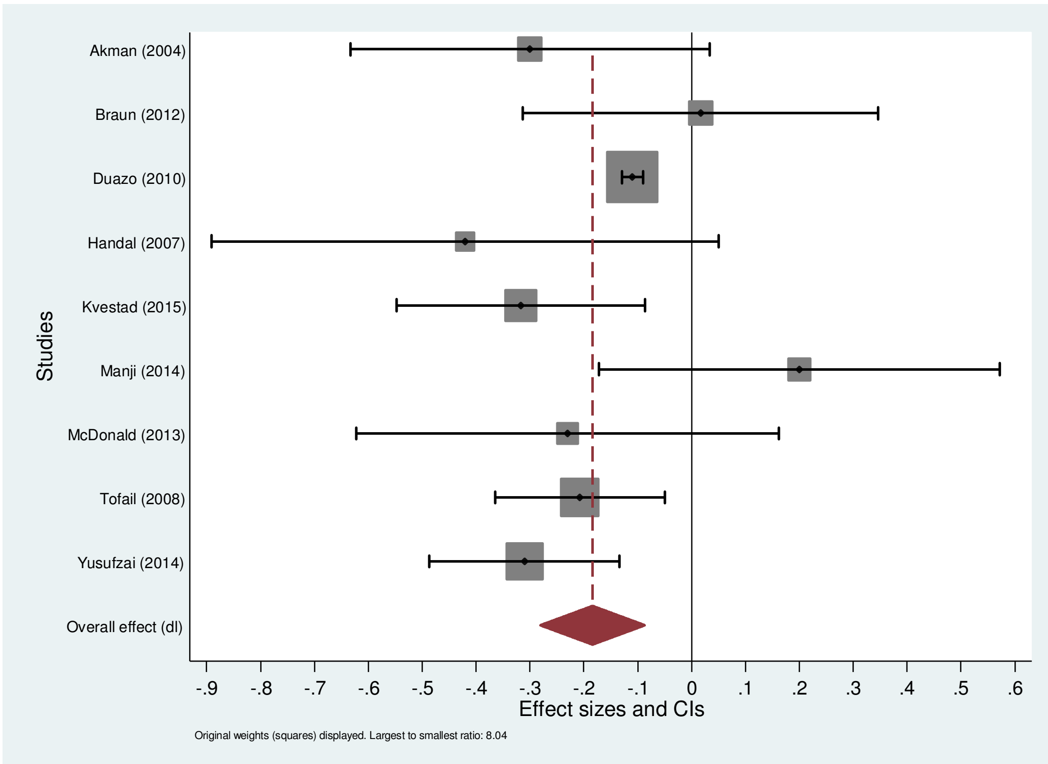

Figure 19: Association between child moderate anemia (reference: no anemia) and motor development.

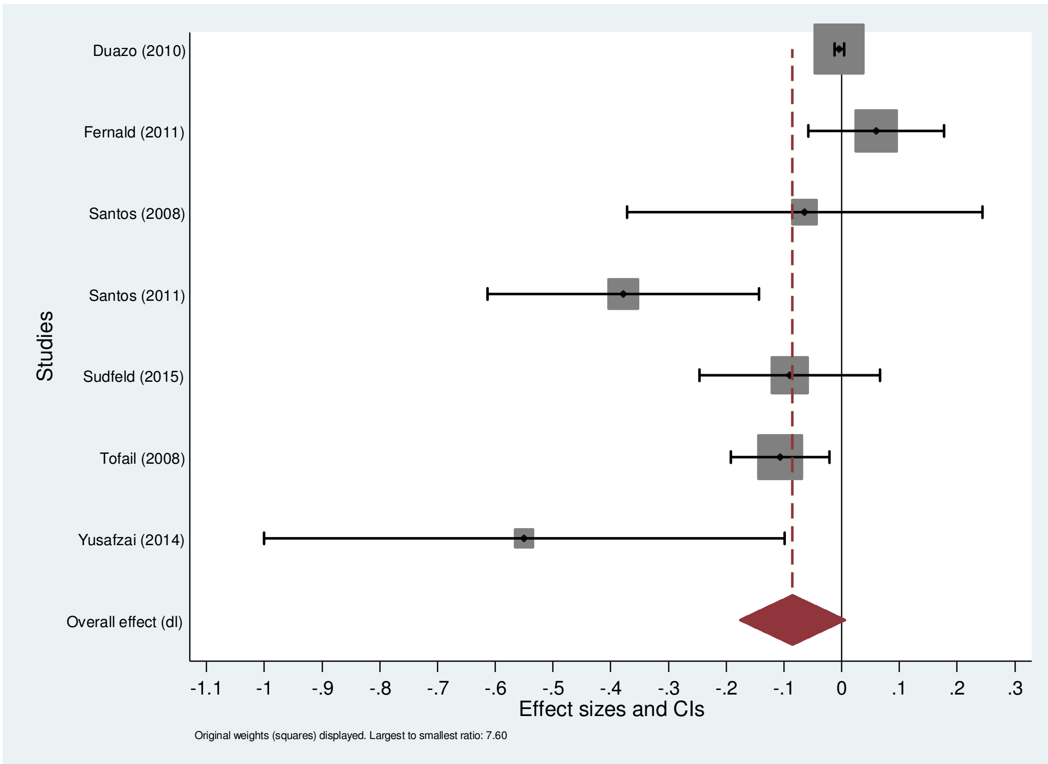

Figure 20: Association between lack of access to clean water (reference: access to clean water) and motor development.

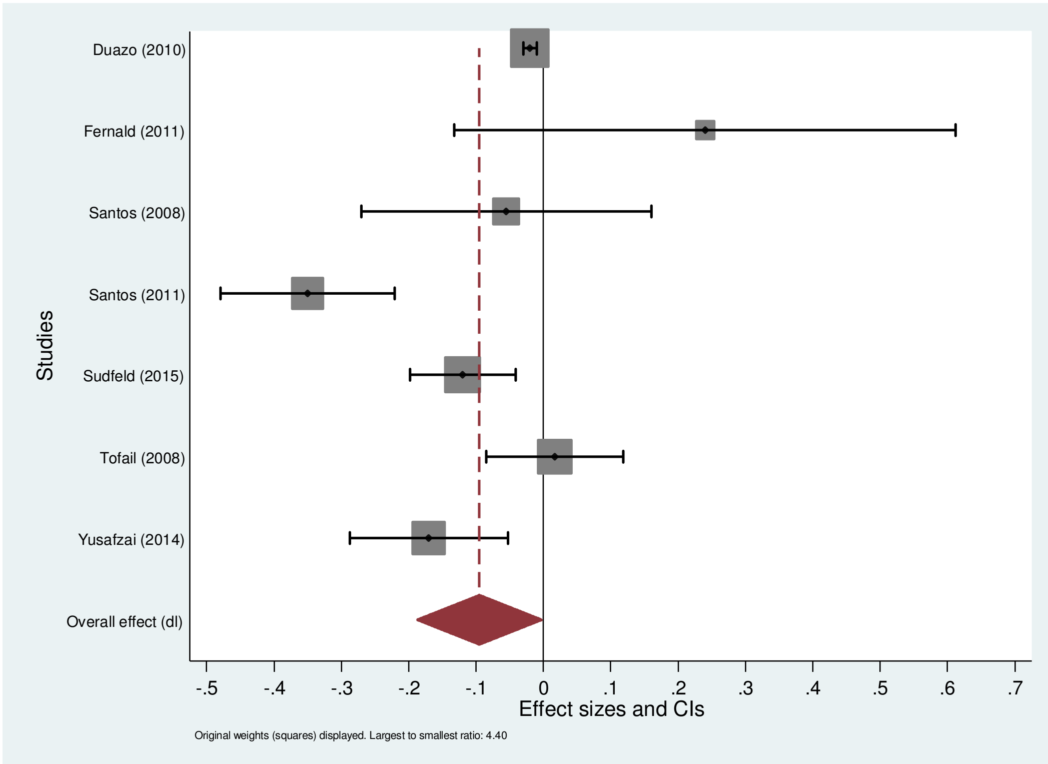

Figure 21: Association between lack of access to sanitation (reference: access to sanitation) and motor development.

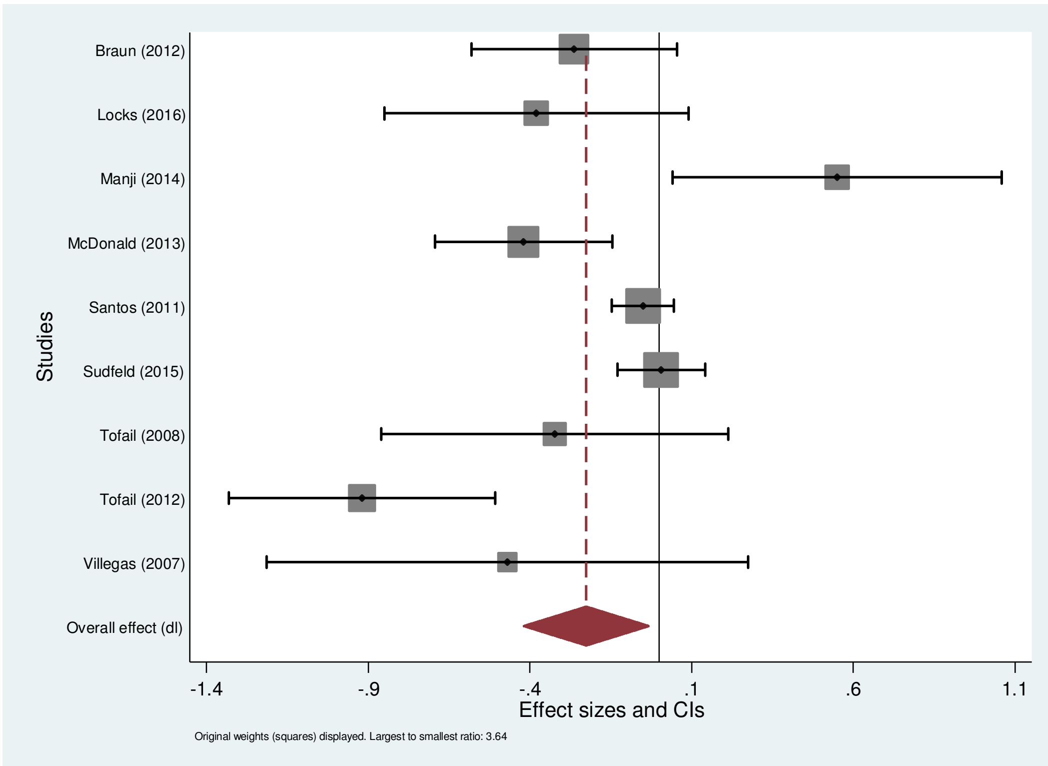

Figure 22: Association between preterm-AGA (reference: term-AGA) and motor development.

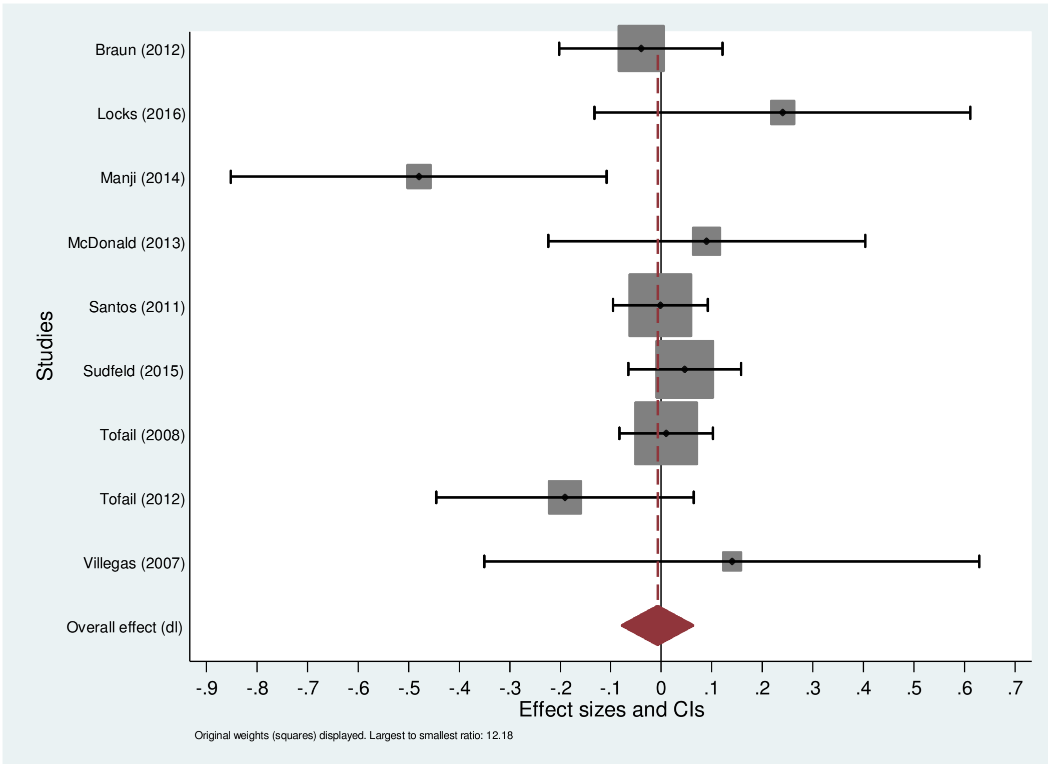

Figure 23: Association between term-SGA (reference: term-AGA) and motor development.

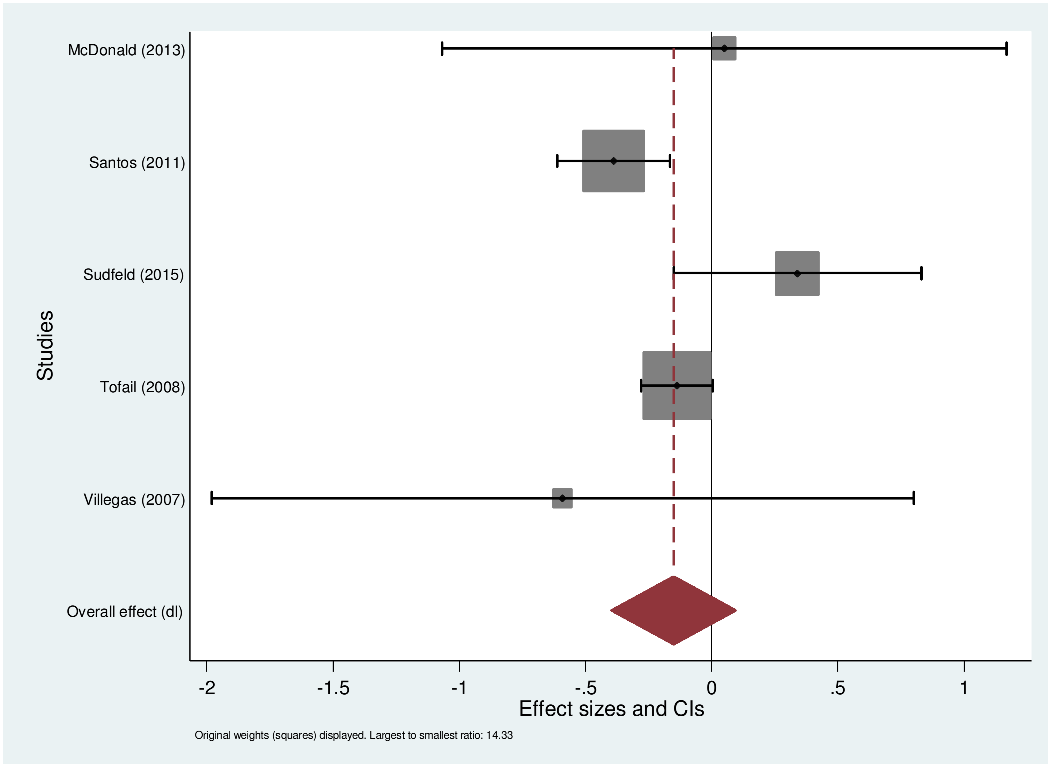

Figure 24: Association between preterm-SGA (reference: term-AGA) and motor development.

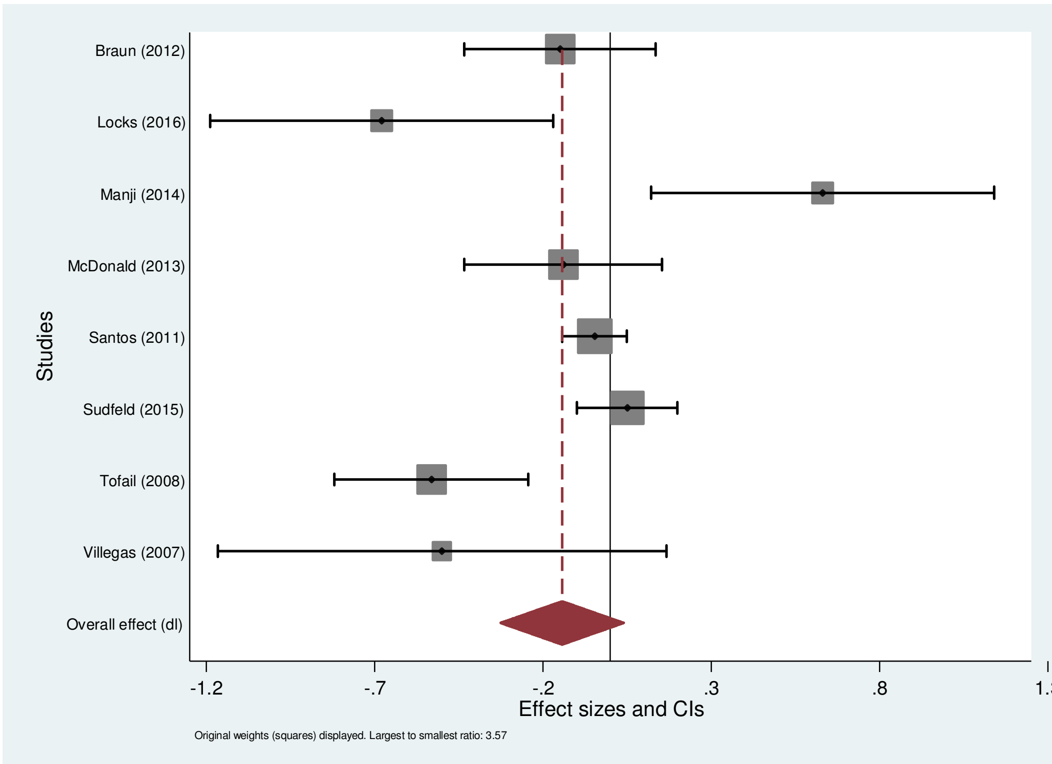

Figure 25: Association between late preterm birth, 34-37 weeks (reference: term) and motor development.

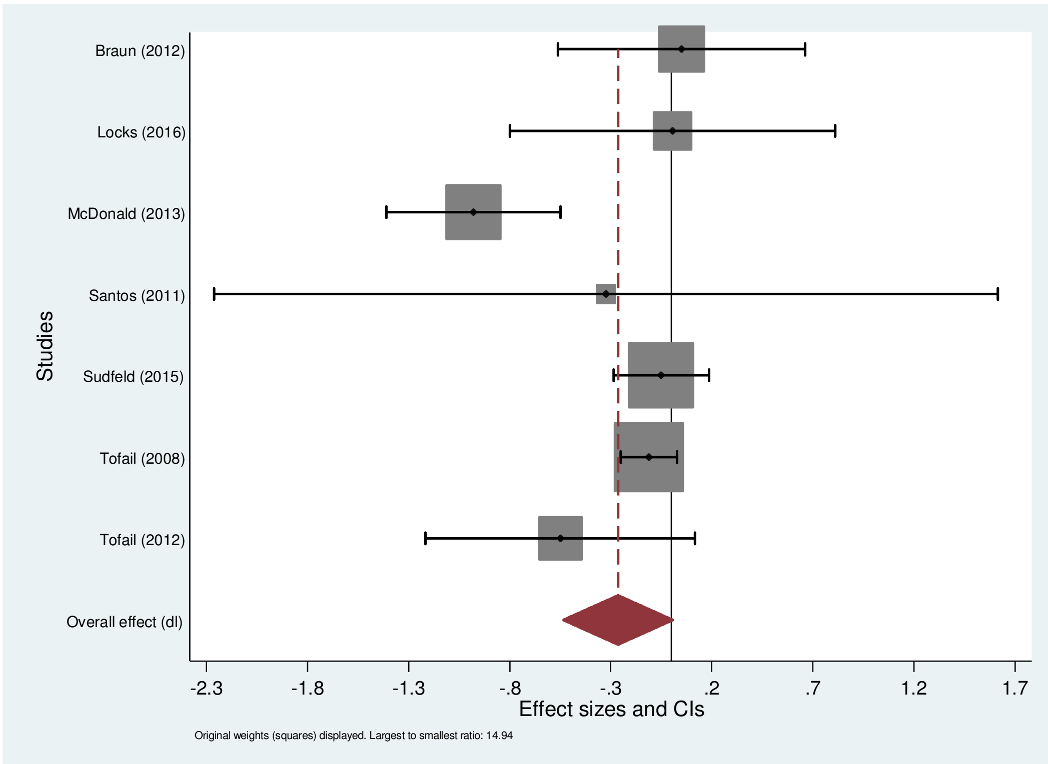

Figure 26: Association between early preterm birth, < 34 weeks (reference: term) and motor development.

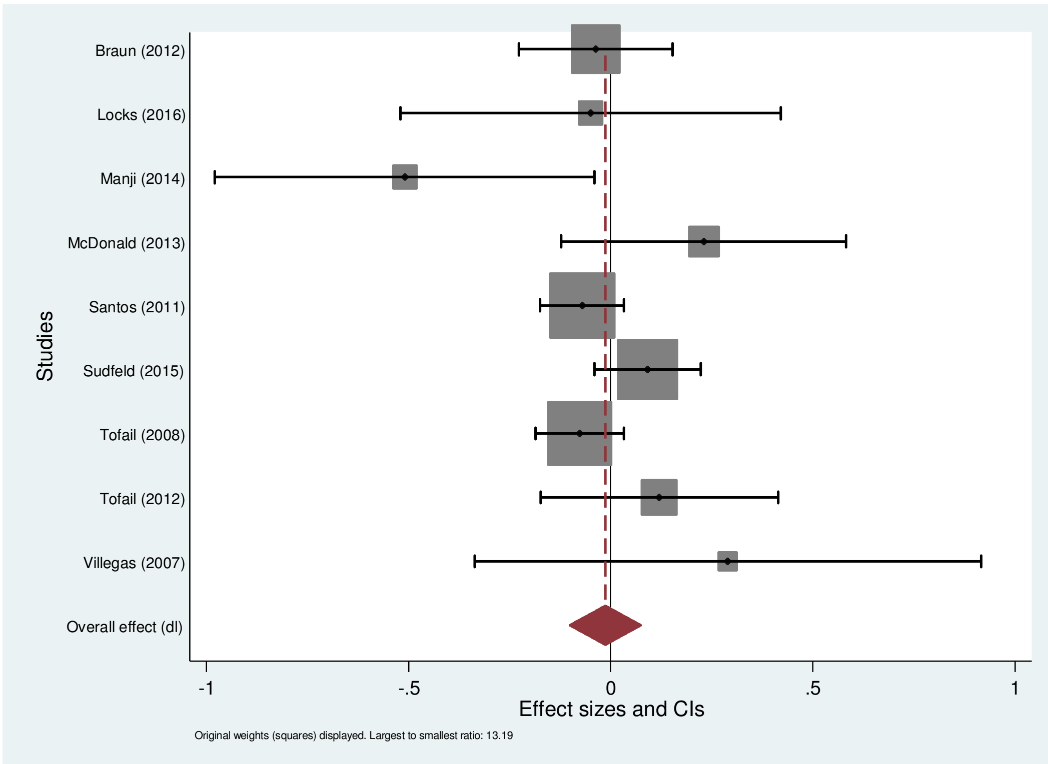

Figure 27: Association between moderate SGA (reference: AGA) and motor development.

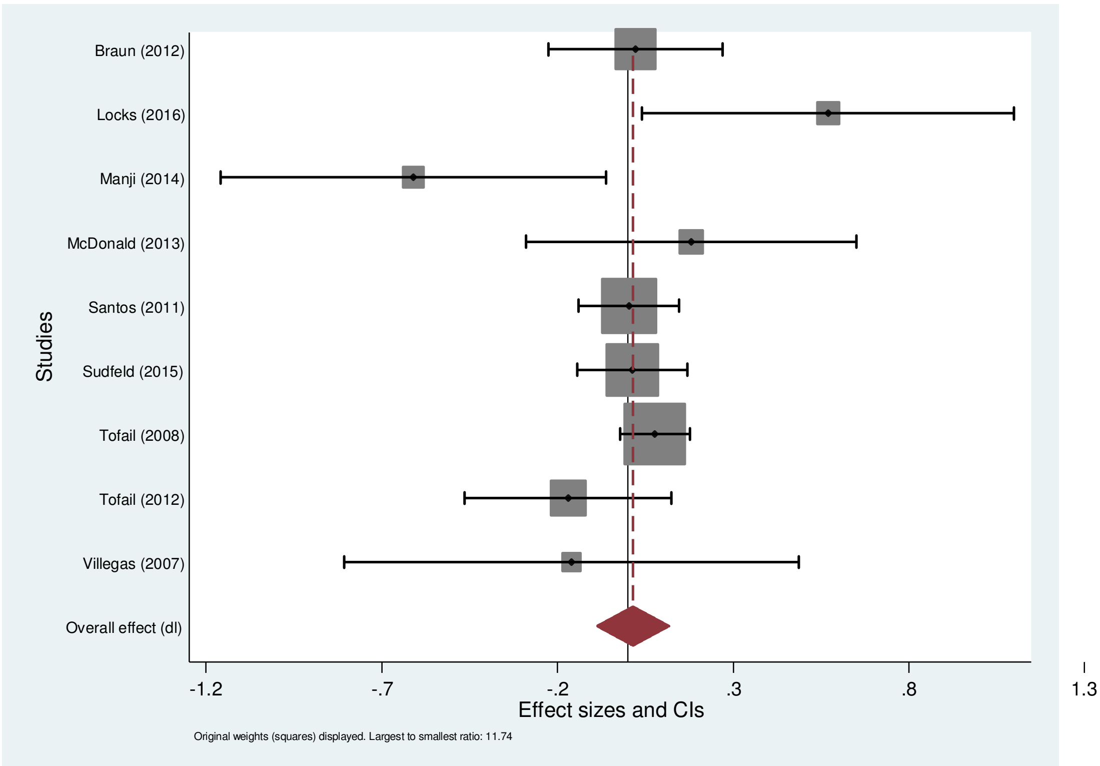

Figure 28: Association between severe SGA (reference: AGA) and motor development.

3. Child Risk Factors on Child's Language Development

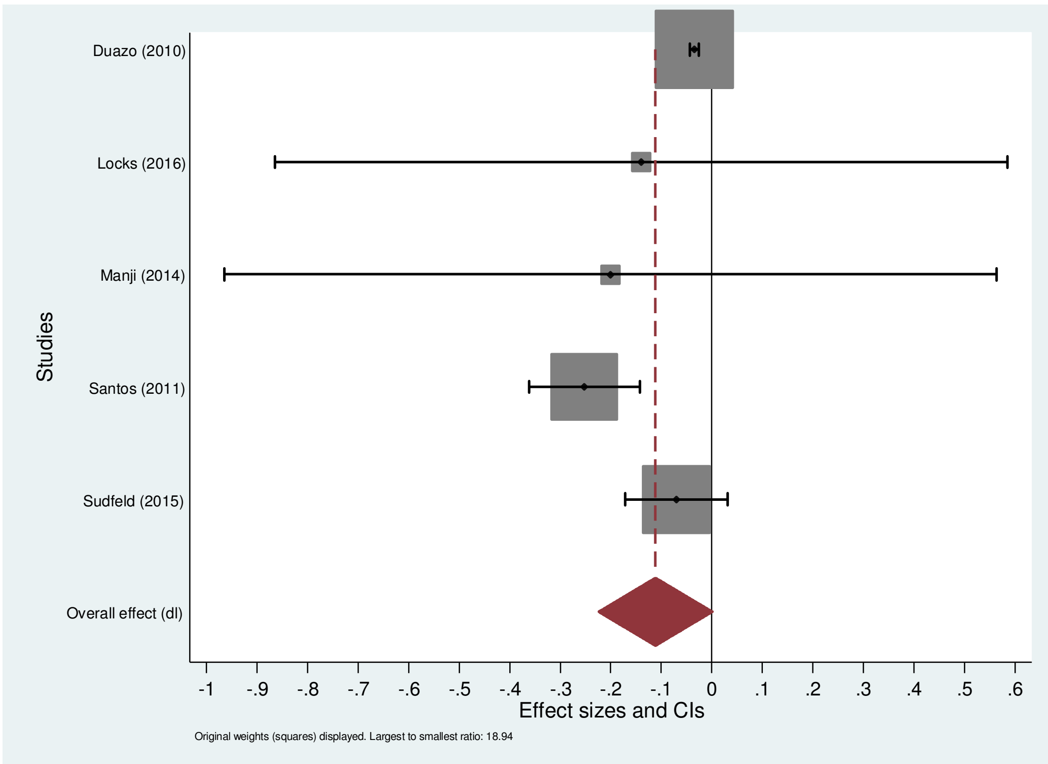

Figure 29: Association between low birth weight (LBW) and (reference: normal birth weight) and language development.

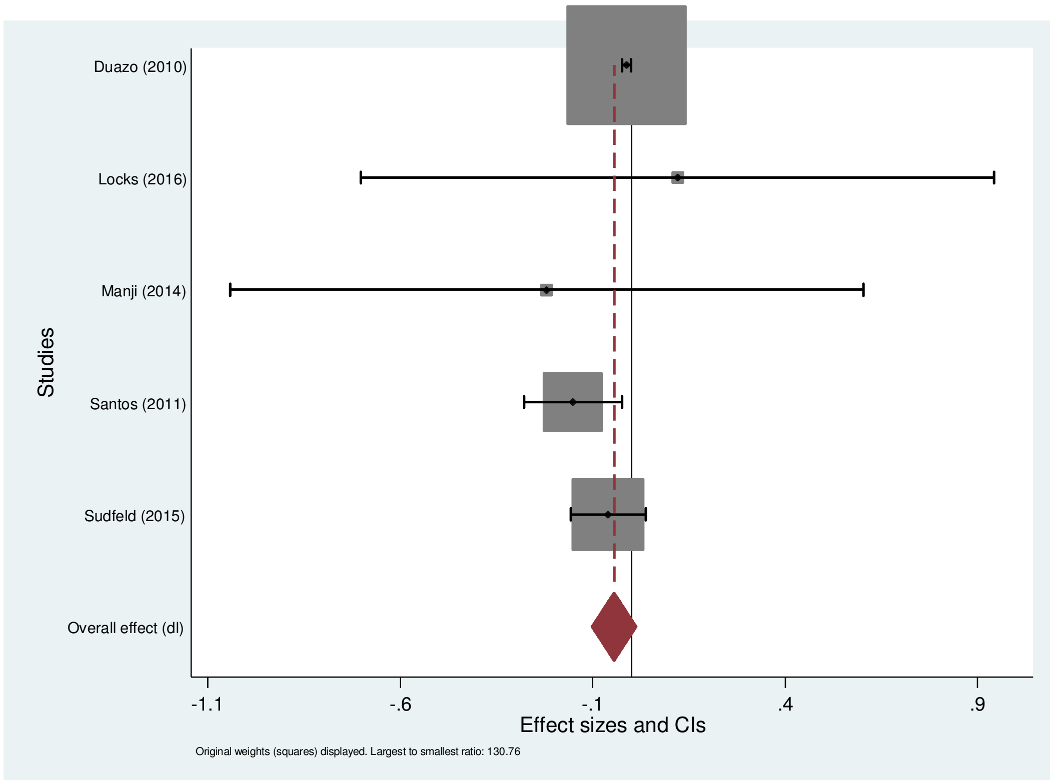

Figure 30: Association between moderately low birth weight and (reference: normal birth weight) and language development.

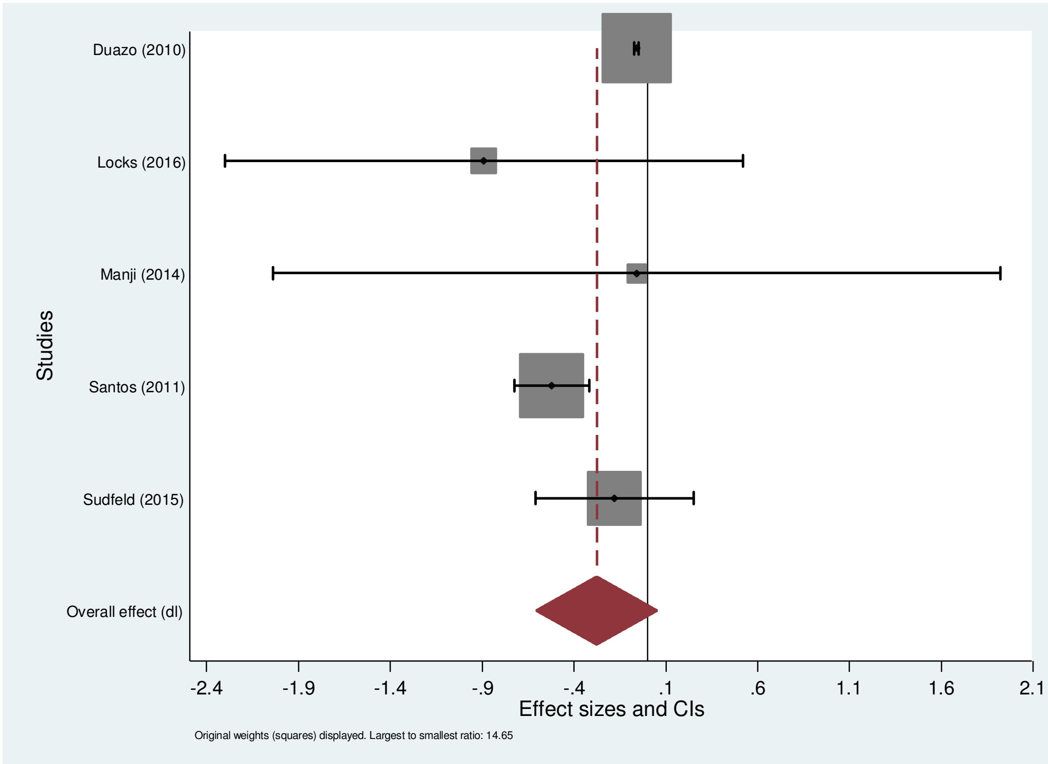

Figure 31: Association between very low birth weight and (reference: normal birth weight) and language development.

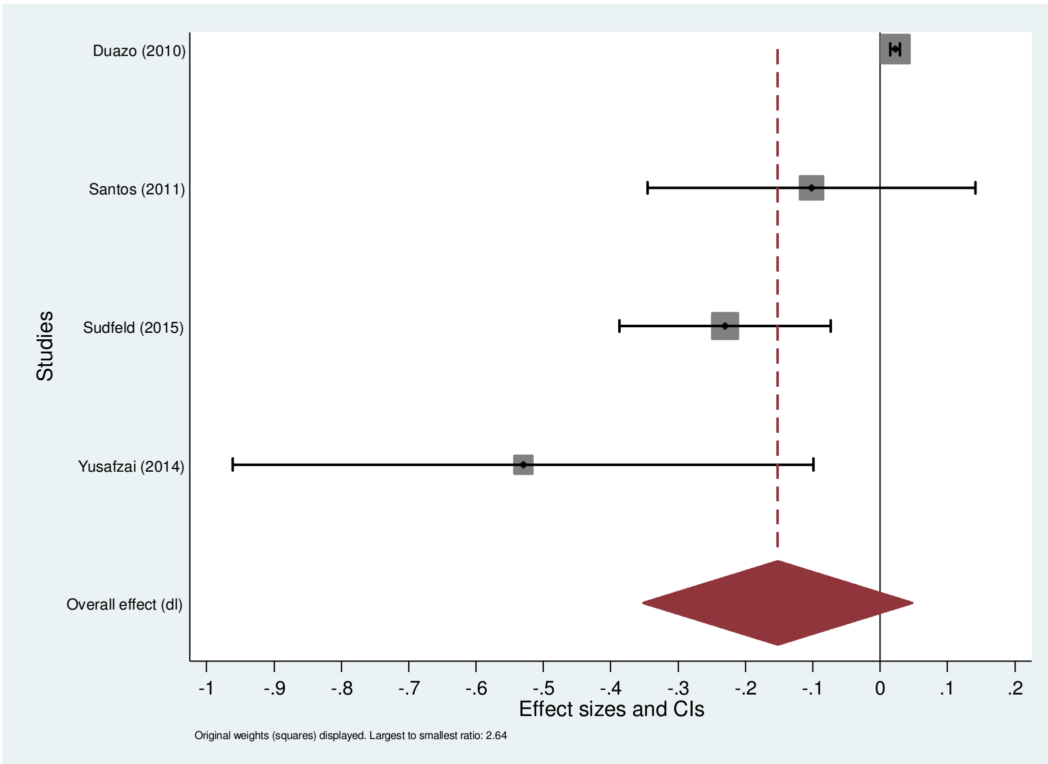

Figure 32: Association between lack of access to clean water (reference: access to clean water) and language development.

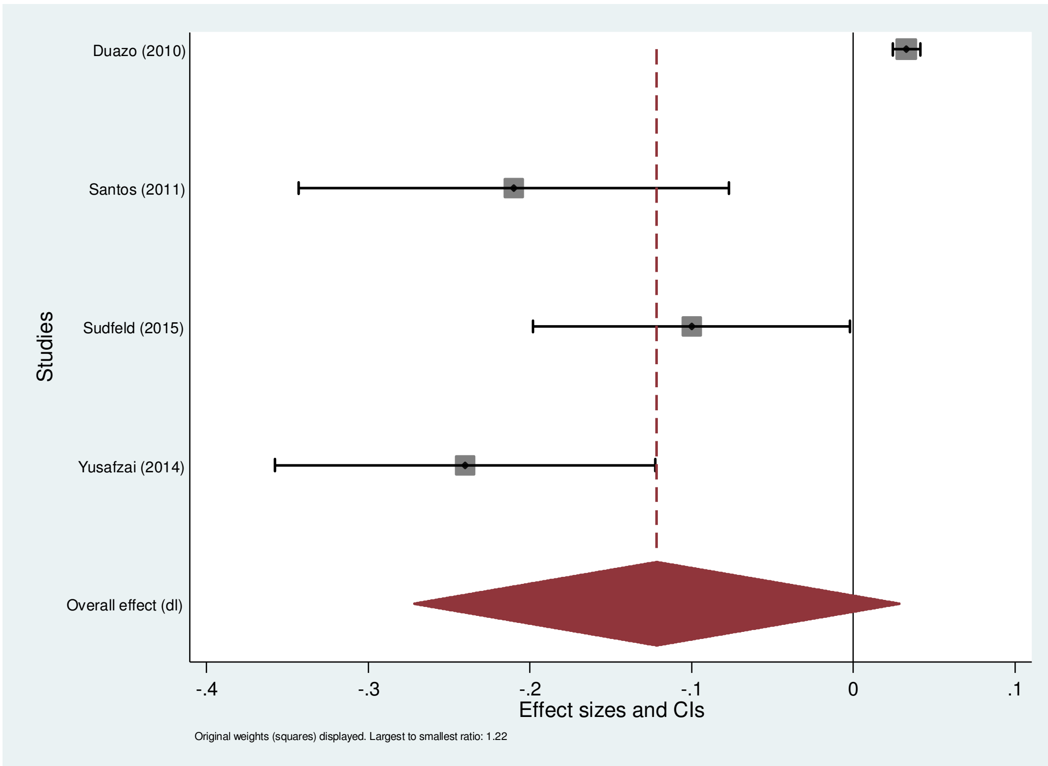

Figure 33: Association between lack of access to sanitation (reference: access to sanitation) and language development.

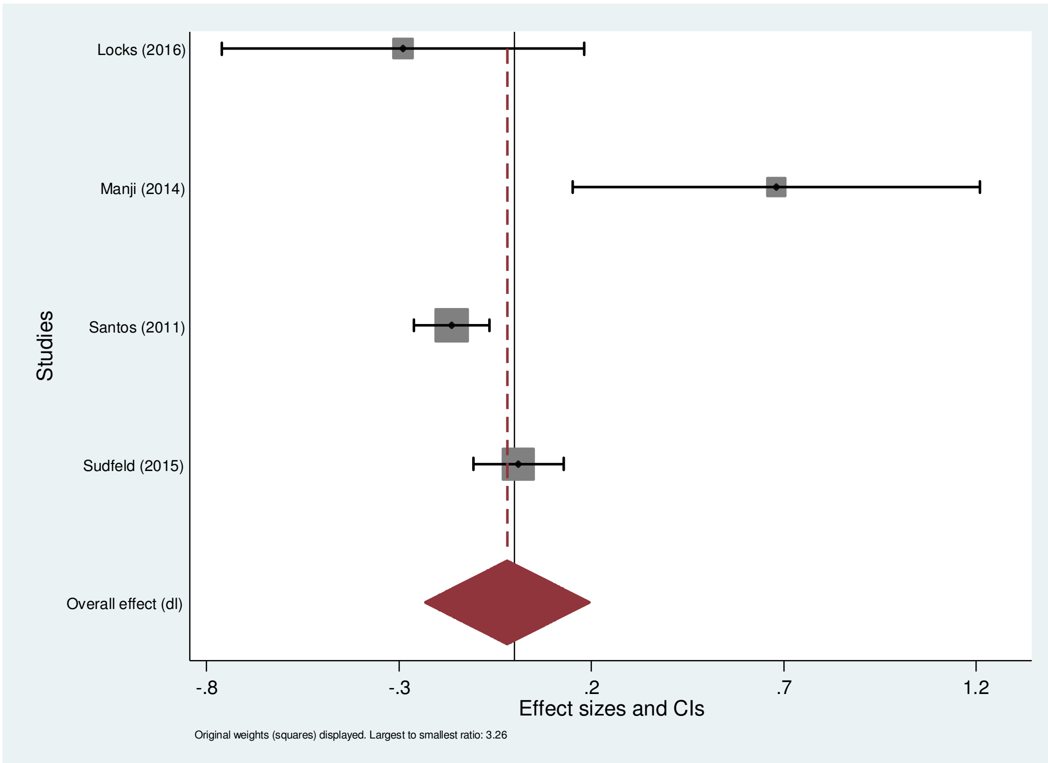

Figure 34: Association between preterm-AGA (reference: term-AGA) and language development.

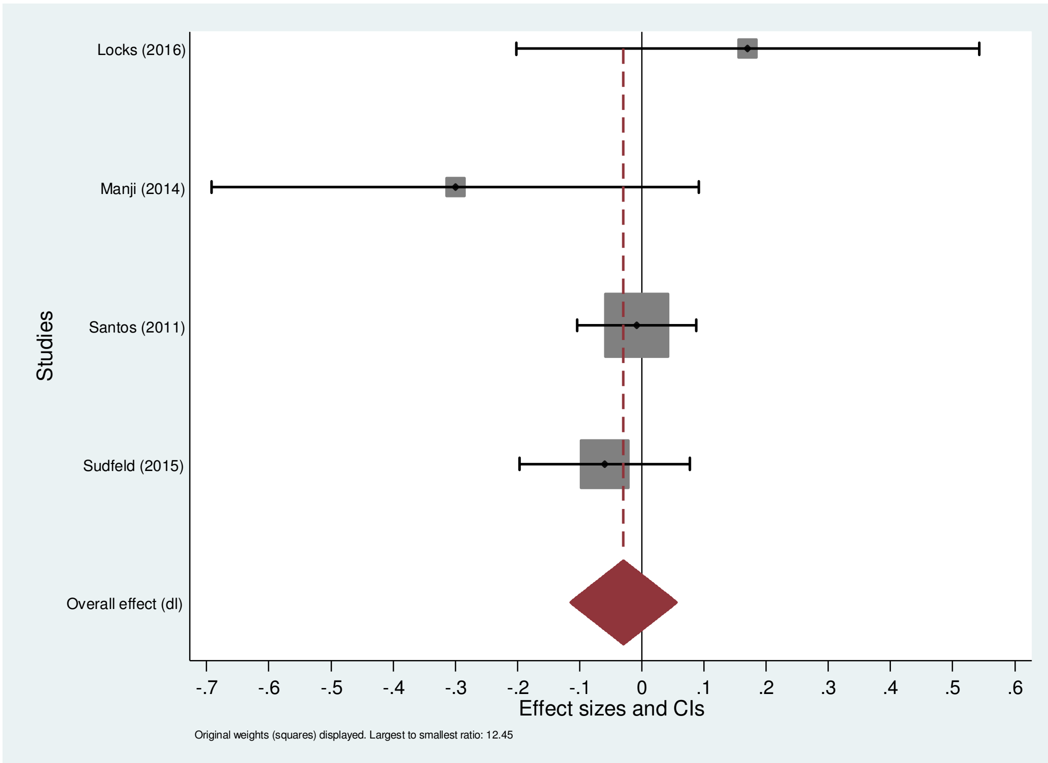

Figure 35: Association between term-SGA (reference: term-AGA) and language development.

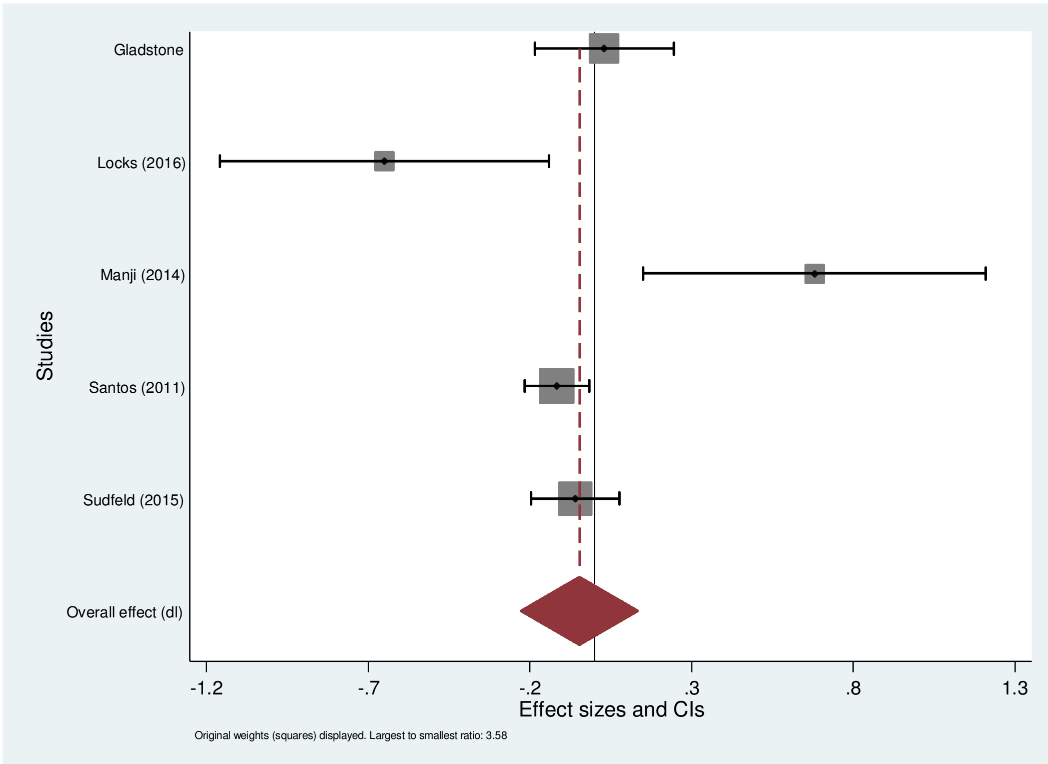

Figure 36: Association between late preterm birth, 34-37 weeks (reference: term) and language development.

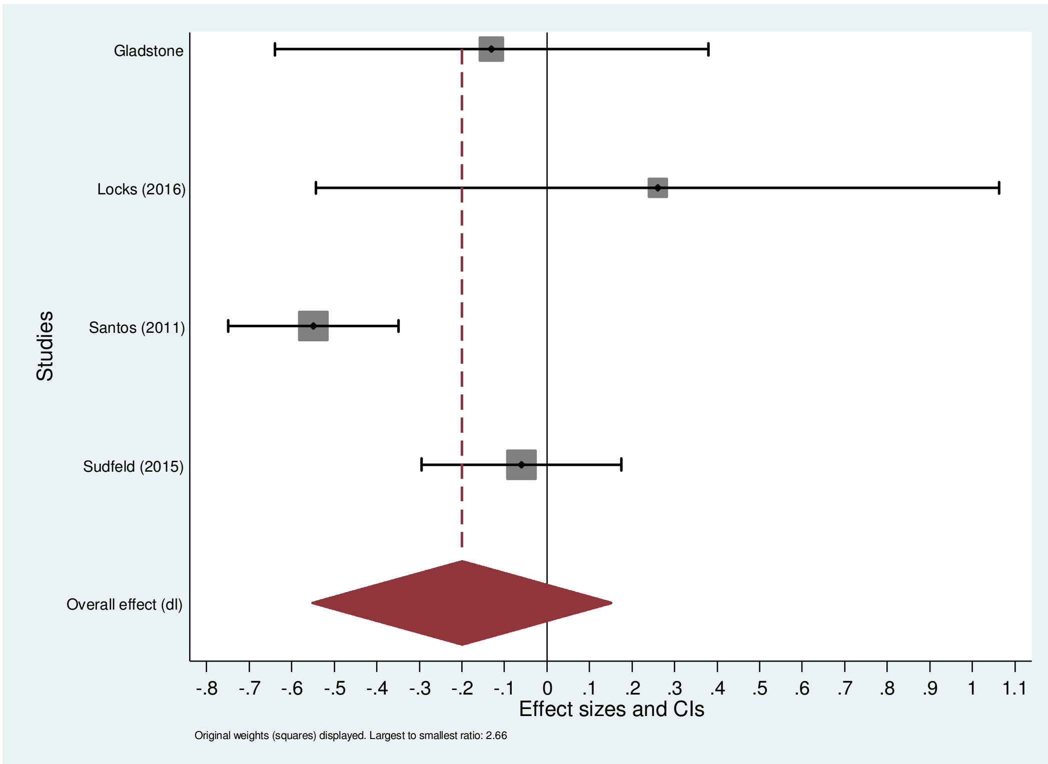

Figure 37: Association between early preterm birth, < 34 weeks (reference: term) and language development.

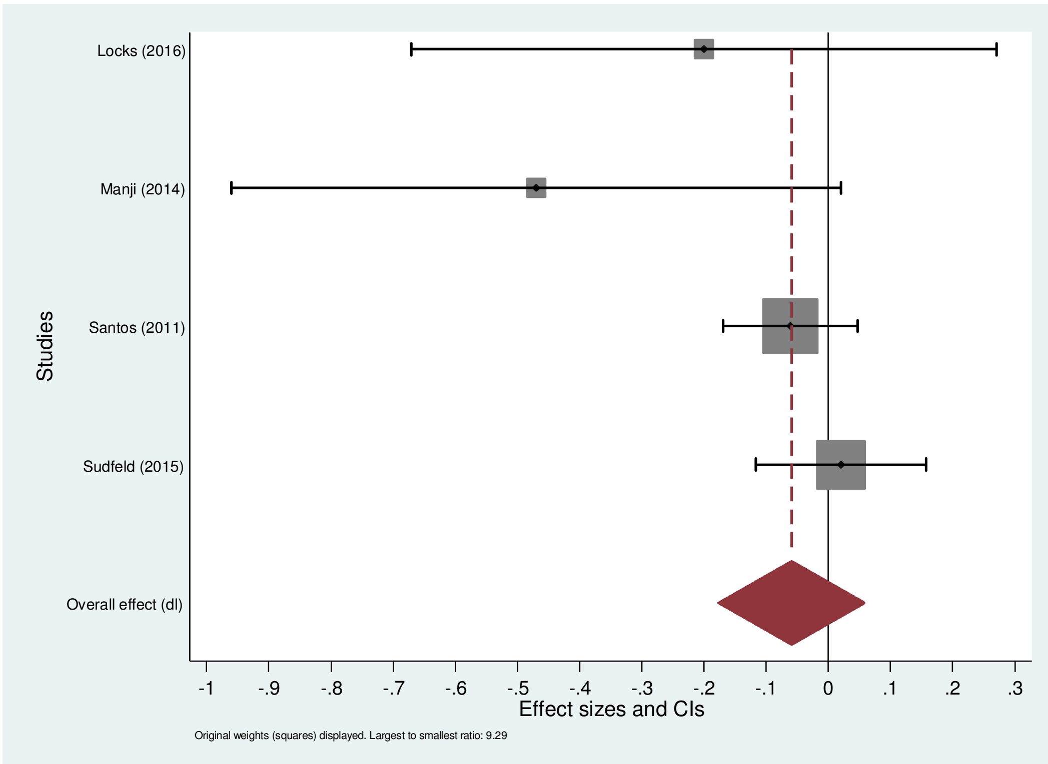

Figure 38: Association between moderate SGA (reference: AGA) and language development.

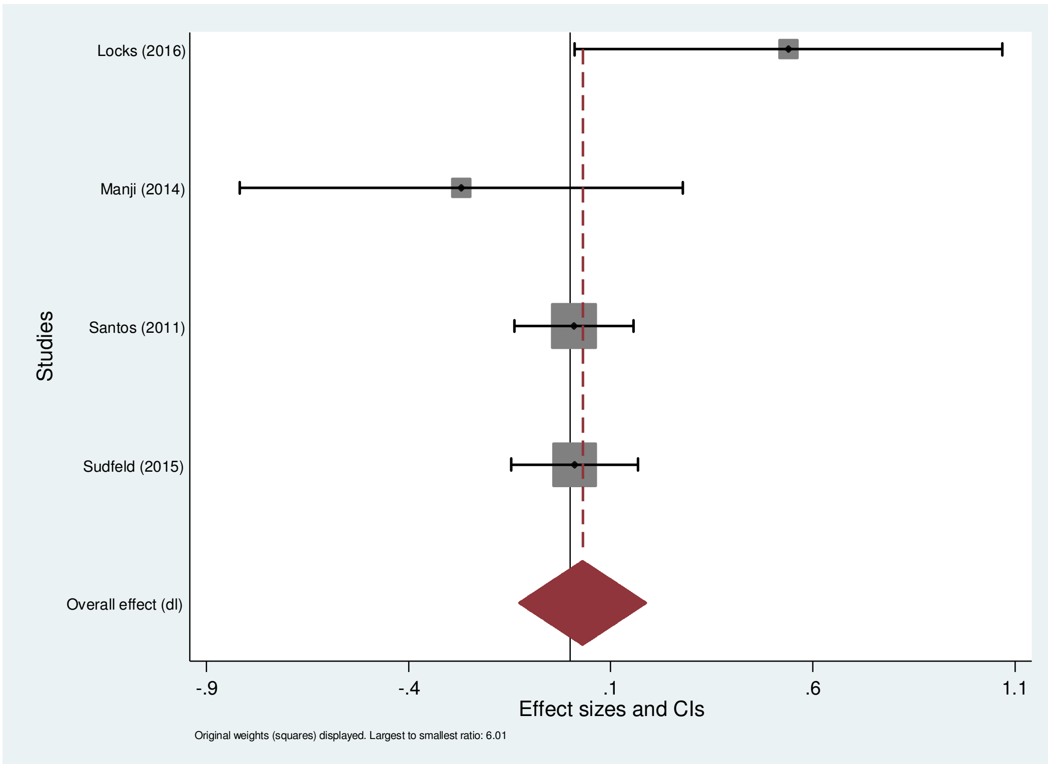

Figure 39: Association between severe SGA (reference: AGA) and language development.

4. Parental Risk Factors on Child's Cognitive Development

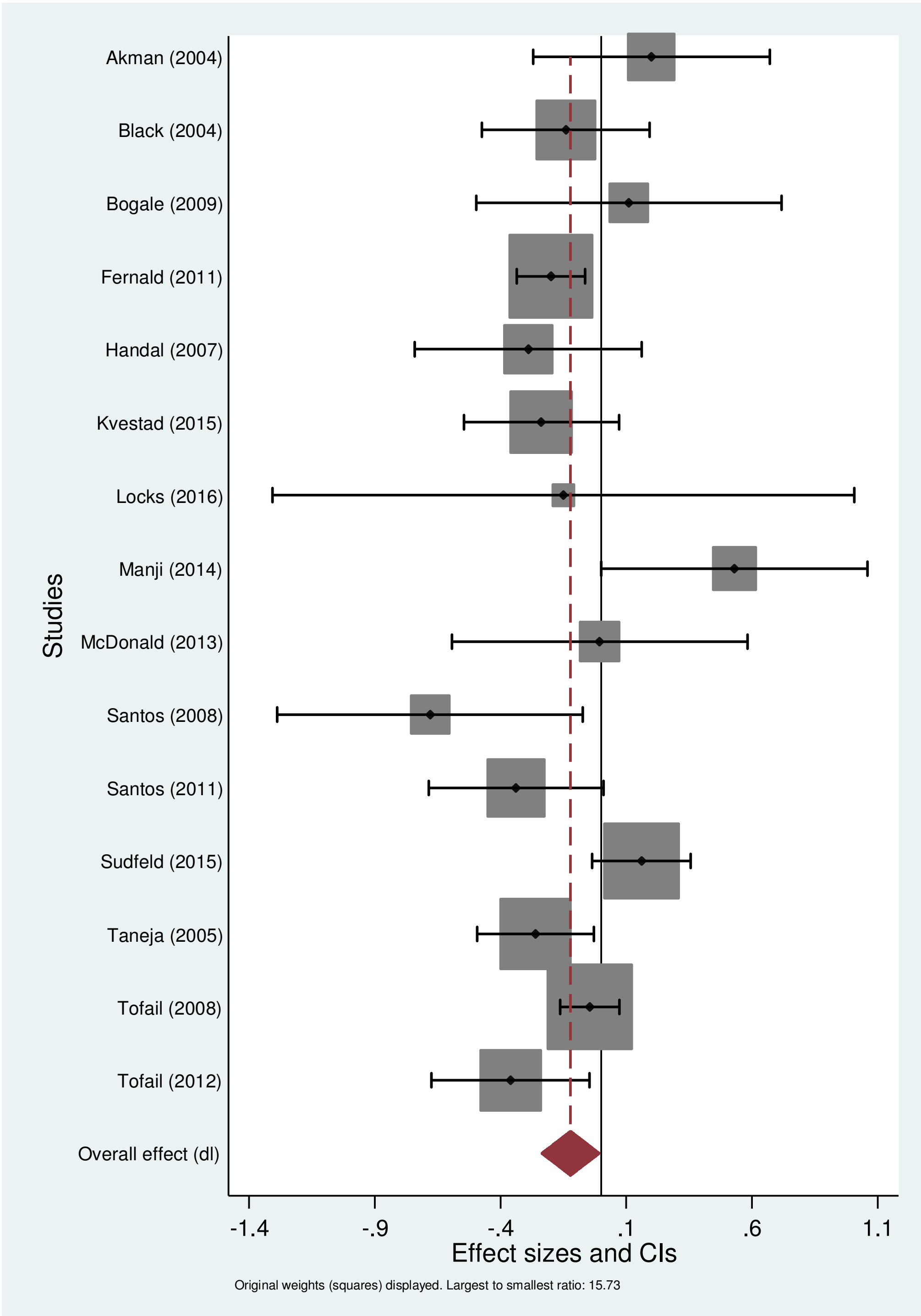

Figure 40: Association between no maternal education (reference: primary education) and cognitive development.

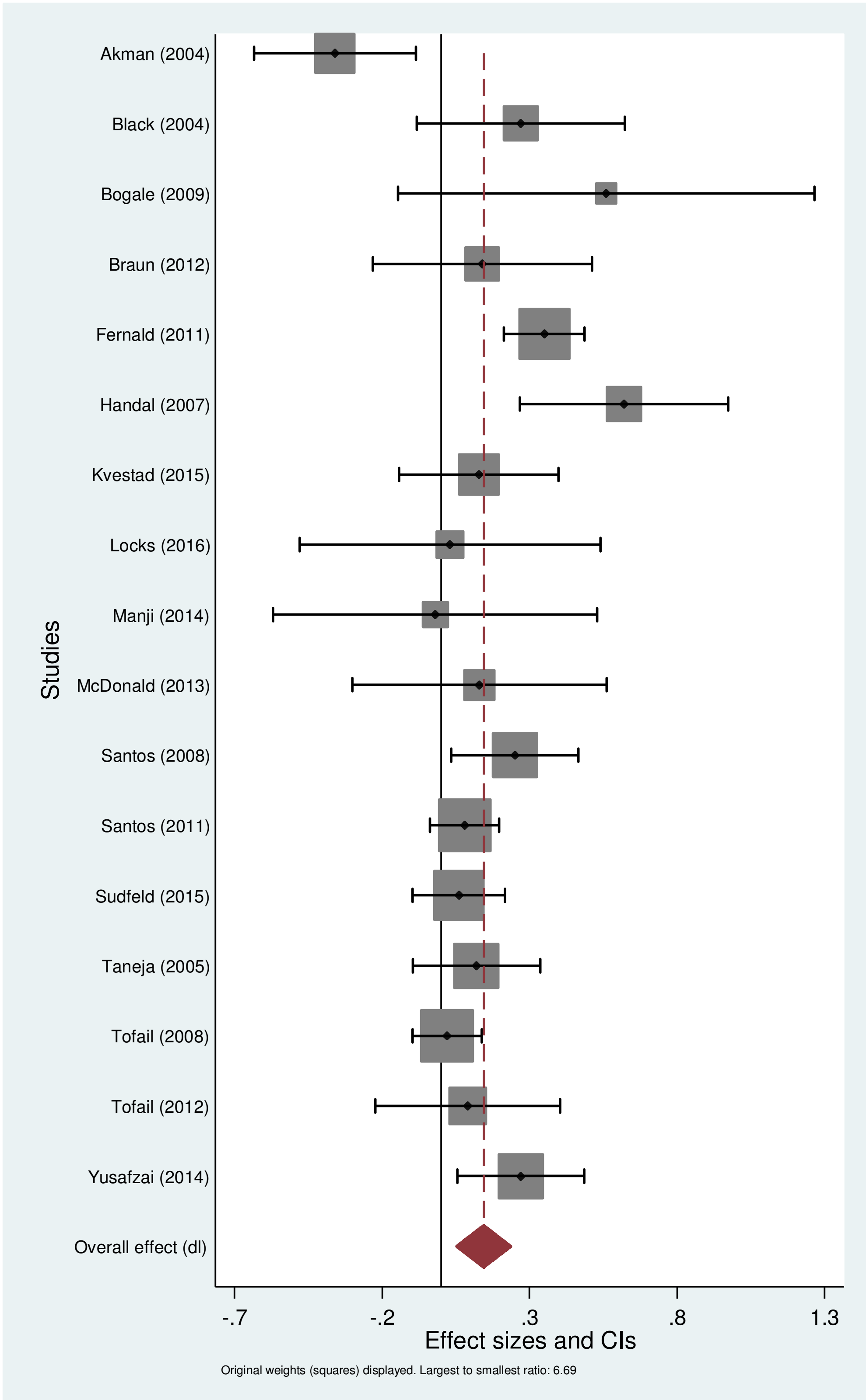

Figure 41: Association between maternal secondary education (reference: primary education) and cognitive development.

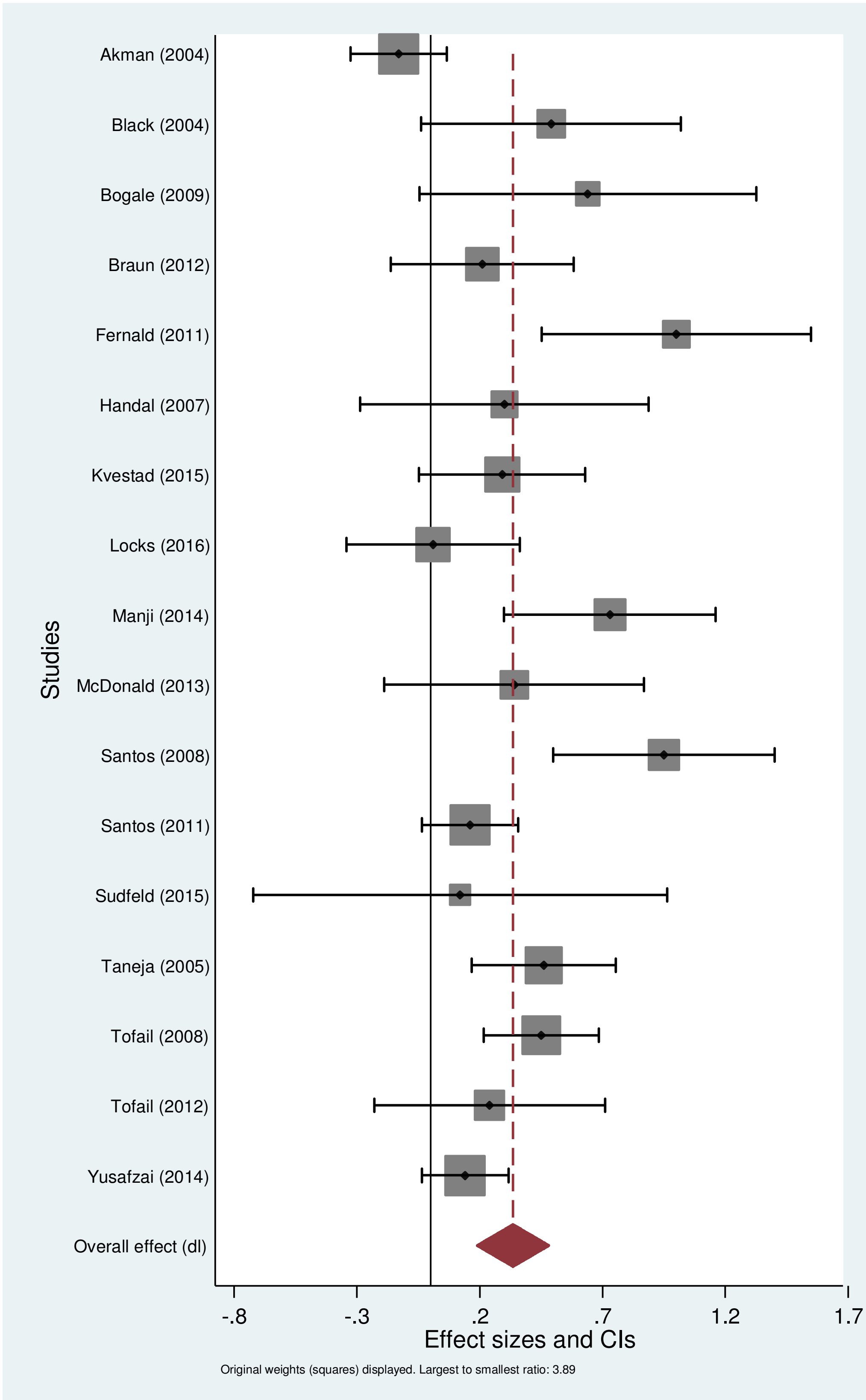

Figure 42: Association between maternal higher education (reference: primary education) and cognitive development.

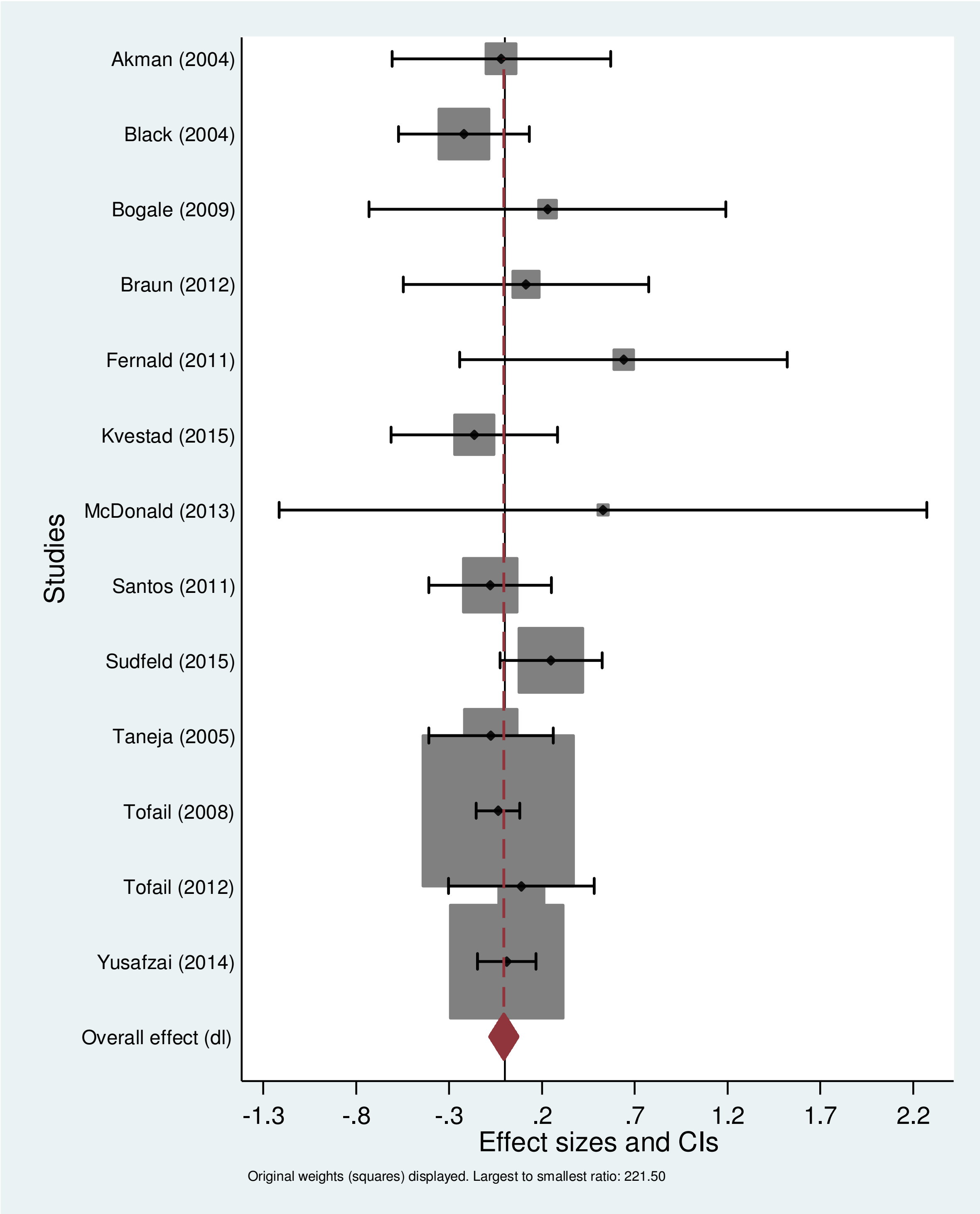

Figure 43: Association between no paternal education (reference: primary education) and cognitive development.

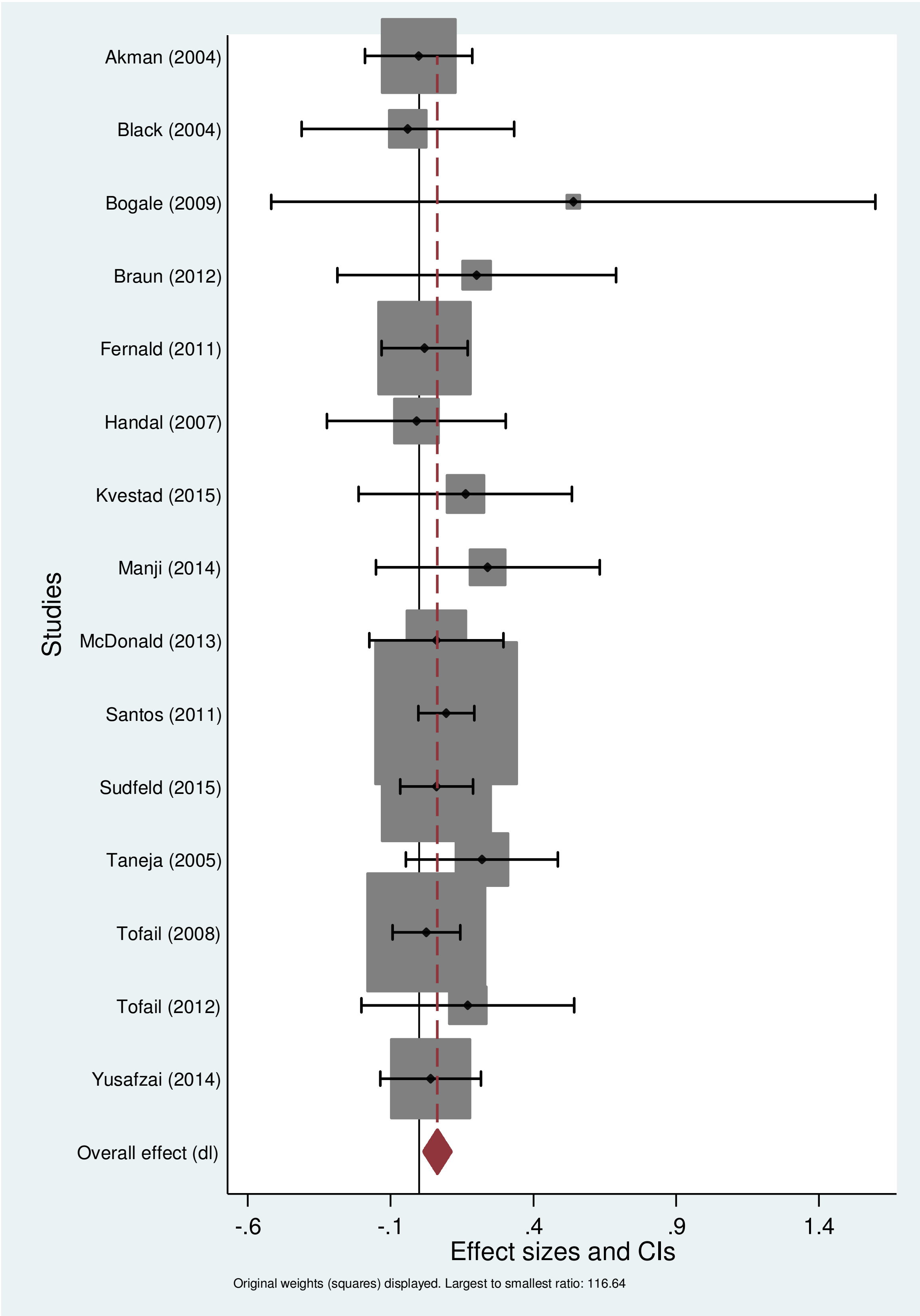

Figure 44: Association between paternal secondary education (reference: primary education) and cognitive development.

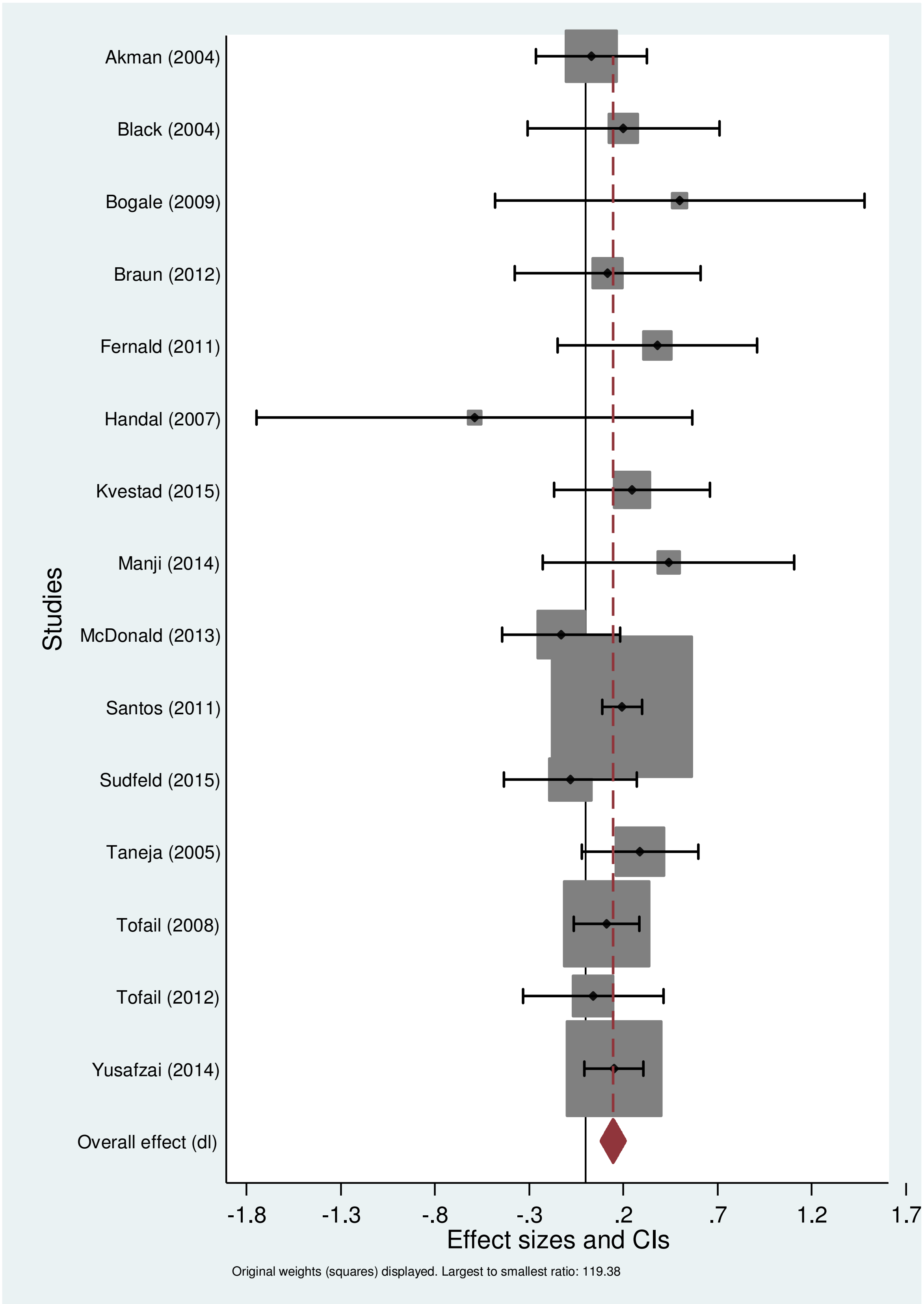

Figure 45: Association between paternal higher education (reference: primary education) and cognitive development.

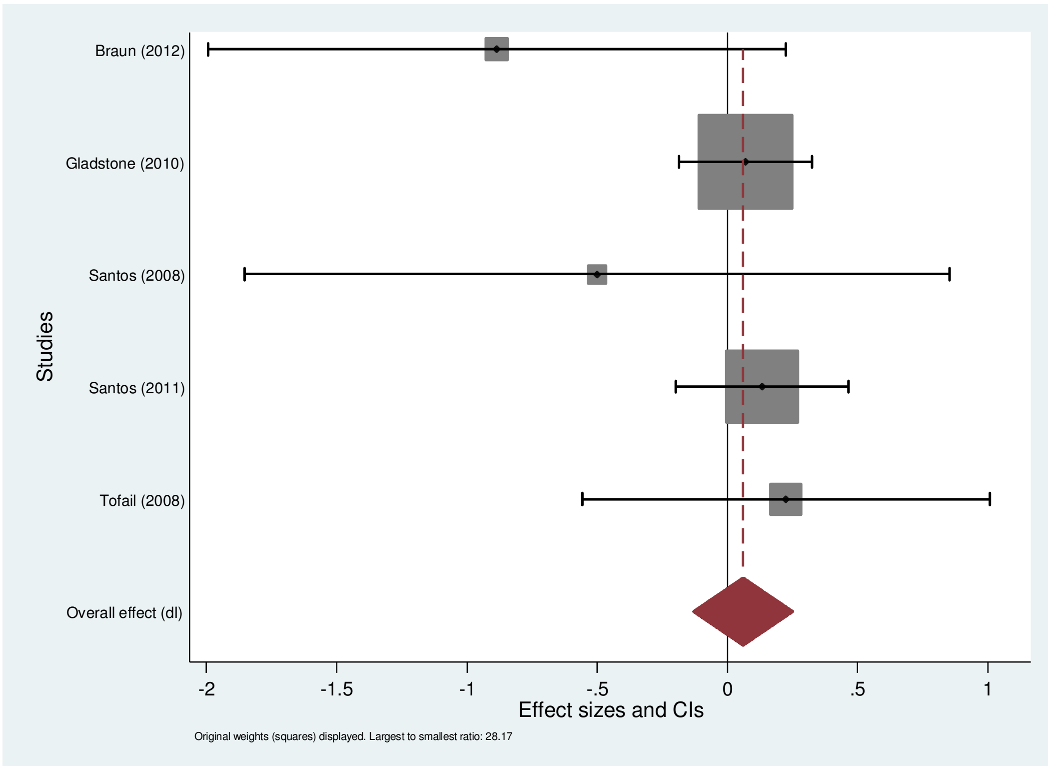

Figure 46: Association between maternal ages < 15 (reference: ages 20-34) and cognitive development.

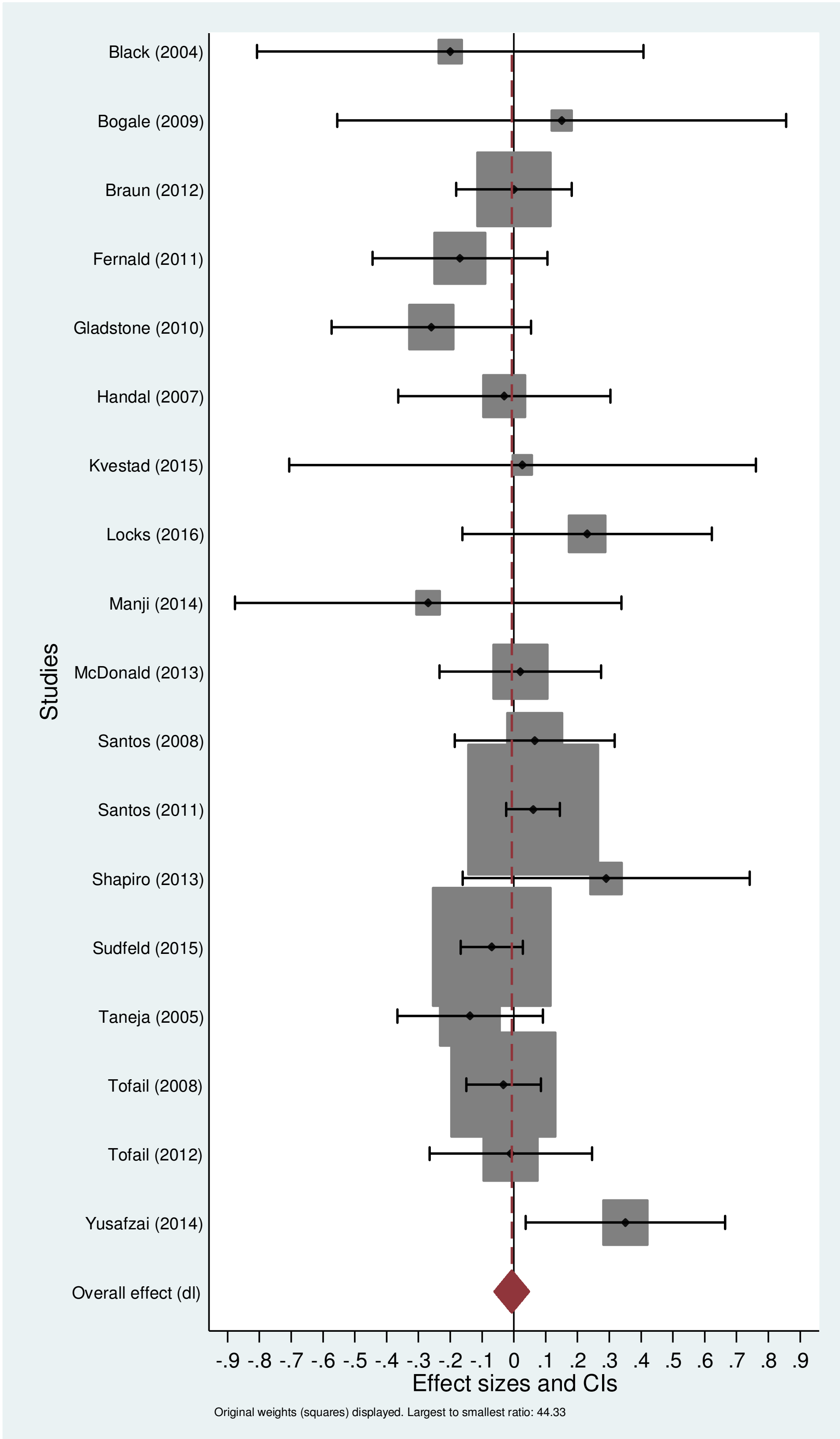

Figure 47: Association between maternal ages 15-20 (reference: ages 20-34) and cognitive development.

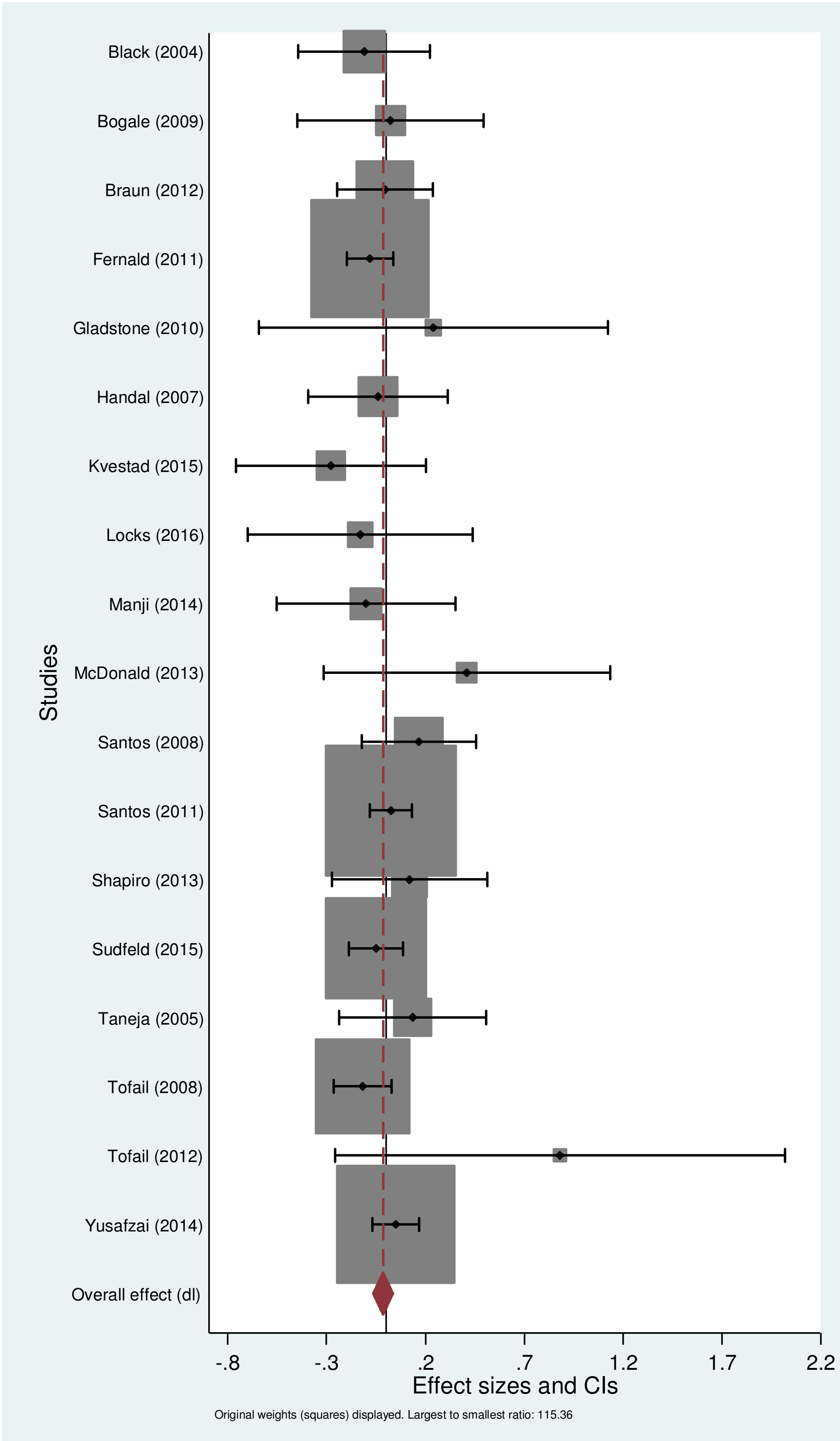

Figure 48: Association between maternal ages >35 (reference: ages 20-34) and cognitive development.

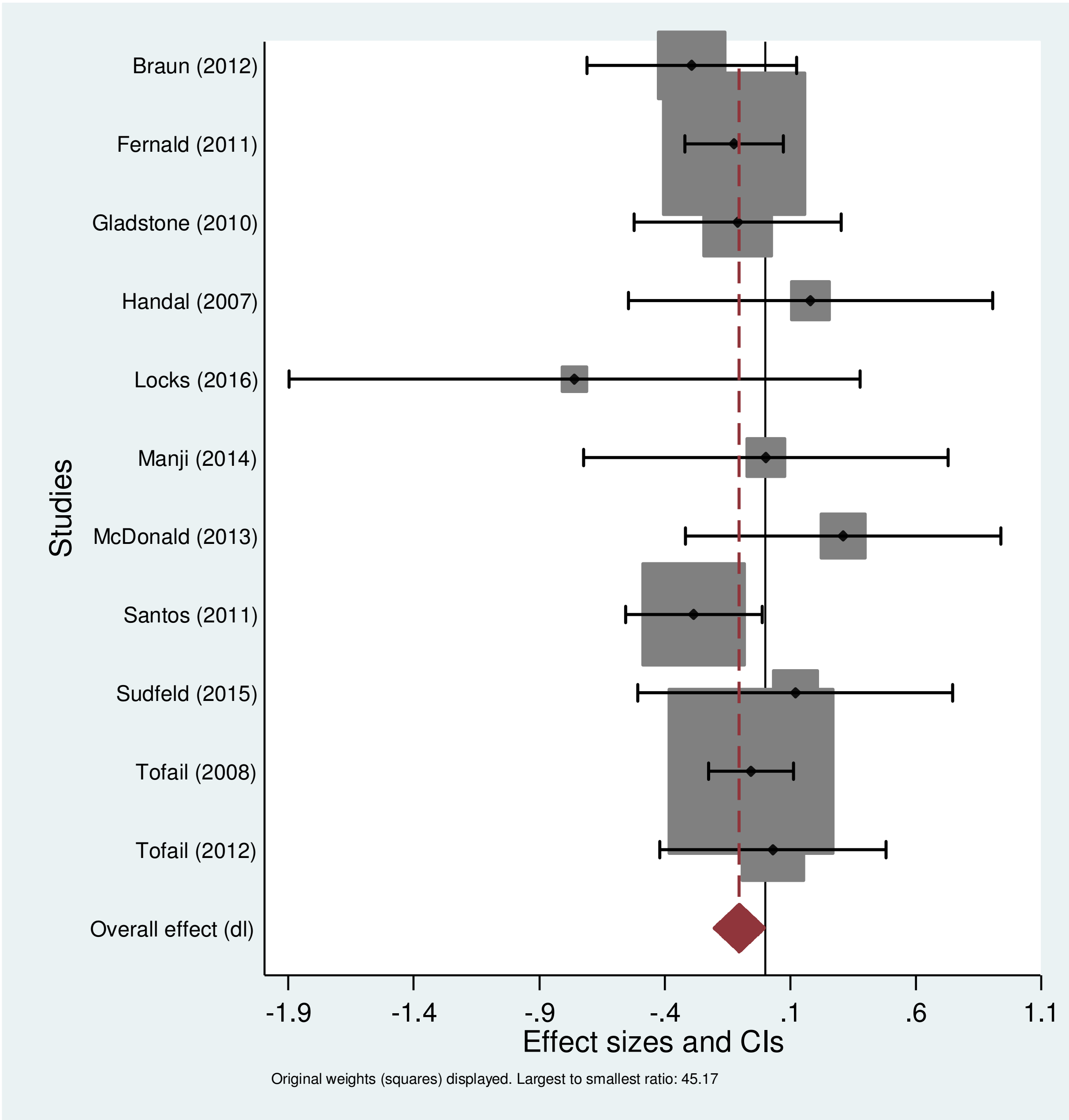

Figure 49: Association between maternal height < 145cm (reference: >155 cm) and cognitive development.

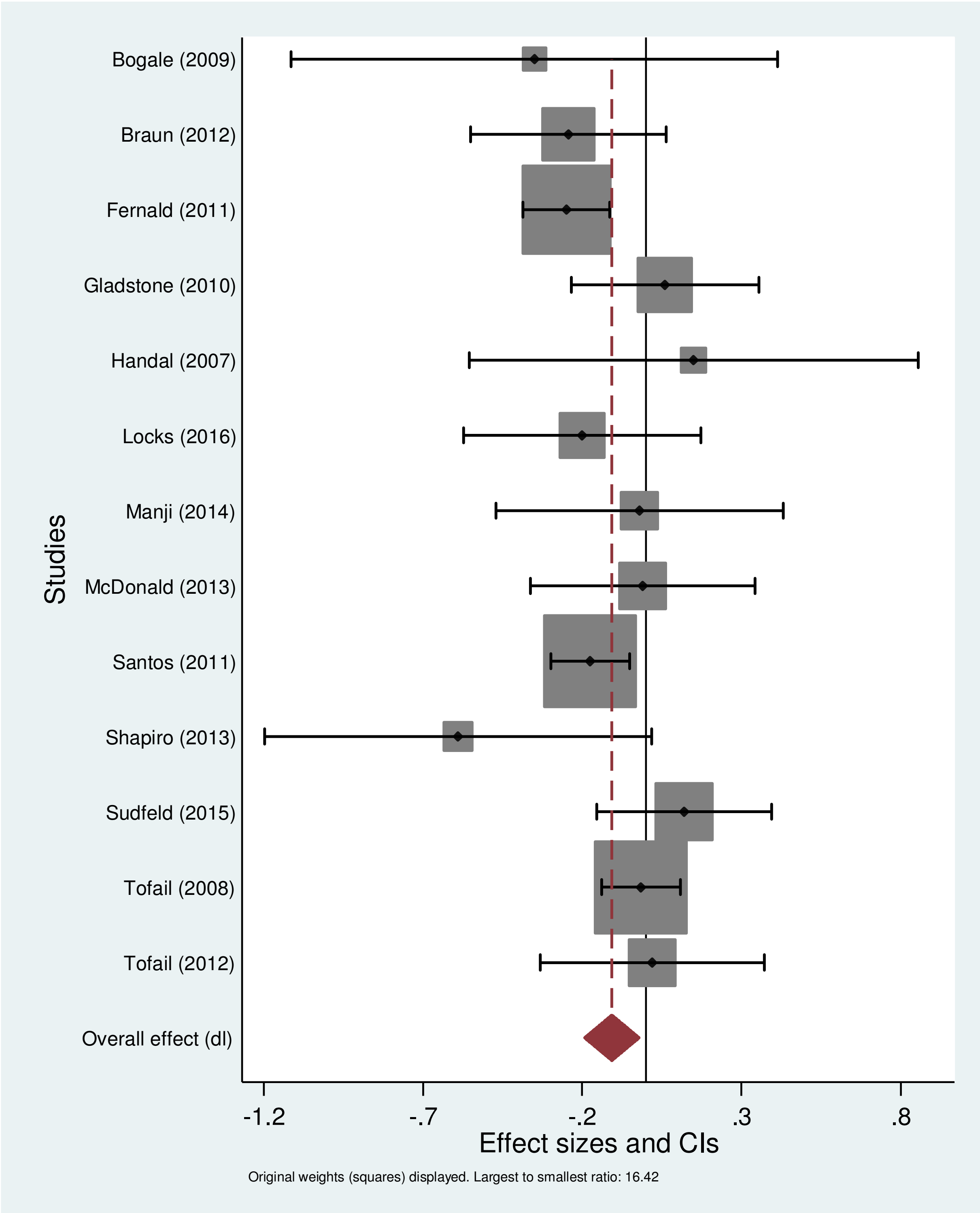

Figure 50: Association between maternal height 145-150cm (reference: >155 cm) and cognitive development.

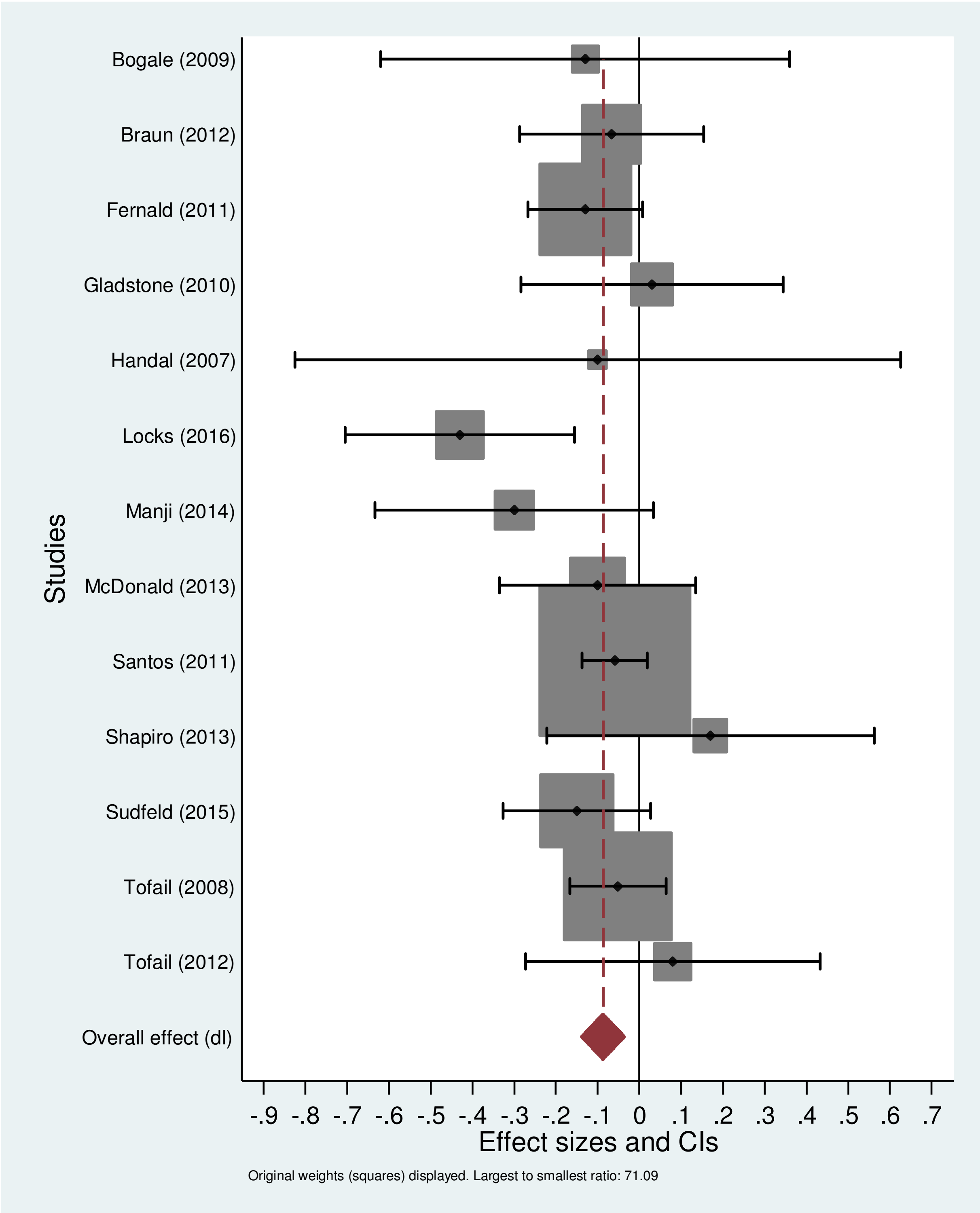

Figure 51: Association between maternal height 150-155 cm (reference: >155 cm) and cognitive development.

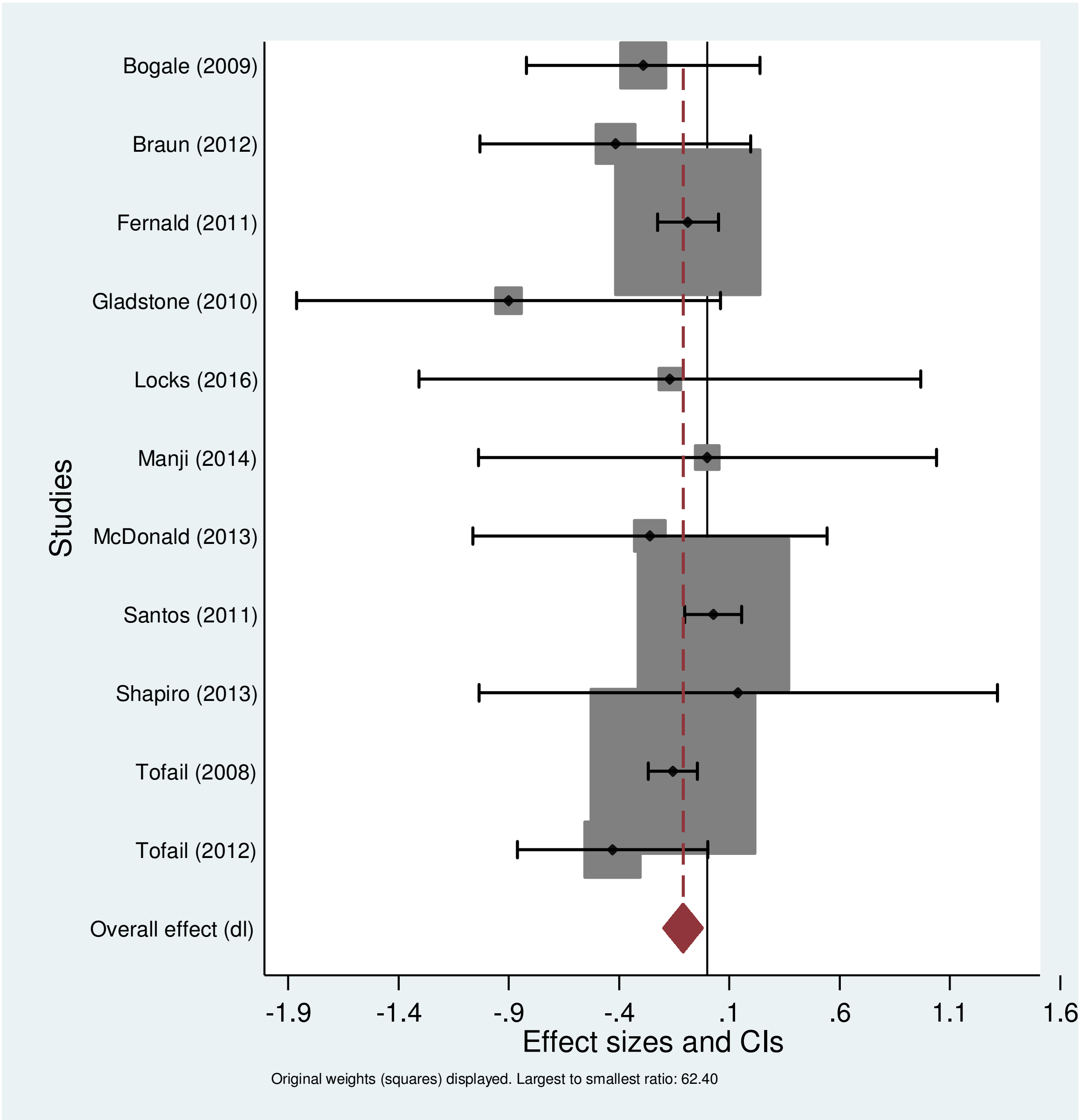

Figure 52: Association between maternal BMI <18.5 kg/m² (reference: 18.5-25) and cognitive development.

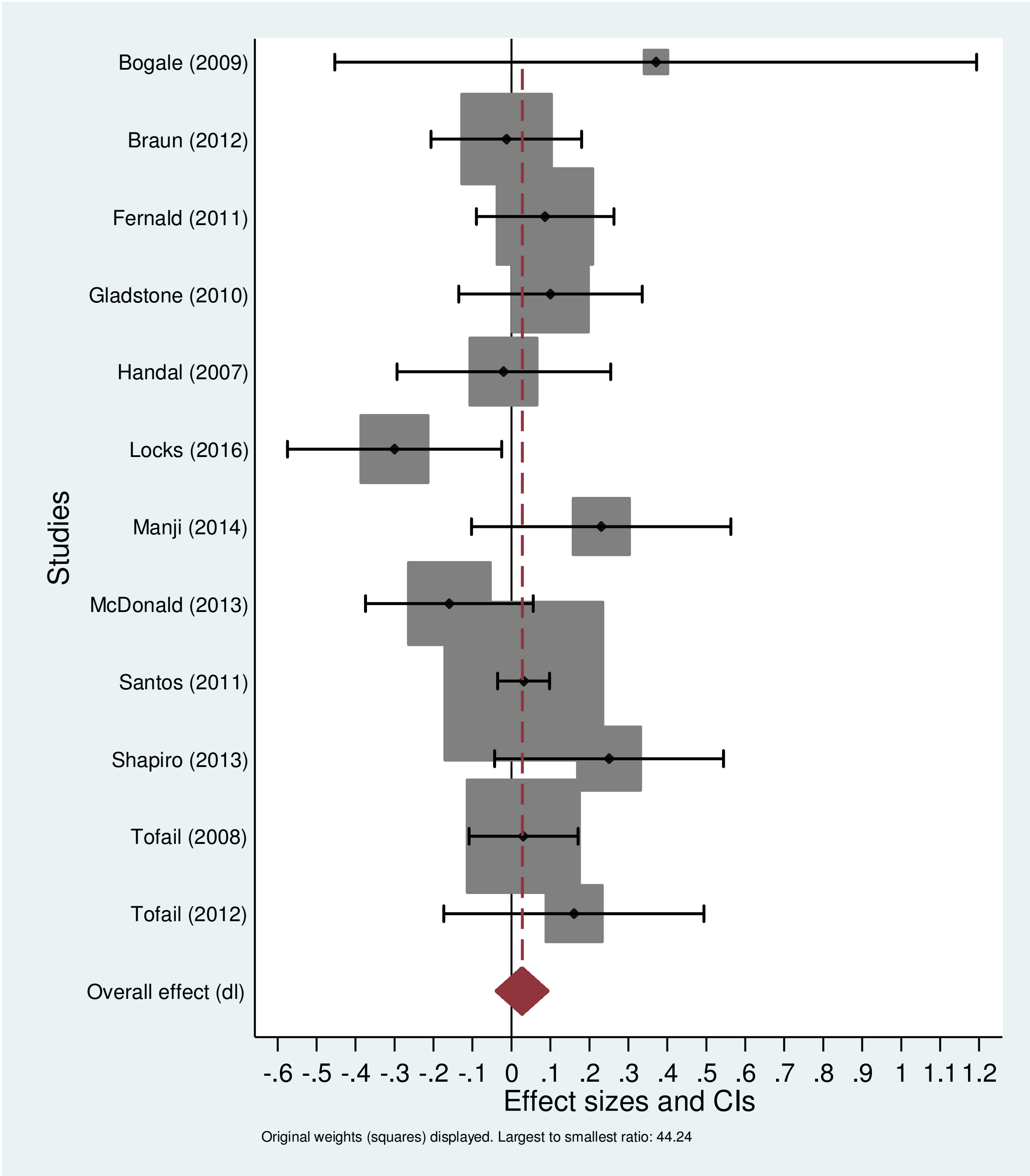

Figure 53: Association between maternal BMI 25-30 kg/m² (reference: 18.5-25) and cognitive development.

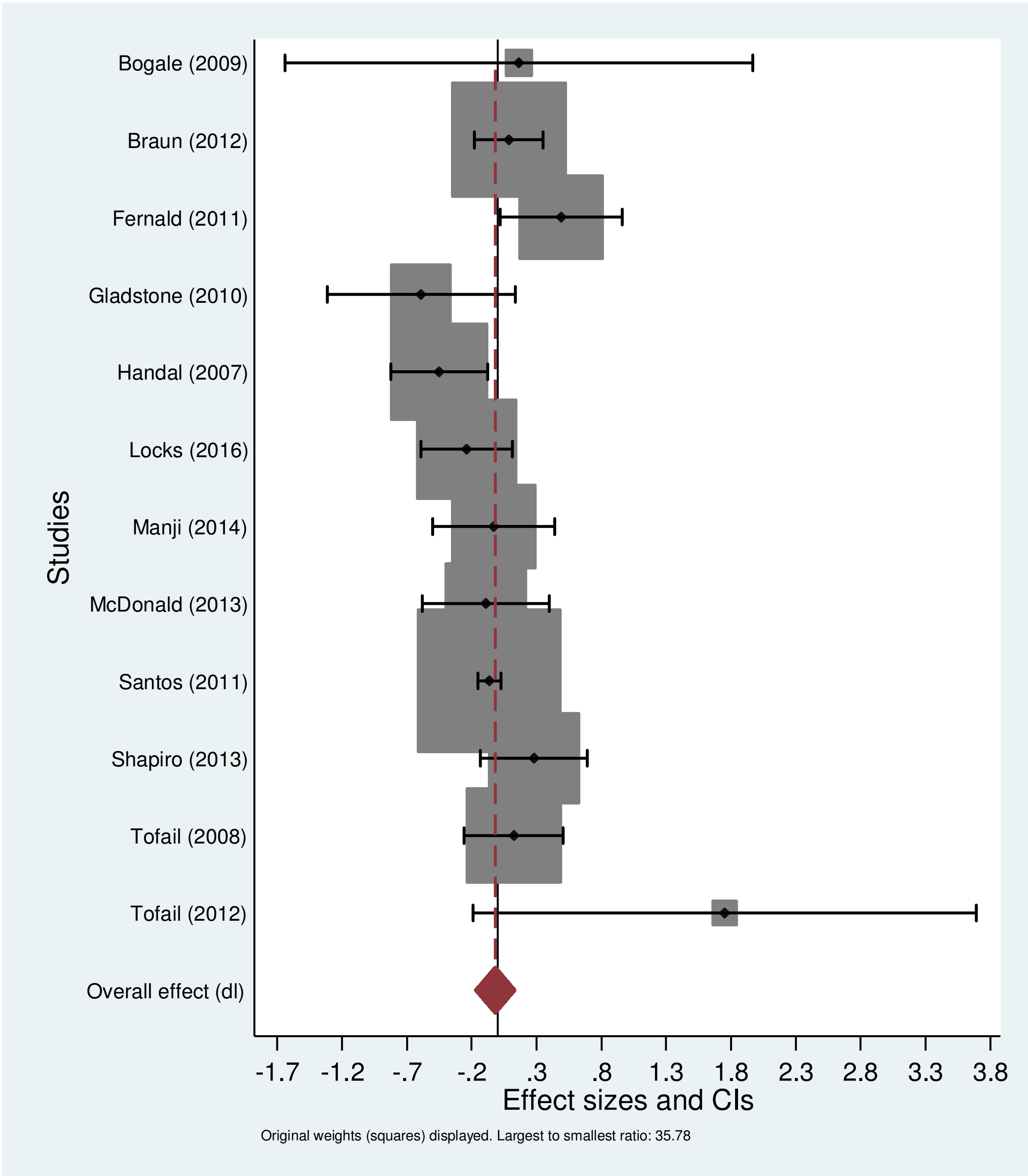

Figure 54: Association between maternal BMI >30 kg/m² (reference: 18.5-25) and cognitive development.

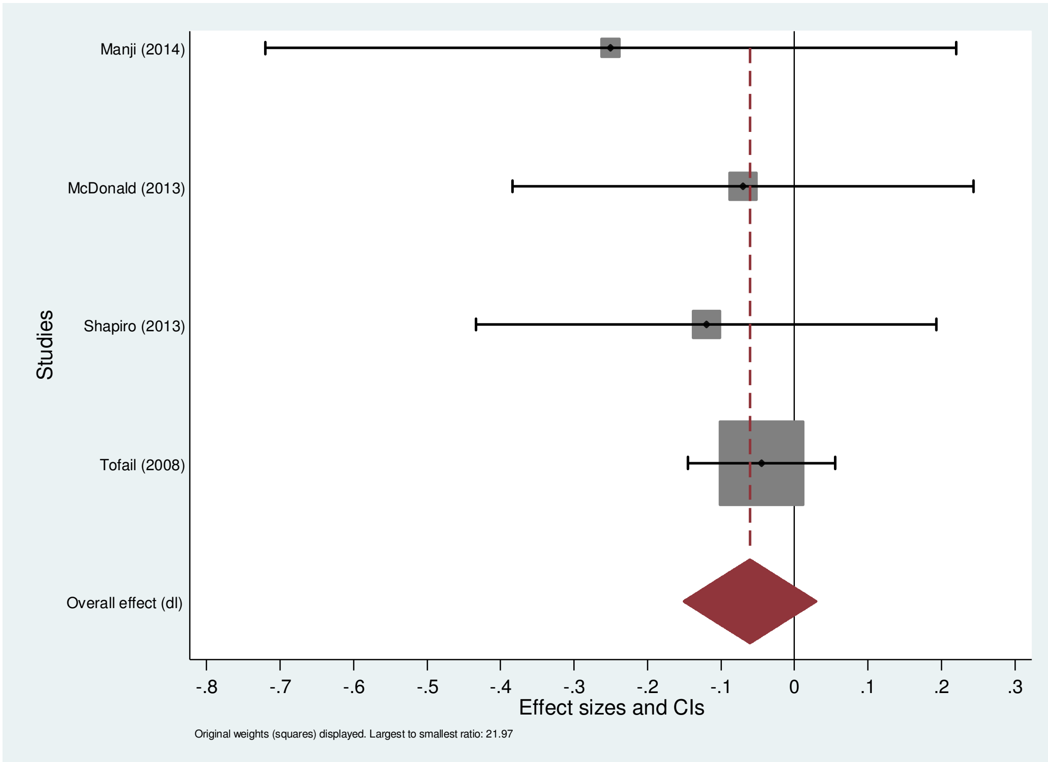

Figure 55: Association between mild anemia in pregnancy (reference: no anemia) and cognitive development.

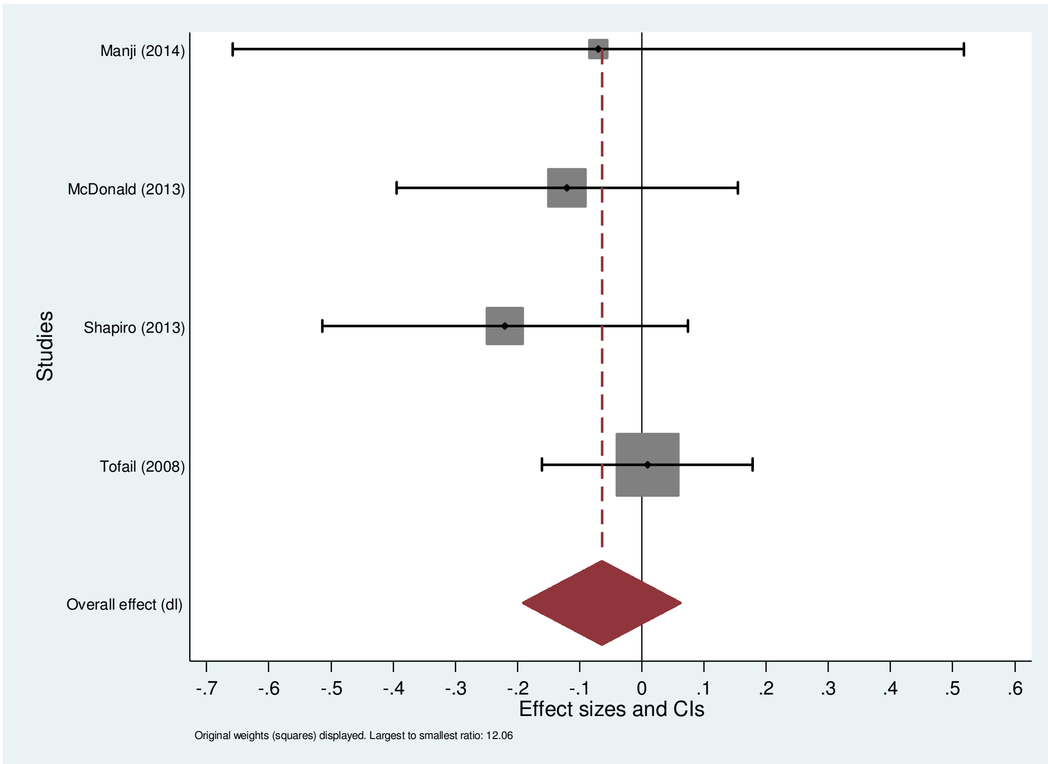

Figure 56: Association between maternal moderate anemia (reference: no anemia) and cognitive development.

5. Parental Risk Factors on Child's Motor Development

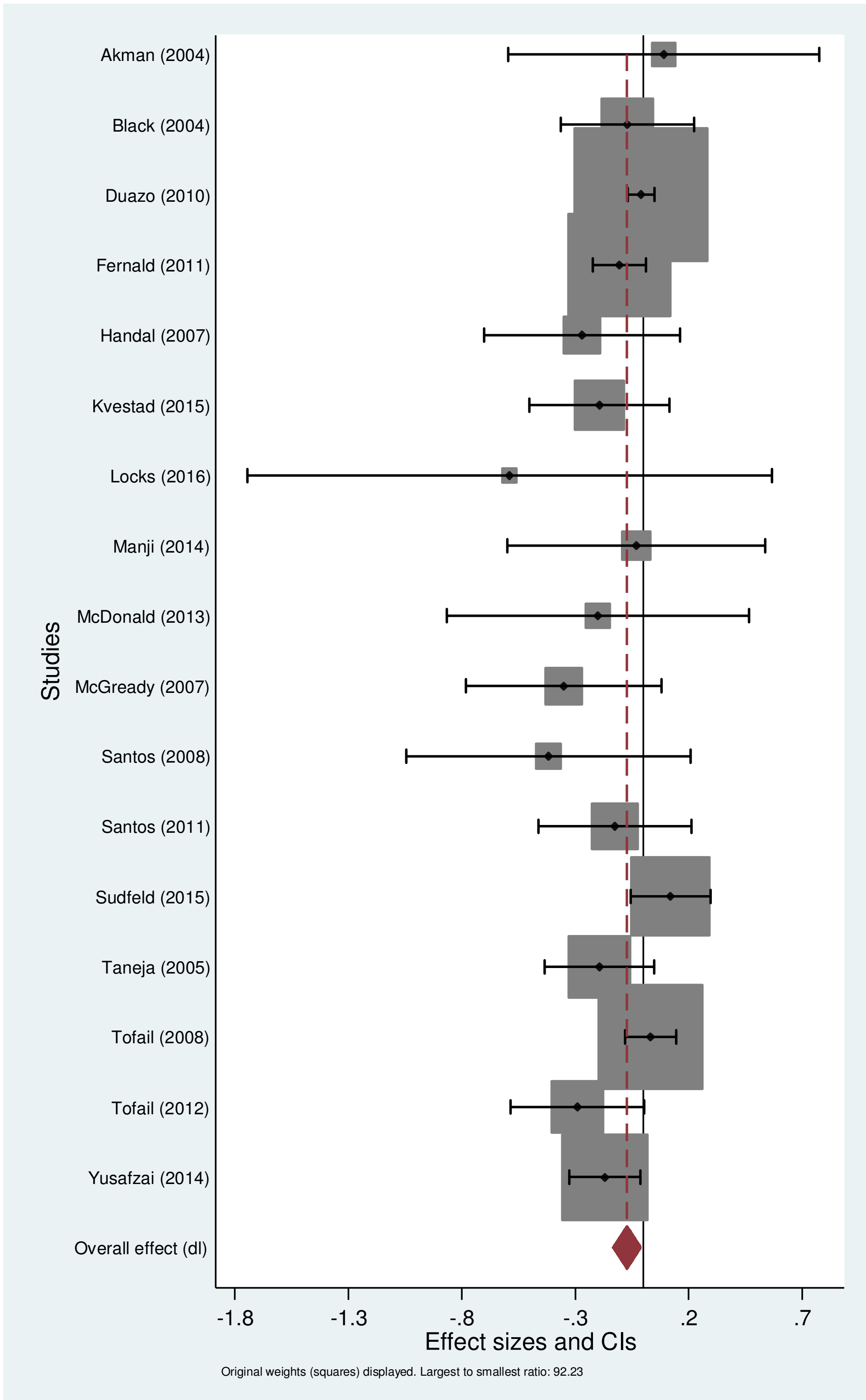

Figure 57: Association between no maternal education (reference: primary education) and motor development.

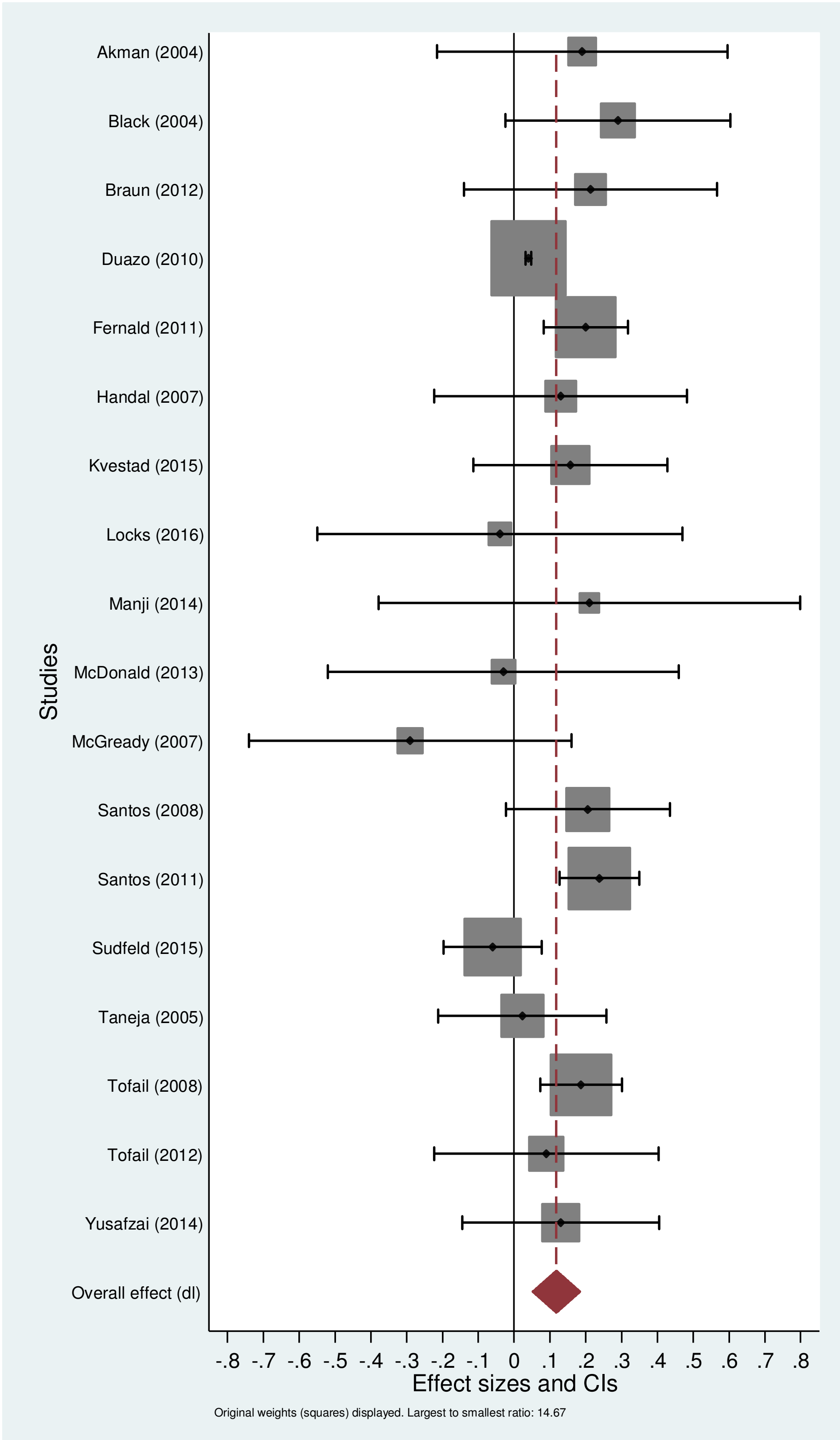

Figure 58: Association between maternal secondary education (reference: primary education) and motor development.

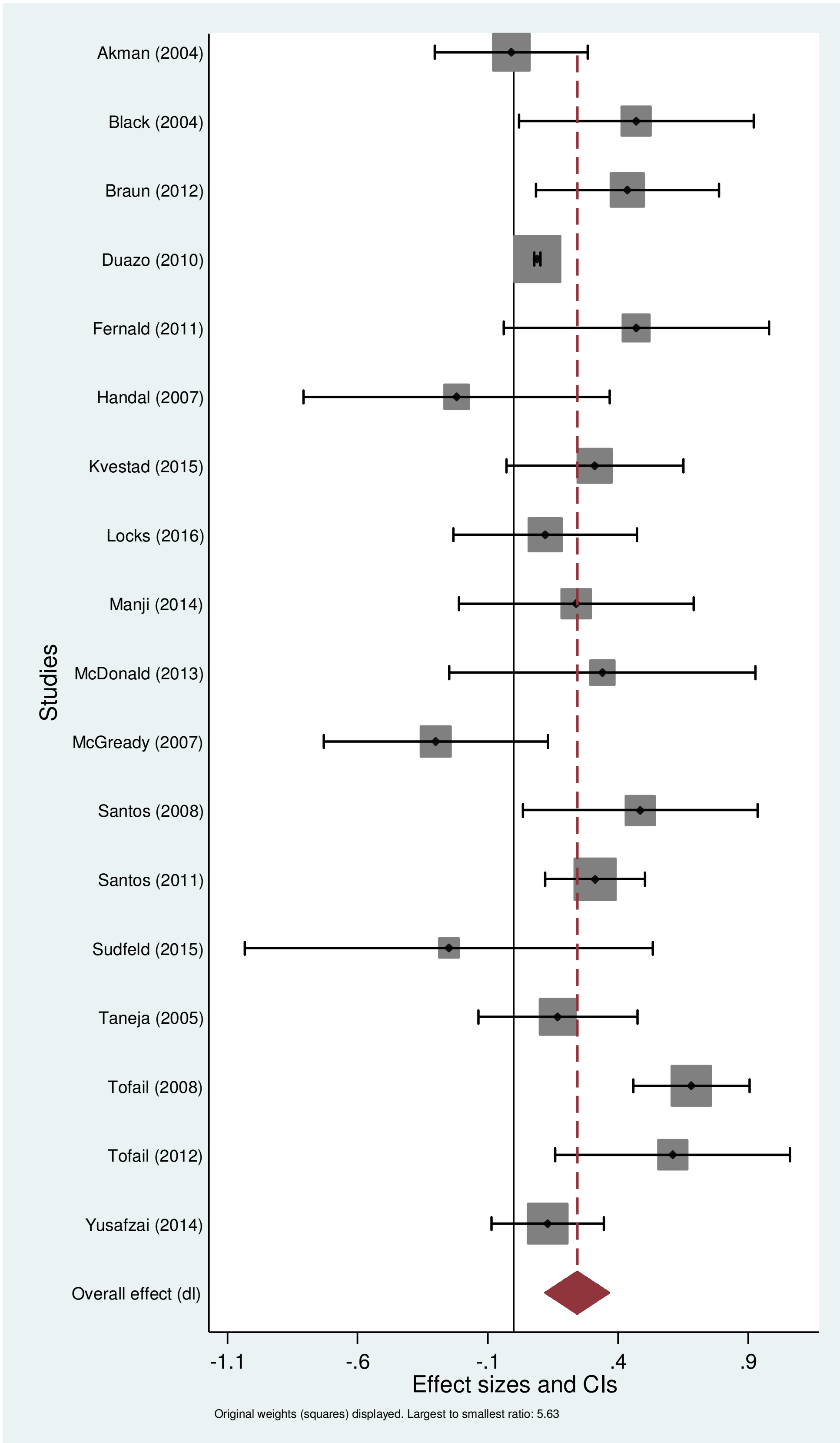

Figure 59: Association between maternal higher education (reference: primary education) and motor development.

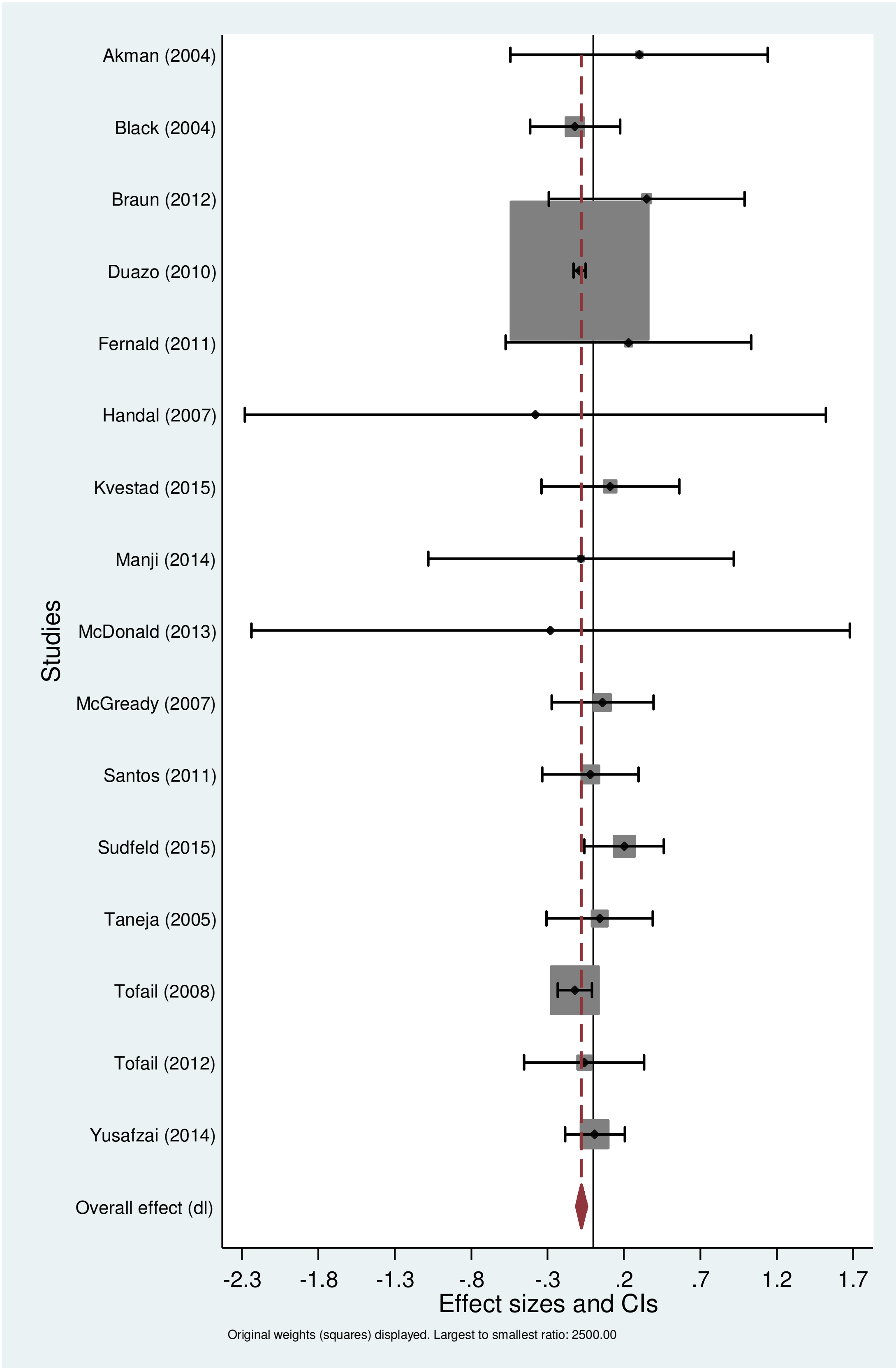

Figure 60: Association between no paternal education (reference: primary education) and motor development.

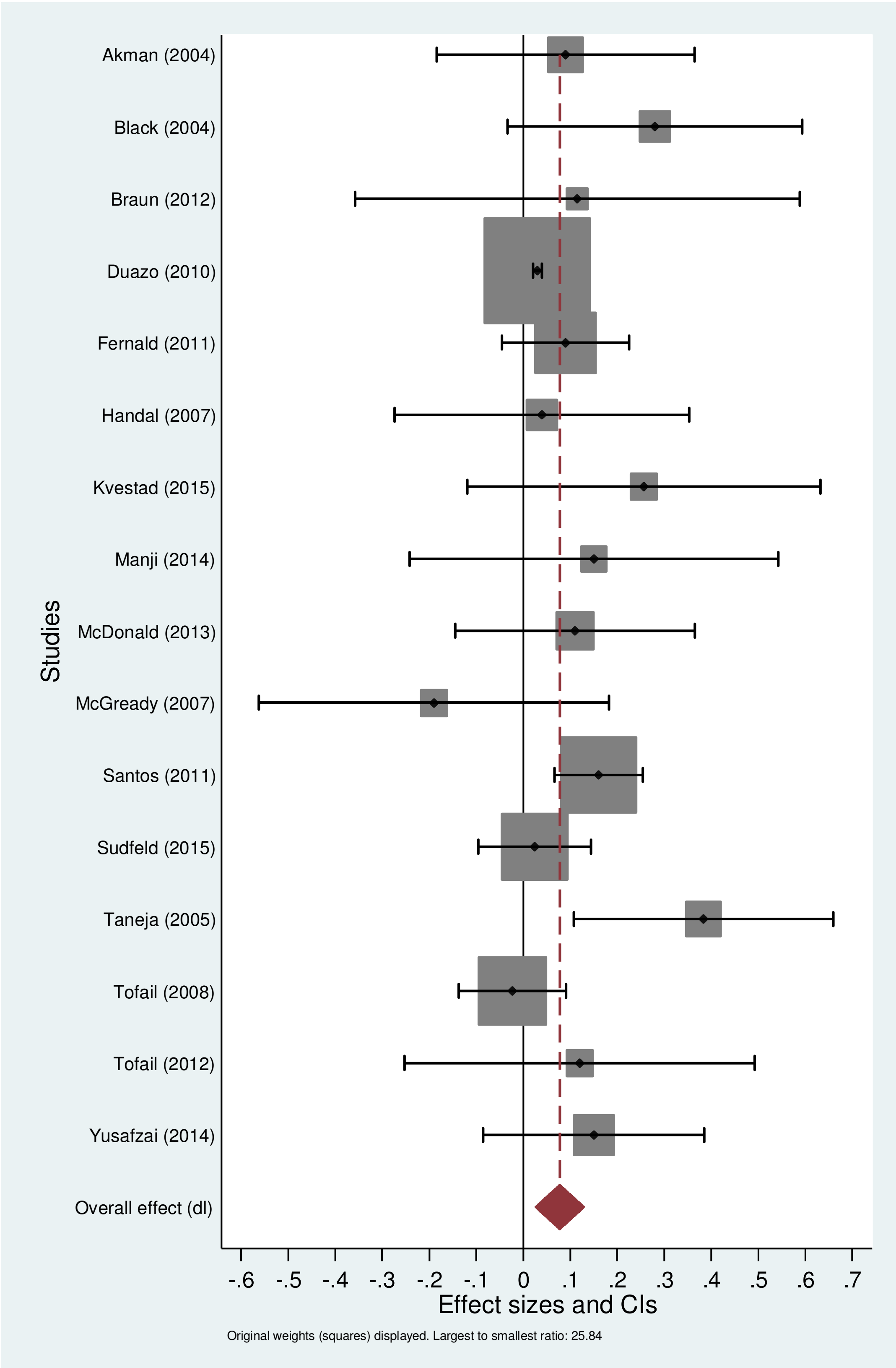

Figure 61: Association between paternal secondary education (reference: primary education) and motor development.

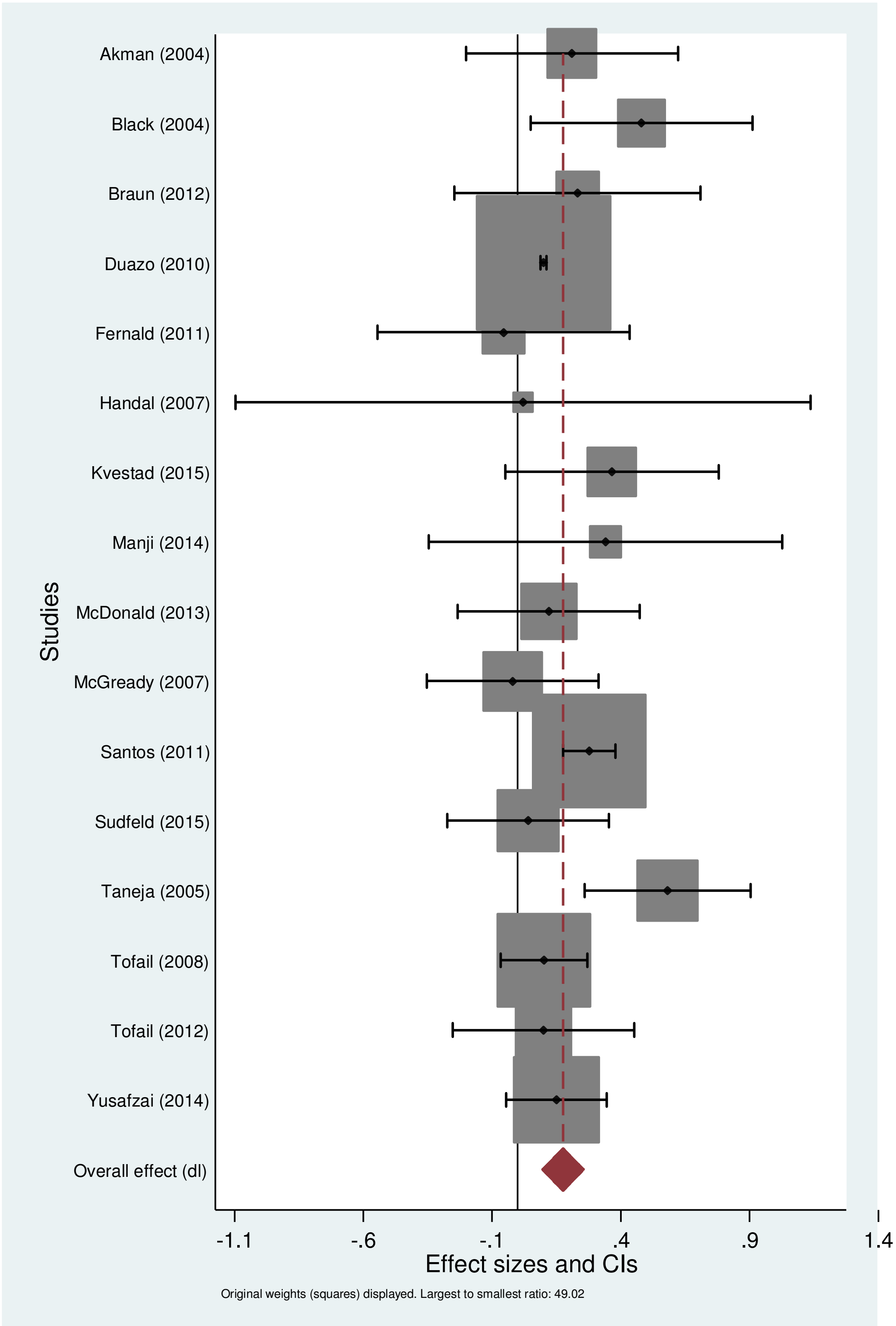

Figure 62: Association between paternal higher education (reference: primary education) and motor development.

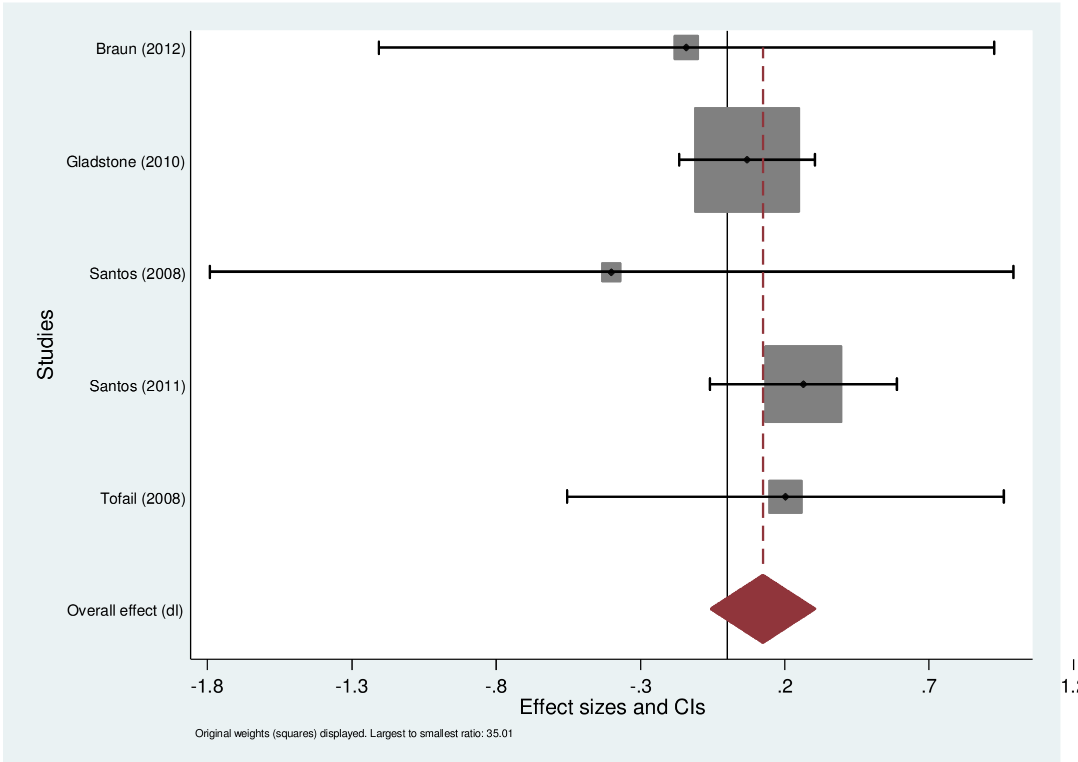

Figure 63: Association between maternal ages < 15 (reference: ages 20-34) and motor development.

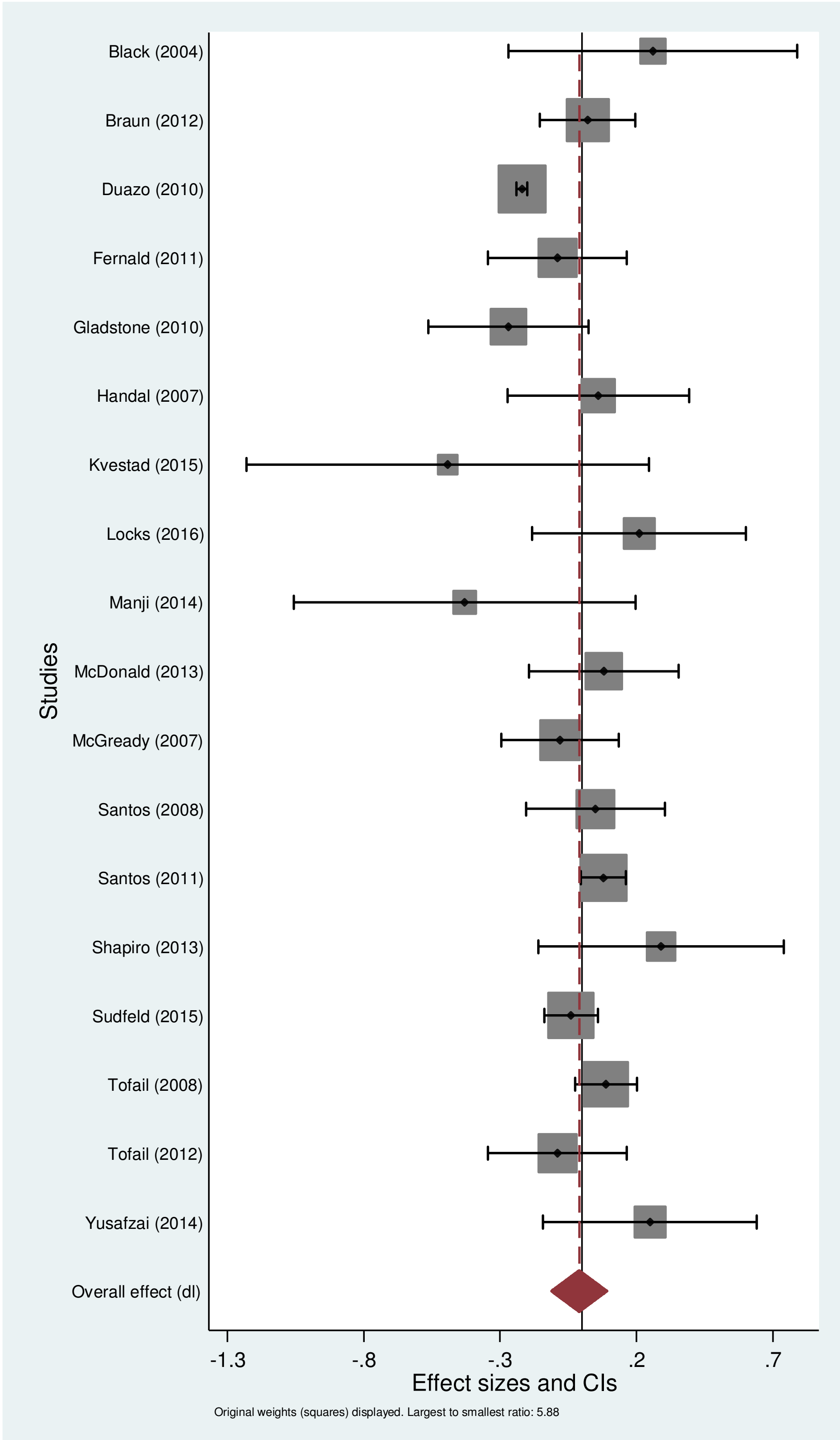

Figure 64: Association between maternal ages 15-20 (reference: ages 20-34) and motor development.

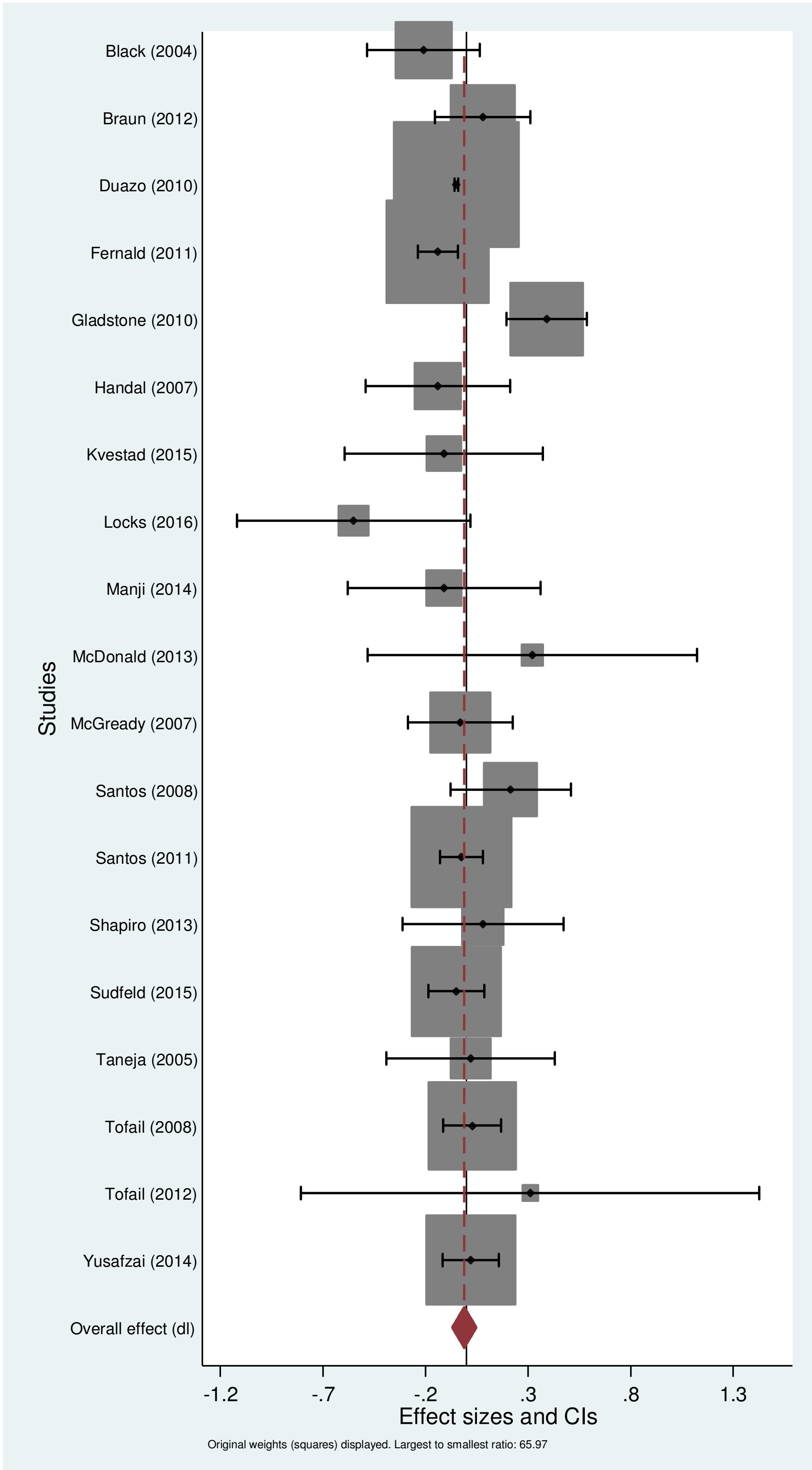

Figure 65: Association between maternal ages >35 (reference: ages 20-34) and motor development.

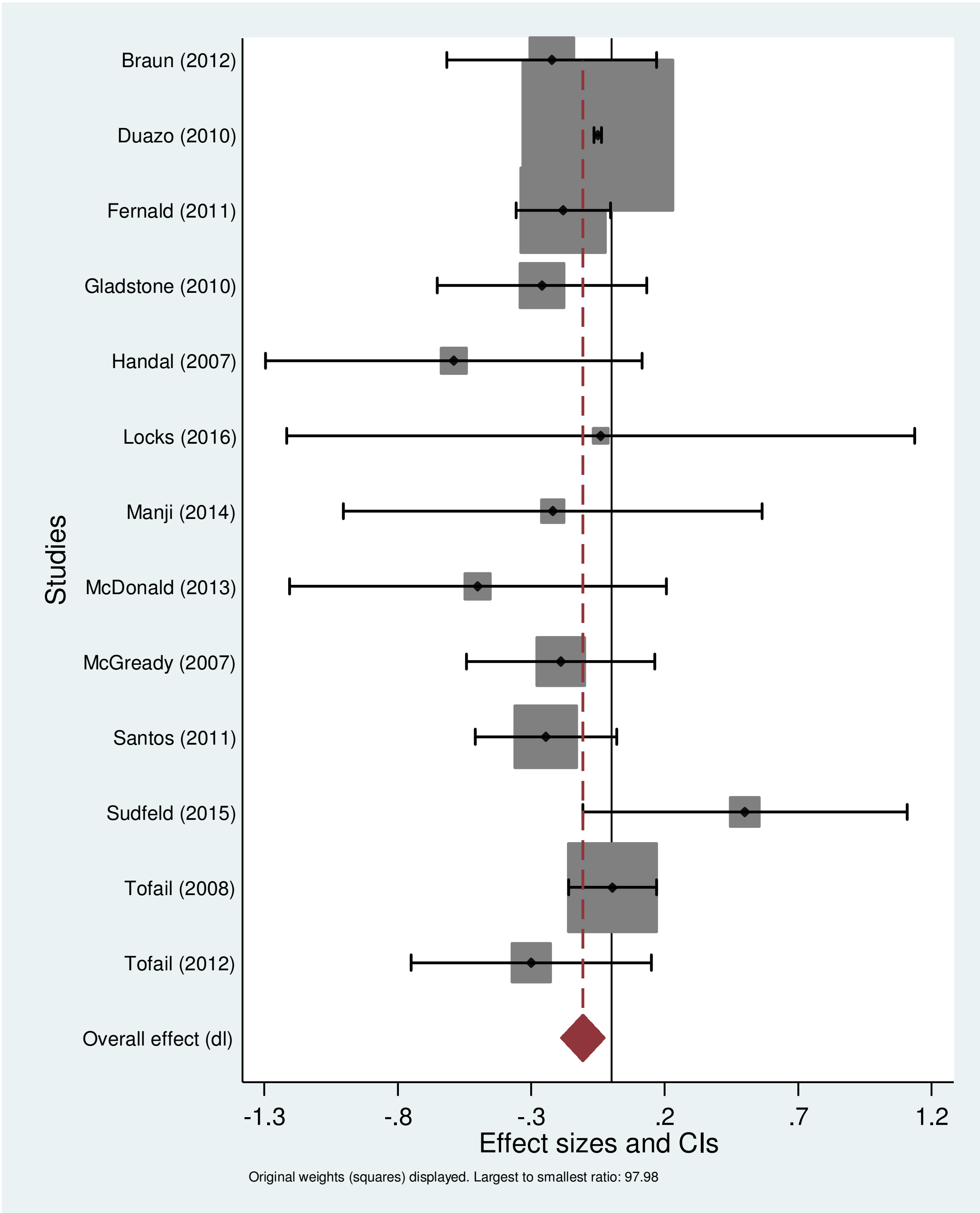

Figure 66: Association between maternal height <145 (reference: >155 cm) and motor development.

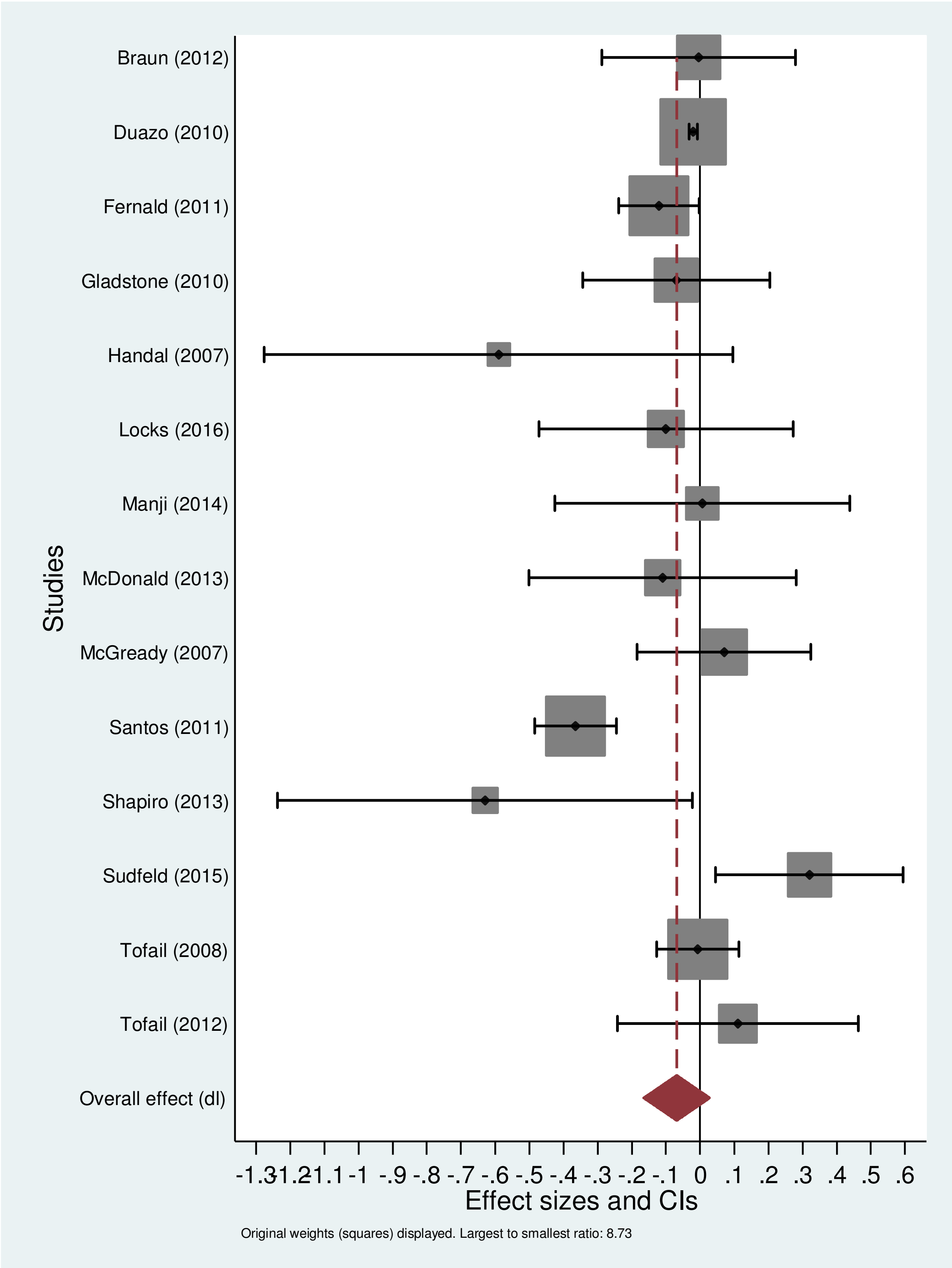

Figure 67: Association between maternal height 145-150 (reference: >155 cm) and motor development.

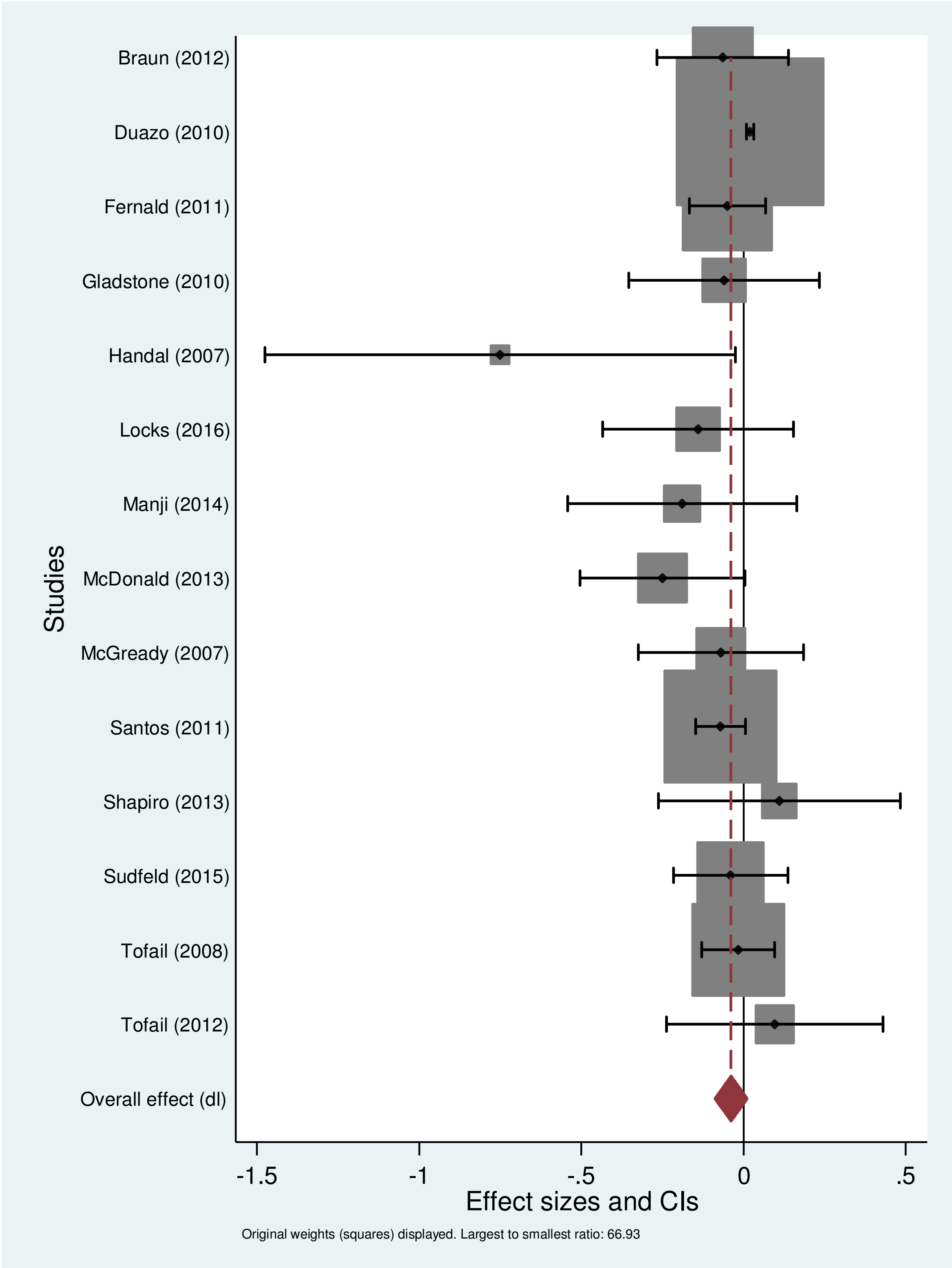

Figure 68: Association between maternal height 150-155 (reference: >155 cm) and motor development.

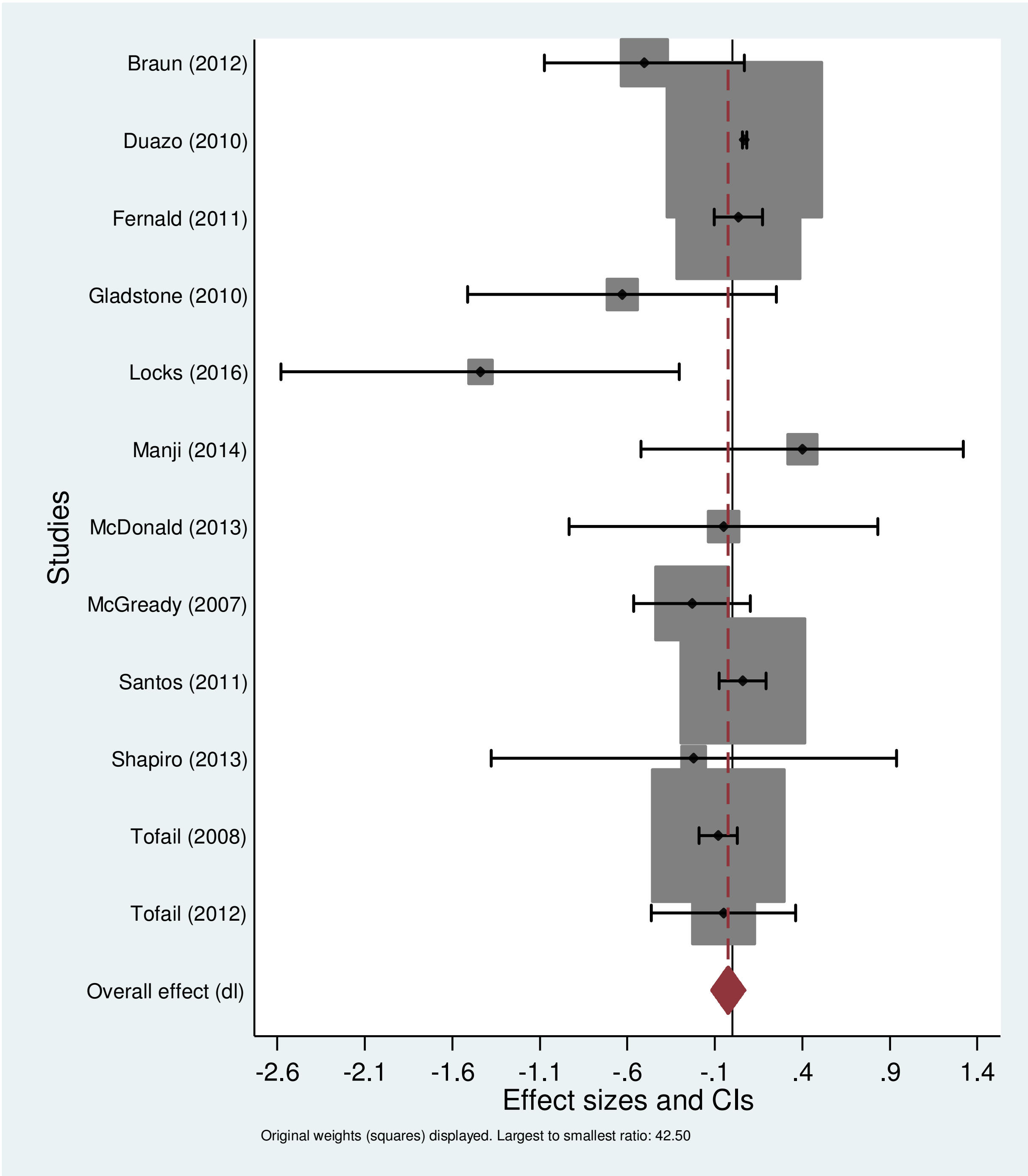

Figure 69: Association between maternal BMI <18.5 kg/m² (reference: 18.5-25) and motor development.

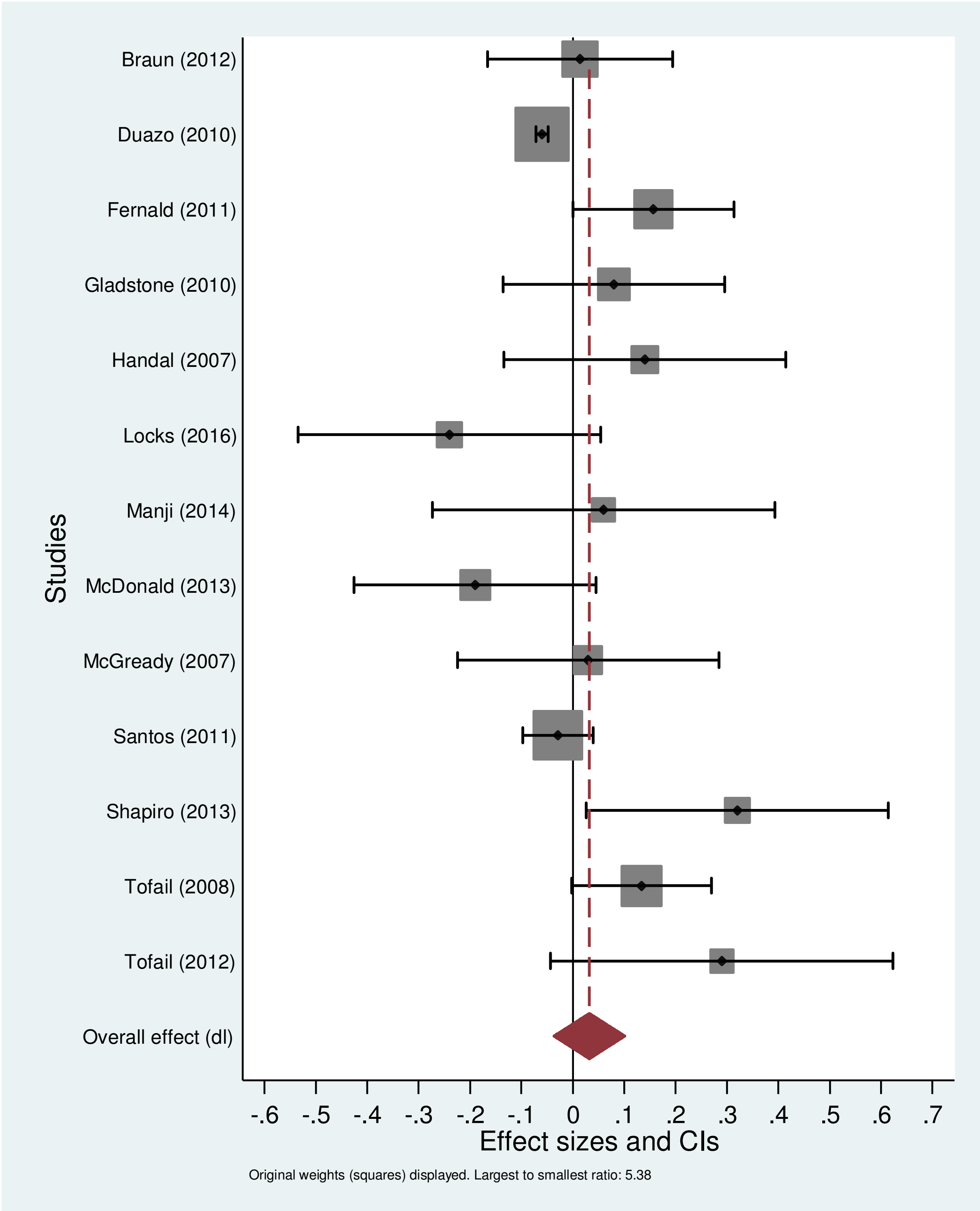

Figure 70: Association between maternal BMI <25-30 kg/m² (reference: 18.5-25) and motor development.

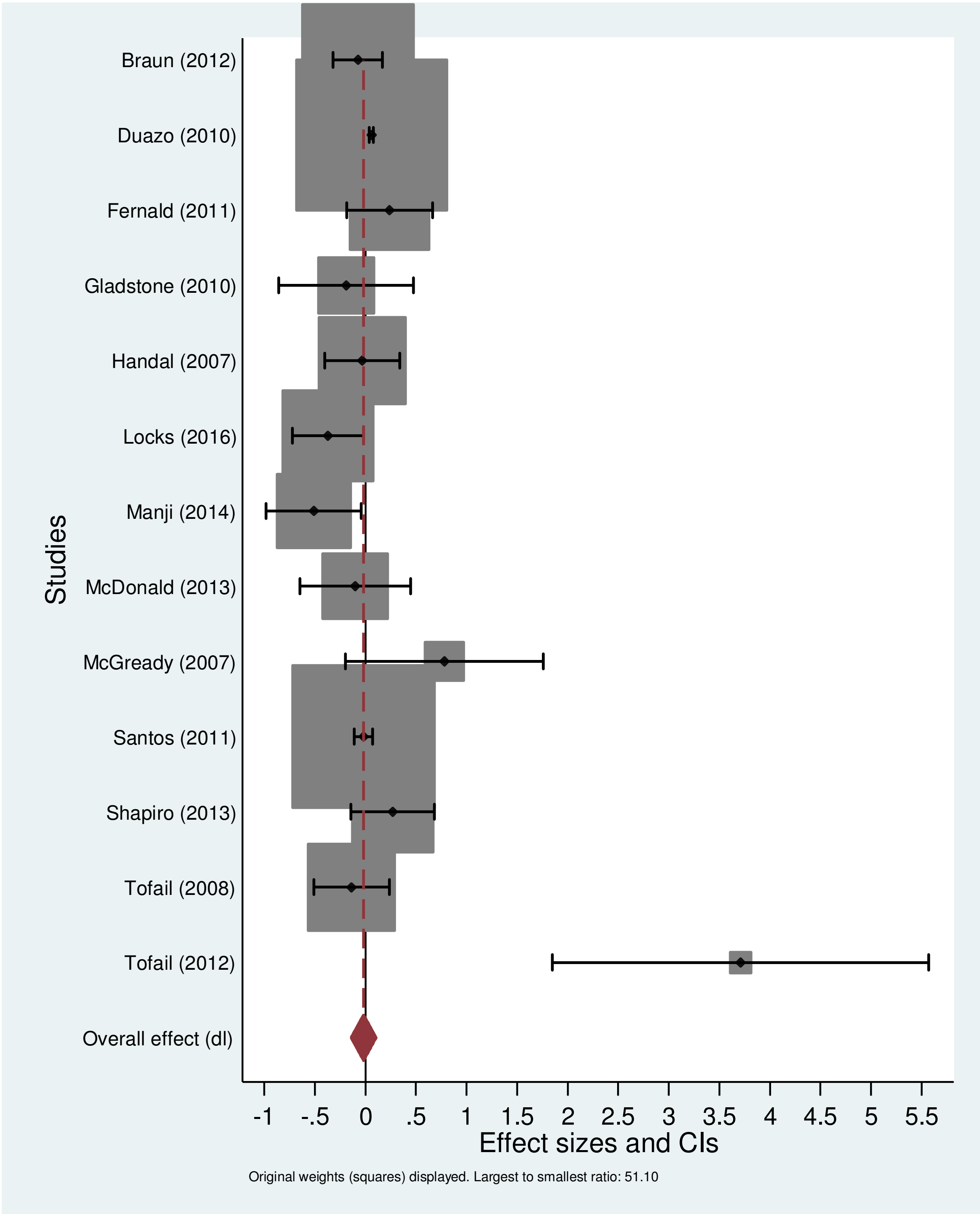

Figure 71: Association between maternal BMI >30 kg/m² (reference: 18.5-25) and motor development.

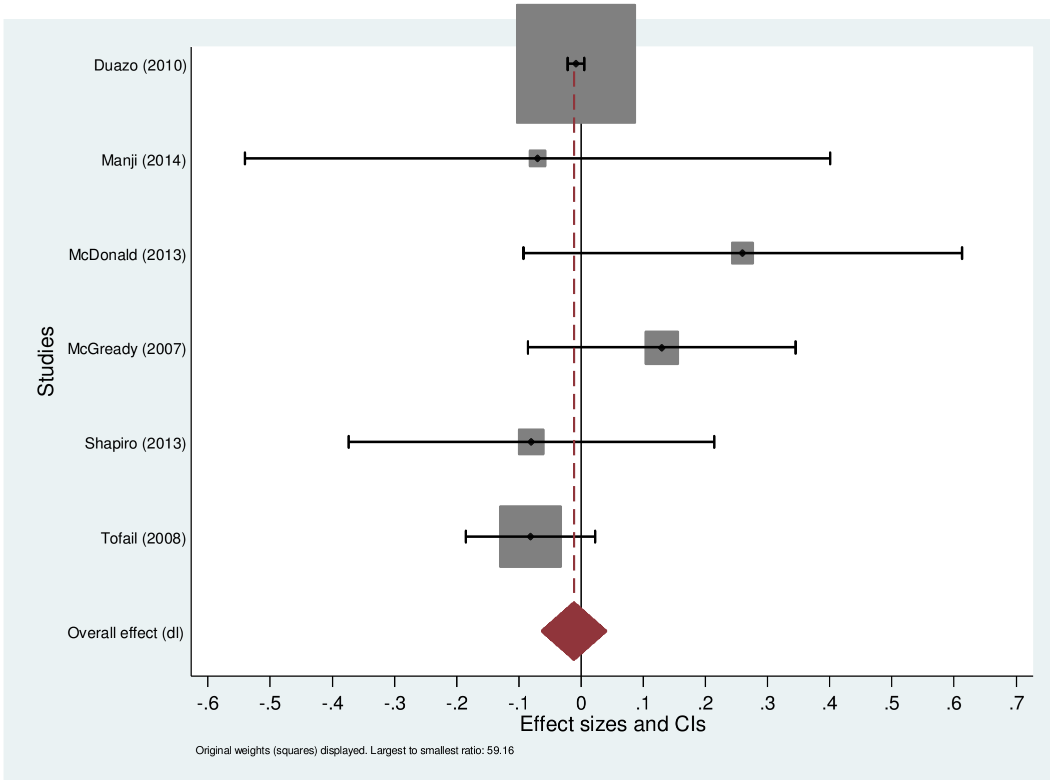

Figure 72: Association between maternal mild anemia (reference: no anemia) and motor development.

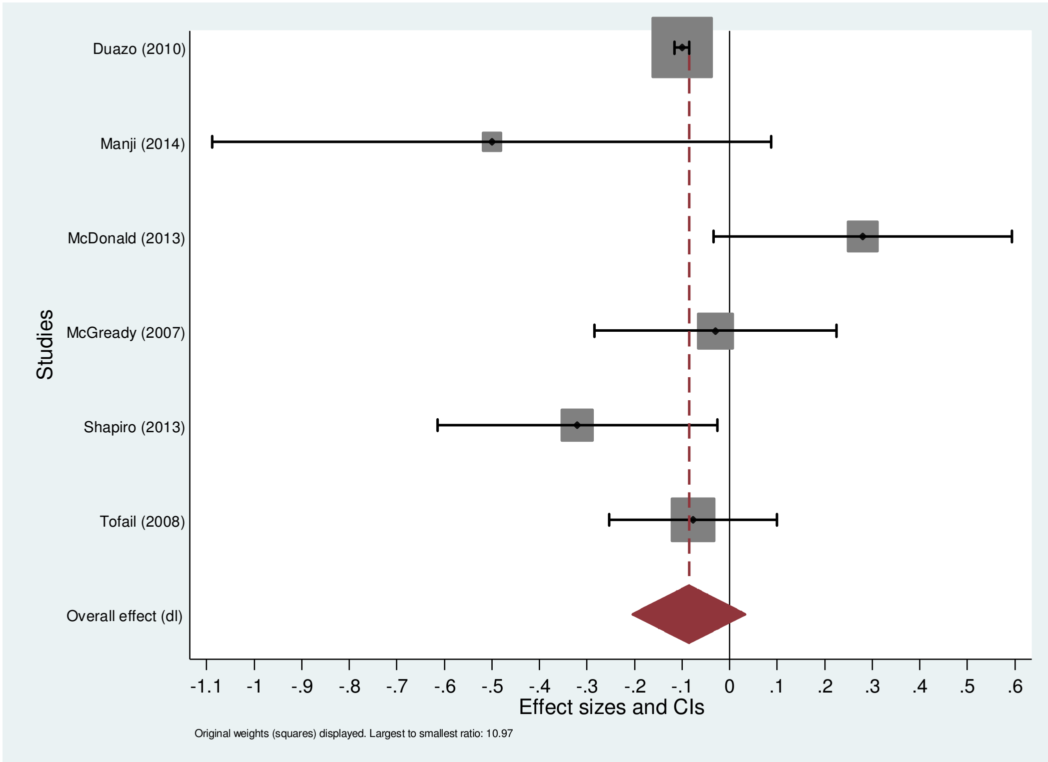

Figure 73: Association between maternal moderate anemia (reference: no anemia) and motor development.

6. Parental Risk Factors on Child's Language Development

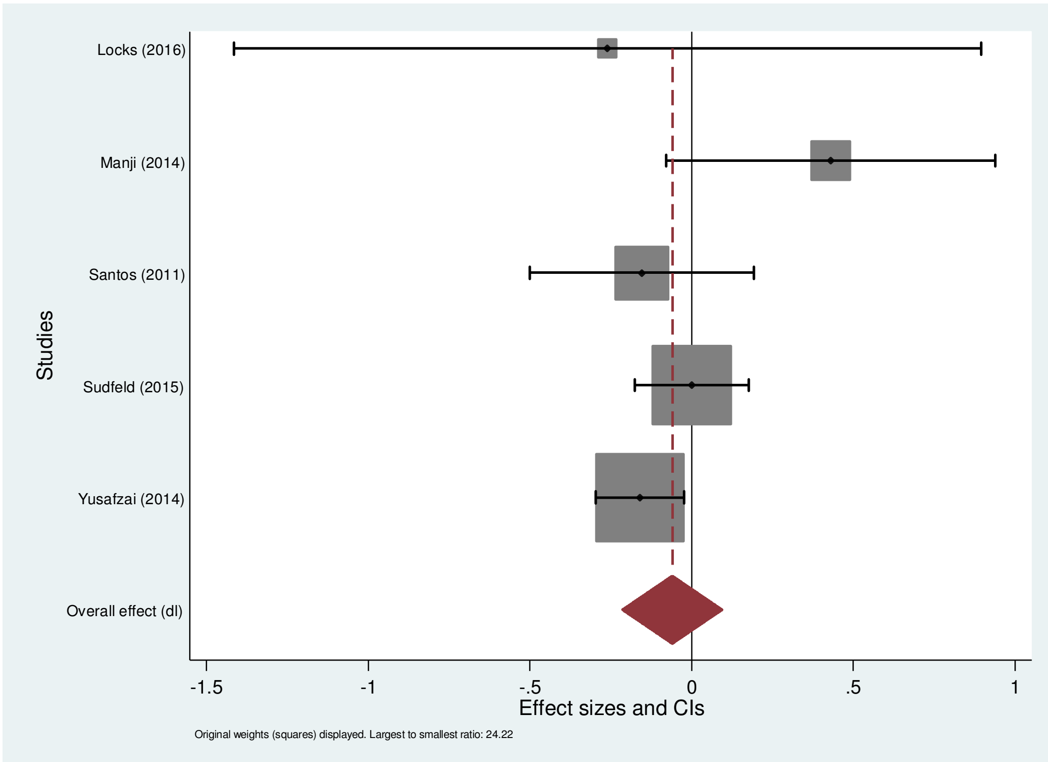

Figure 74: Association between no maternal education (reference: primary education) and language development.

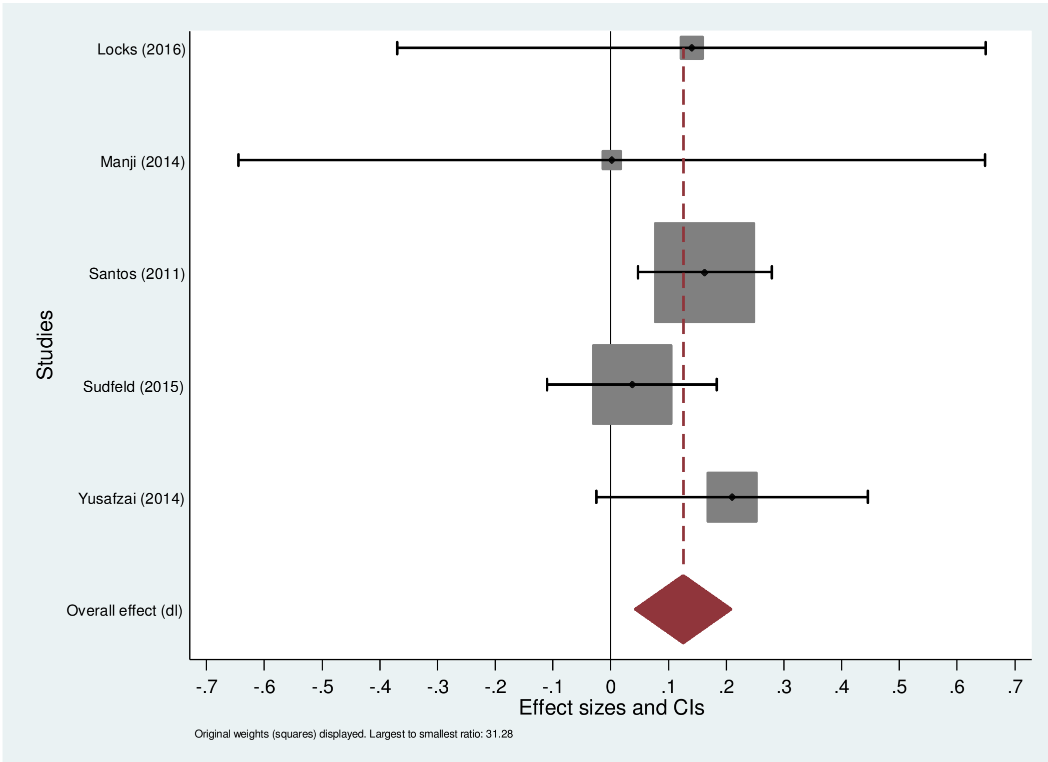

Figure 75: Association between maternal secondary education (reference: primary education) and language development.

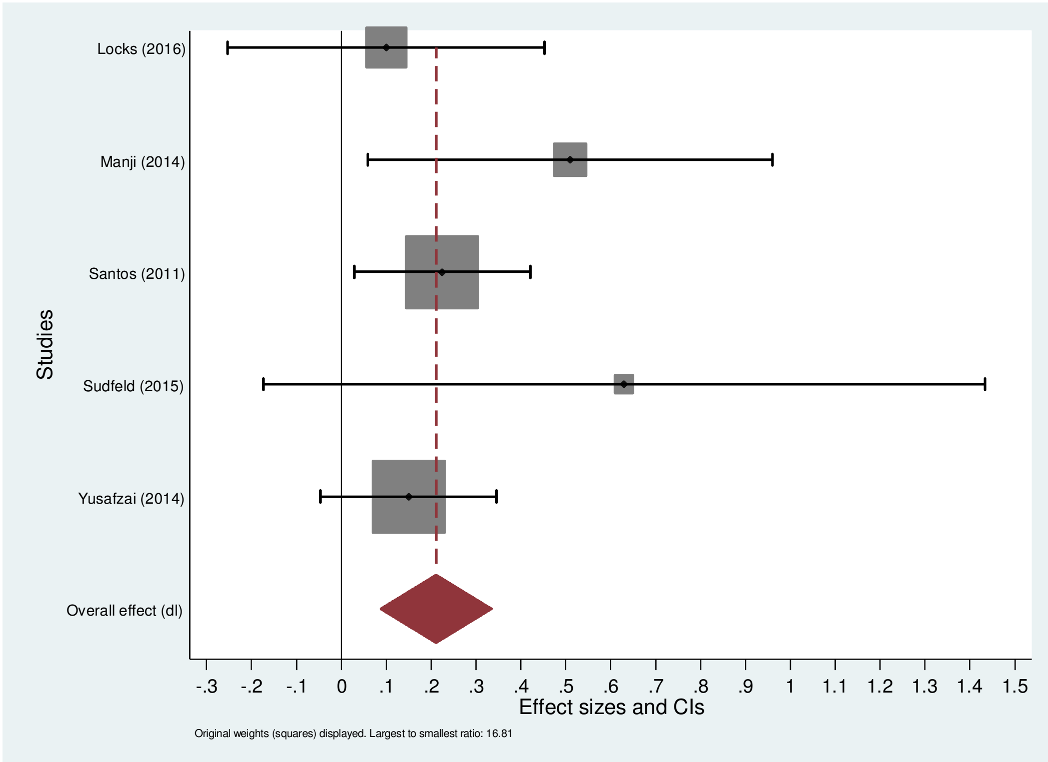

Figure 76: Association between maternal higher education (reference: primary education) and language development.

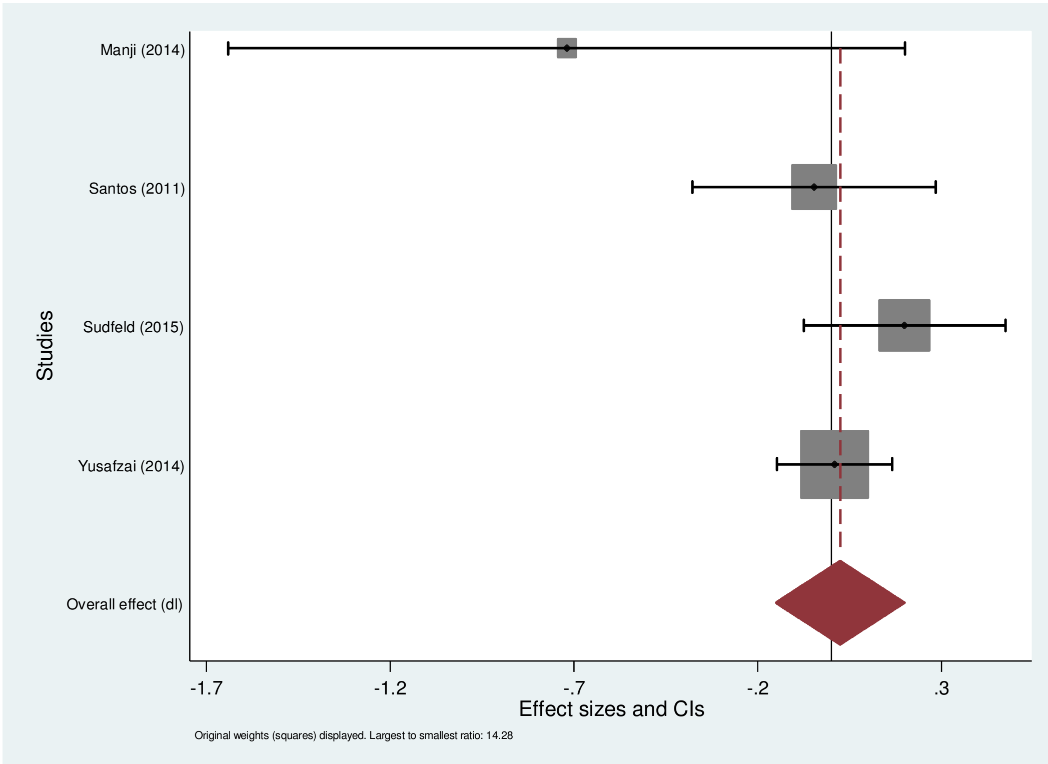

Figure 77: Association between no paternal education (reference: primary education) and language development.

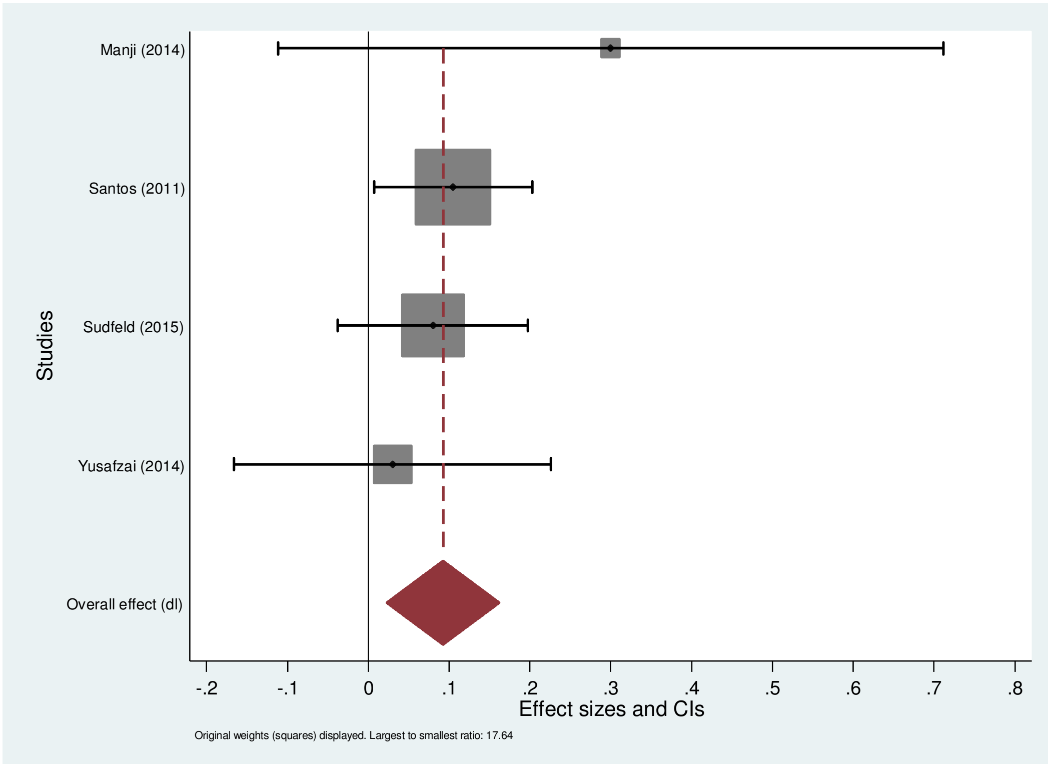

Figure 78: Association between paternal secondary education (reference: primary education) and language development.

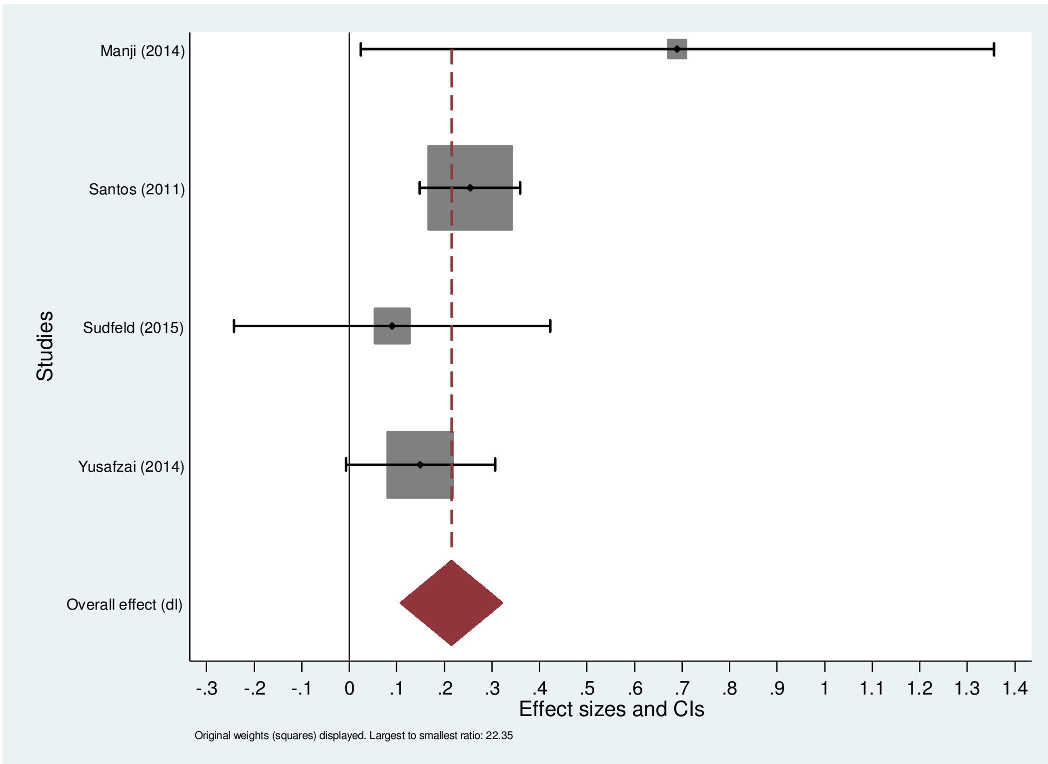

Figure 79: Association between paternal higher education (reference: primary education) and language development.

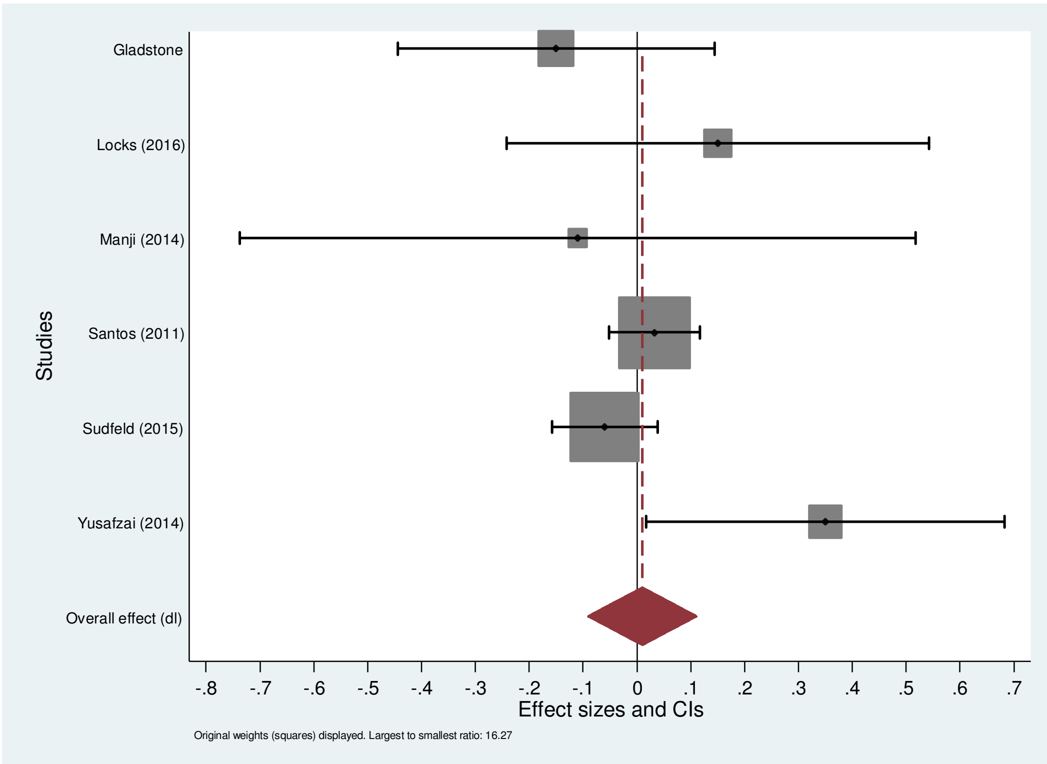

Figure 80: Association between maternal ages 15-20 (reference: ages 20-34) and language development.

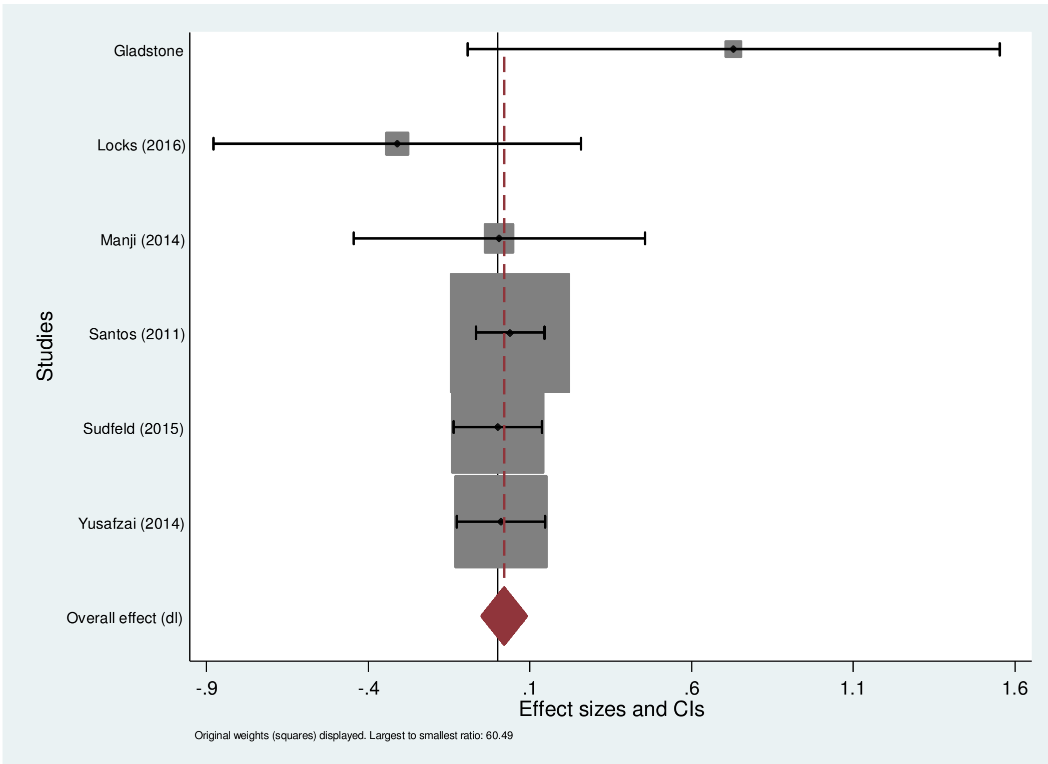

Figure 81: Association between maternal ages >35 (reference: ages 20-34) and language development.

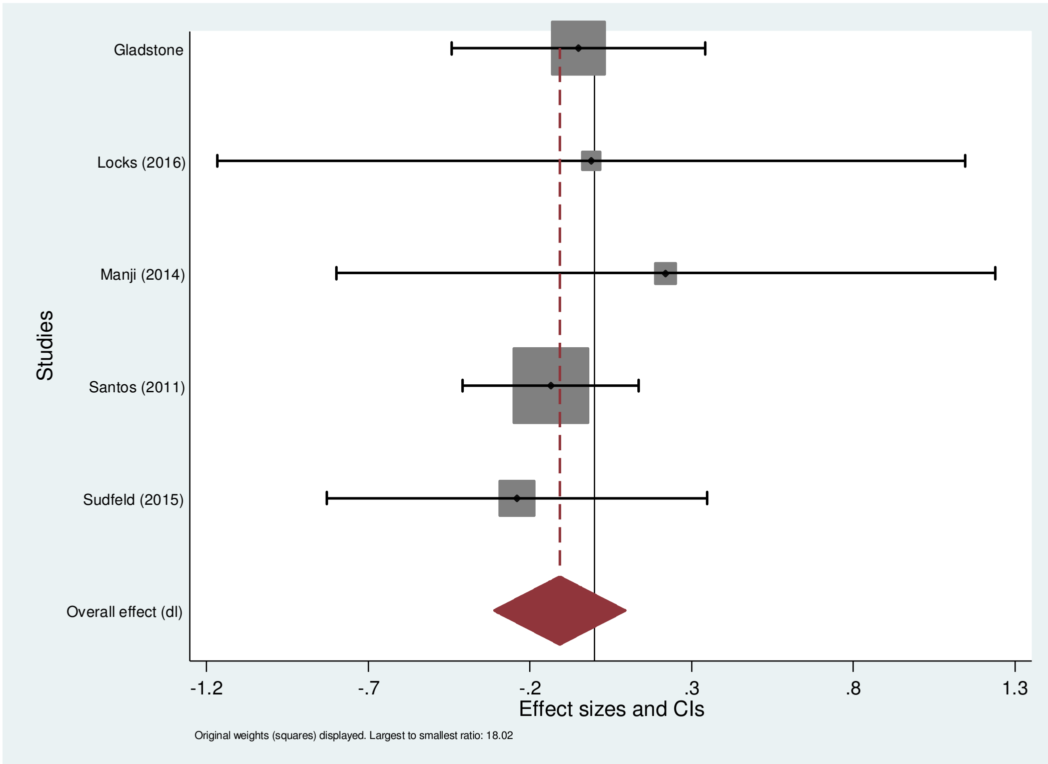

Figure 82: Association between maternal height <145 cm (reference: >155 cm) and language development.

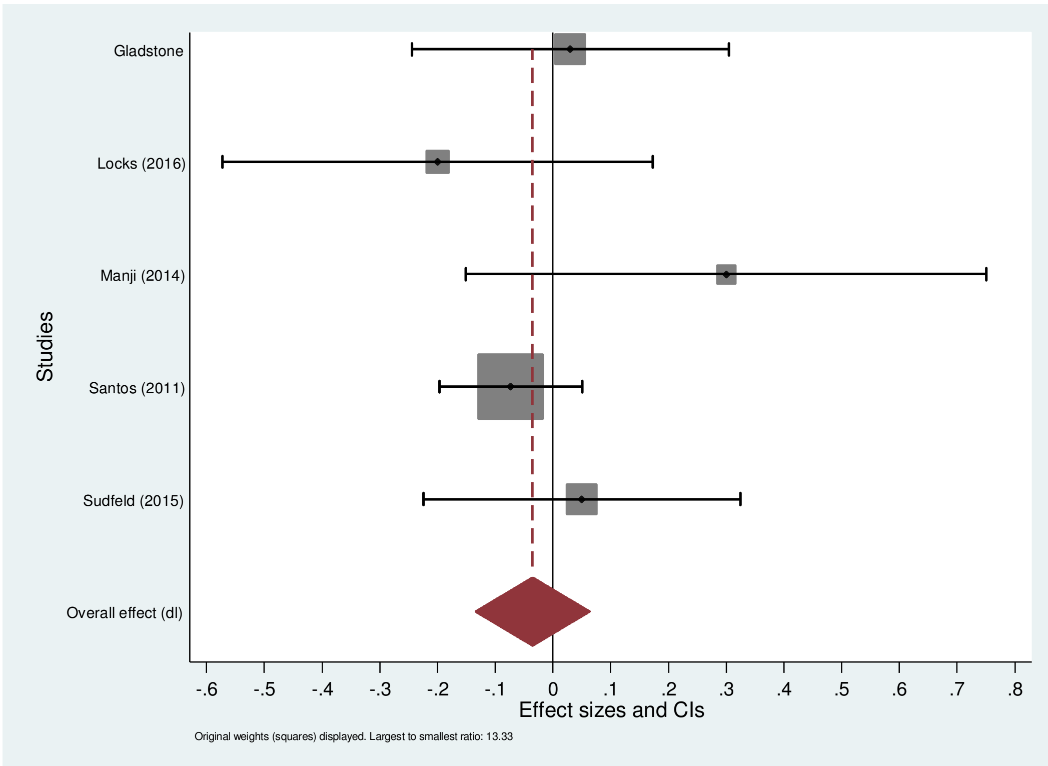

Figure 83: Association between maternal height 145-150cm (reference: >155 cm) and language development.

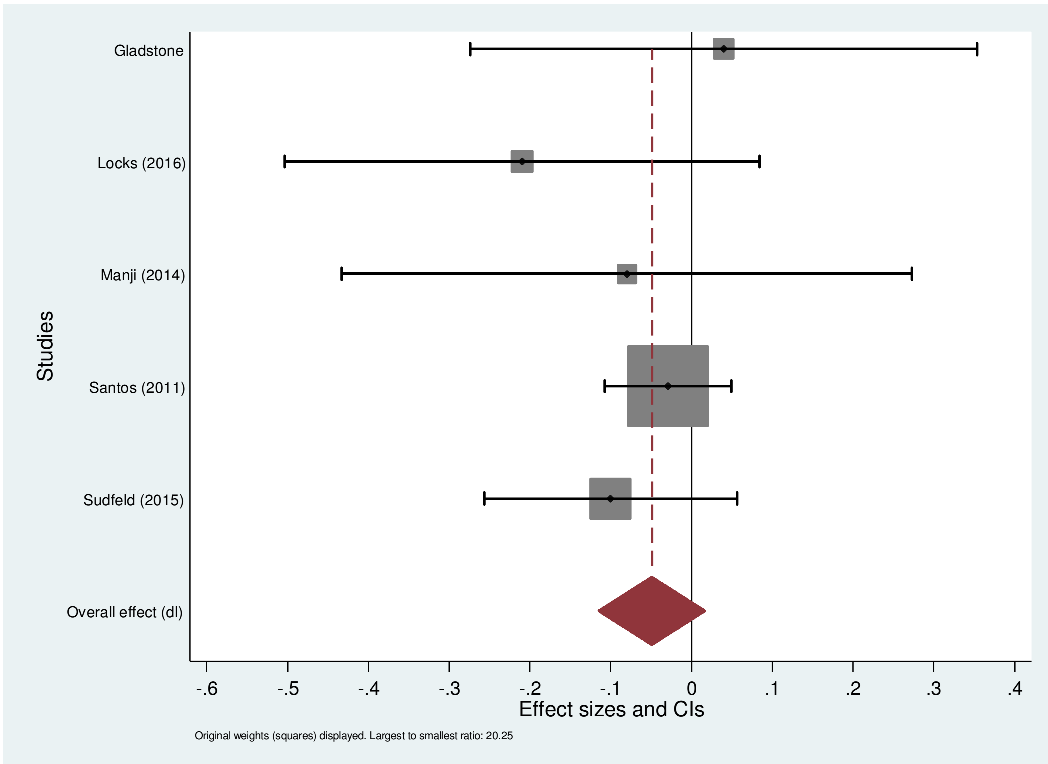

Figure 84: Association between maternal height 150-155 cm (reference: >155 cm) and language development.

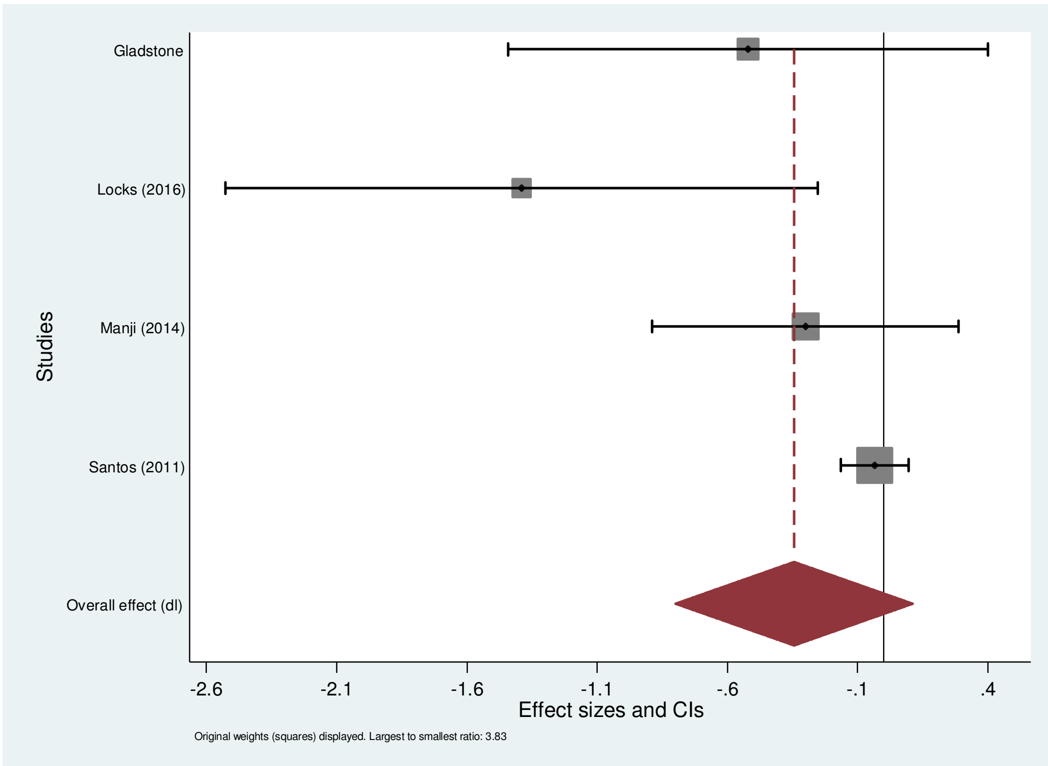

Figure 85: Association between maternal BMI 25-30 kg/m² (reference: 18.5-25) and language development.

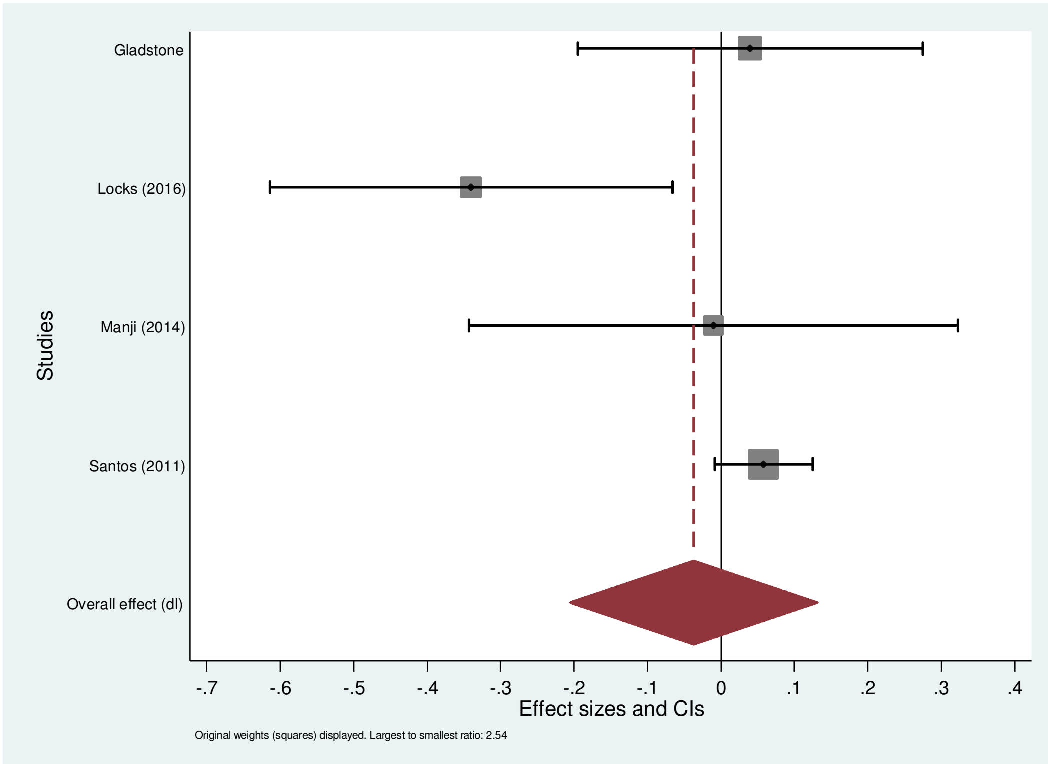

Figure 86: Association between maternal BMI >30 kg/m² (reference: 18.5-25) and language development.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	No
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6-7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration numbers.	yes
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8 & 10
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	N/A[a]
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	10

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A[b]
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A[b]
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Appendix 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Tables 2 and 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A[b]
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11-13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18 &19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	3

a. Same analyses were conducted in all individual studies by the authors and then estimates from individual studies were combined in pooled estimates. Therefore, assessment of quality of individual studies were not done.
b. Selection of studies were not based on published literature only, a large number of the studies were unpublished

PRISMA 2009 Checklist

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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