Language and Motor Skills in Siblings of Children with Autism Spectrum Disorder. A Meta-Analytic Review

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Abstract

Children with autism spectrum disorder (ASD) show significant linguistic and motor impairments compared to children with typical development (TD). Findings from studies of siblings of children with ASD show similarities to conclusions from studies of children with ASD. The current meta-analysis reviewed studies reporting linguistic and/or motor skills in siblings of children with ASD compared to siblings of children with TD. Thirty-four studies published between 1994 and 2016 met all inclusion criteria. We compared three different age groups (12 months or younger, 13 to 24 months, and 25 to 36 months). At 12 months, compared to siblings of children with TD, siblings of children with ASD had worse receptive language (d=-.43, 95% CI [-.53 -.33]) and expressive language skills (d=-.40, 95% CI [-.57,-.23]), and these effects were sustained at 24 and 36 months. Similar, albeit smaller differences in fine motor skills were detected at 12 months (d=-.22, 95% CI [-.39,-.04]), and these differences were larger at 36 months (d=-.36, 95% CI [-.54,-.17]). There were differences in gross motor skills at 12 months (d=-.22, 95% CI [-.40,-.04]), but only a few studies were available at later ages. Compared to siblings of children with TD, infants who have siblings with ASD have worse linguistic and motor skills. These differences are detectable as early as when infants are 12 months old and seem to be sustained until they are 3 years old. Differences in language skills are larger than those in motor skills, especially during the first year.

Lay abstract: We reviewed studies reporting linguistic and/or motor skills in siblings of children with ASD compared to those in siblings of children with typical development. The results showed that as a group, those infants who have siblings with ASD have less advanced linguistic and motor skills. These differences are detectable when infants are 12 months old and seem to be sustained until they are 3 years old. Differences in language skills are larger than those in motor skills.

Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by symptoms in two broad domains, i.e., notable deficits in communication and social interaction, and the presence of restricted and/or repetitive interests and behaviors (American Psychiatric Association, 2013). Early signs of ASD can be detected in some children during the first year of life (Bolton, Golding, Emond, & Steer, 2012), with diagnoses often possible before age 3 (Ozonoff et al., 2015).

Impairments in language and communication are central components of ASD, even though the specific nature and extent of the impairments in children with ASD is variable (Bishop, 2010). Impairment in the social use of language and communication is required for a diagnosis of ASD, but impairments in the development of linguistic structure and vocabulary are not. Despite this, children with ASD often show notable delays in the development of expressive language (e.g., syntax, expressive vocabulary) (Hudry et al., 2010), receptive language (Kamio, Robins, Kelley, Swainson, & Fein, 2007), and phonology (Rapin, Dunn, Allen, Stevens, & Fein, 2009).

Besides language and communication problems, atypical or delayed motor skills are other potential symptoms associated with ASD. A meta-analysis showed that individuals with ASD demonstrate significant and generalized alterations in motor performance (Fournier, Hass, Naik, Lodha, & Cauraugh, 2010) and about 80-90% of children with ASD show some degree of motor difficulties (Hilton, Zhang, Whilte, Klohr, & Constantino, 2012). Such motor difficulties could include atypical fine and

gross motor skills (Landa & Garret-Mayer, 2006; Barbeau, Meilleur, Zeffiro, & Mottron, 2015).

Siblings of children with ASD: language and motor skills

Research confirms that siblings of children with ASD (often referred to as high risk children; HR) have an increased likelihood of developing ASD themselves, or of developing sub-clinical symptoms of ASD, compared to siblings of children with typical developmental (TD) (also referred to as low risk children; LR) (Messinger et al., 2013). For instance, studies estimate that about 2-19% of HR children receive an ASD diagnosis, compared to 0.6% of LR children (Newschaffer, Fallin, & Lee, 2002; Muhle, Trentacoste, & Rapin, 2004; Levy, Mandel, & Schultz, 2009; Ozonoff et al., 2011). In addition, one study found that about 19% of HR children not later diagnosed with ASD nevertheless showed significantly elevated autistic traits by 12 months of age, (e.g. reduced eye contact, orienting to name, and social smiling; Georgiades et al., 2013). This suggests that even if HR children do not show the pattern or severity of symptoms that warrant an ASD diagnosis, they can have different or less severe developmental problems such as language delays (Johnson, Myers, & American Academy of Pediatrics Council on Children with Disabilities, 2007; Gamliel, Yirmiya, Jaffe, Manor, & Sigman, 2009; Paul, Fuerst, Ramsay, Chawarska, & Klin, 2011).

Indeed, HR children are more likely to show developmental impairments in language and communication (Drumm & Brian, 2013), and language difficulties are among the main indicators of the Broader Autism Phenotype (BAP, the presence of autistic-like traits) during preschool years (Elsabbagh & Johnson, 2007; Toth, Dawson, Meltzoff, Greenson, & Fein, 2007). Such difficulties can range from lack of fluency (Ozonoff, Rogers, Farnham, & Pennington, 1993) to severe pragmatic difficulties (Ben-

Yizhak et al., 2011; Levy & Bar-Yuda, 2011). Some studies have shown that as a group, compared to LR children, HR children demonstrate lower receptive and expressive language skills (i.e., fewer canonical syllables and use of words) already during the first three years of life (Toth et al., 2007; Paul et al., 2011).

HR children are also at increased risk for motor difficulties, although the literature does not provide the same level of evidence related to motor skills in this population as is available for language skills. Interestingly, whereas most HR children have motor skills falling within the typical developmental range, they may nevertheless use less sophisticated functional movements than expected (Mulligan & White, 2012). It has also been suggested that HR children may show relatively high scores in gross motor skills but low scores in fine motor tasks due to difficulties in motor imitation (Klin, Saulnier, Tsatsanis, & Volkmar, 2005). For instance, one study detected some movement anomalies in HR children compared to LR children as early as 6 months of age (i.e., difficulties with postural control; Flanagan, Landa, Bhat, & Bauman, 2012).

The results reported above suggest that studies of HR infants can provide valuable information about early markers of the BAP (Paul et al., 2011; Pisula & Ziegart-Sadowska, 2015). Further research on the development of HR children could also help us attend early on to potential intervention needs that these children may have. However, the results of the existing studies are mixed and it is not clear (a) to what extent there are developmental differences in language and motor skills between HR and LR children, (b) when these differences can be detected, and (c) whether the differences increase or decrease with age. To help clarify these issues, and to provide a synthesized overview of the differences between siblings of children with ASD and siblings of children with TD in the areas of language and motor development, we

systematically reviewed the available literature using meta-analytic methods and compared language and motor skills in HR and LR children.

Our focus on impairments in language and motor skills is motivated by theoretical models positing mechanistic links between the two domains (e.g., Alcock & Krawczyk, 2010; Leary & Hill, 1996) along with empirical evidence that they are strongly related. For instance, some evidence supports an assumption that motor skills (i.e. locomotor experiences) facilitate social interaction and social communication (Bhat, Landa, & Galloway, 2011; Karasik, Tamis-LeMonda, & Adolph, 2011). Empirically, receptive and expressive language skills correlate with motor skills in children with ASD (Luyster, Kadlec, Carter, & Tager-Flusberg, 2008), and poor motor skills may predict small gains for children with ASD in interventions targeting oral expressive language (Belmonte, Saxena-Chandhok, Cherian, Muneer, George, & Karanth, 2013). Oral -and manual- motor skills are predictors of speech fluency (Stone & Yoder, 2001; Thurm, Lord, Lee & Newschaffer, 2007; Gernsbacher, Sauer, Geye, Schweigert, & Hill Goldsmith, 2008), and gesture use is one of the best predictors of receptive and expressive language skills (Luyster et al., 2008). However, it is not clear to what extent deficits in language and motor skills in HR children are related (e.g., what deficits are observed earlier or more strongly).

Consequently, the purpose of this meta-analysis is to estimate the size and consistency of the differences in both language and motor skills between HR and LR children, and to describe how these differences compare to each other (e.g. Are differences in language skills detected earlier? Are they bigger?). In particular, we considered both receptive and expressive language skills, as well as both fine and gross motor skills at different key developmental ages (from 1 to 3 years old). We elected to

compare siblings of children with TD (LR) to siblings of children with ASD (HR), regardless of any subsequent diagnosis. Because our interest was studying development in HR children in the period before definitive diagnoses are typically provided, we focused on studies assessing children 3 years old or younger.

Methods

Data collection, inclusion criteria and identification of studies

We conducted a systematic review of empirical articles examining development in siblings of children diagnosed with ASD. We selected those articles that compared siblings of children with ASD (HR children) to siblings of children with TD (LR children) on linguistic and/or motor skills. Our search was limited to articles written in English and published between 1994 (publication date of the DSM-IV establishing diagnostic criteria for ASD) and 2016. We searched the following databases: Web of Science, PubMed, PsycINFO, ERIC, and Medline, using combinations of the following keywords: Autism Spectrum Disorder, ASD, autis[1], siblings, at risk, high risk, low risk, unaffected, affected, language, linguistics, and motor. We identified additional studies from the reference lists of the articles already selected and searched the grey literature (e.g. unpublished studies and congress abstracts). The initial search returned more than 4000 publications. After review of title and abstract 809 articles remained.

From these, we excluded studies (k=677) according to the following criteria: (a) high risk group did not comprise children with a sibling with ASD, (b) study focused on genetics in HR children, (c) study focused on children at high risk for non-ASD

[1] An asterisk stands for any character that shares the same root (e.g. autis*: autism, autistic).

disorders, (d) article was published outside of the specified dates, (e) study reported neuroimaging measures exclusively, (f) study focused on treatment.

Studies were further excluded based on the following exclusion criteria (k=98): (a) LR group was absent, (b) the LR group did not include siblings of children with TD, (c) HR and LR groups were selected based on mixed criteria, (d) children in the LR and HR samples had an average age over 36 months, (e) HR and LR children were not matched on chronological age, (f) the study did not include monolingual children, (g) the study did not report outcomes for both language and/or motor skills, (h) linguistic and/or motor skills were not evaluated with objective scales, (i) the ASD diagnosis of affected siblings was not based on Autism Diagnostic Interview-Revised (ADI-R; Le Couteur et al., 2003) or Autism Diagnostic Observation Schedules (ADOS-G; Lord et al., 2002), (j) the necessary values required for coding could not be obtained even after contacting the authors, and (k) article was a duplicate of an already included article, or reported data on a sample that was already included from another publication.

Our final sample included 33 articles, reporting 34 studies. Figure 1 offers an overview of the search process. Two authors independently extracted data from the 34 studies and any disagreement was resolved with discussion.

INSERT FIGURE 1 ABOUT HERE

We recorded the following information for each study: publication year, group sample size, age of children (mean, range and standard deviation for HR and LR groups), and the tests used to measure linguistic and motor skills. We recorded means and standard deviations for the following dependent variables: (a) expressive language, (b) receptive language, (c) fine motor skills, and/or (d) gross motor skills, in the age ranges of (a) up to 12 months, (b) between 13 and 24 months, and (c) between 25 and

36 months. When a study contained measurement data from multiple timepoints within the selected age intervals, we chose the measurement that was closest to the upper value within the interval (i.e. 12, 24 or 36 months). When a study used more than one test to assess language or motor skills, we chose the test that was more frequently used across the sample of studies.

Meta-analytic procedure

To conduct the meta-analysis we used the metafor package R (Viechtbauer, 2010). Where data from multiple groups had to be combined (e.g., when the HR group was divided in subgroups depending on the later presence of an ASD diagnosis), we followed procedures recommended in the Cochrane handbook for systematic reviews (Higgins, 2008). As a measure of effect size, we calculated the standardized mean difference and followed Cohen (1988) to interpret the sizes of the obtained effects (.2, .5, and .8 for small, medium, and large, respectively). The analyses were based on unadjusted means because none of the included studies provided means adjusted for covariates.

Studies were weighted using the standard "inverse variance" method. In particular, we fitted random effects models, in which studies were weighted by the inverse of the sum of the sampling variances and the residual heterogeneity (Viechtbauer, 2010). We further fitted mixed-effects models considering the following potential moderators: exact age in months, type of test used, and publication year. Because of the small overall number of studies, each potential moderator was examined separately. The models were fitted with restricted maximum likelihood estimation.

To estimate the amount of heterogeneity between studies we conducted statistical tests for heterogeneity and consulted the I^2 statistic. This statistic estimates (in

percentages) how much of the total variability of the effect size estimates can be attributed to heterogeneity among the true effects, such that 30-60%, 50-90%, and 75-100% are considered to reflect moderate, substantial, and considerable heterogeneity, respectively (Higgins, 2008; Viechtbauer, 2010). To examine publication bias in the data, we generated funnel plots. When the number of studies permitted it, we conducted statistical tests for funnel plot asymmetry (Higgins, 2008). In addition, we examined the data visually, using contour-enhanced funnel plots which permit easy identification of asymmetry due to publication bias (Peters, Sutton, Jones, Abrams, & Rushton, 2008).

Results

Table 1 shows basic information for all studies included in the meta-analysis. The studies were published between 2005 and 2016, and included a total of 2376 children (64% HR and 36% LR) at 12 months, 3764 children (66% HR and 34% LR) at 24 months, and 3422 children (63% HR and 37% LR) at 36 months. The HR and LR groups were not matched a priori on demographic characteristics in any study, and only thirteen studies tested for demographic differences between the groups. In one study (Young et al., 2011), the HR group (N=157) contained 3 LR children who had received an ASD diagnosis. Given the large simple size of the study and the small number of misplaced LR children, we decided not to exclude this study from the meta-analysis. Fifteen studies included information regarding subsequent ASD and other diagnoses; the remaining 19 did not include such information.

INSERT TABLE 1 ABOUT HERE

Language and motor skills tests used

The following tests were used to evaluate language and/or motor skills: Bayley Scales of Infant Development (BSID-II; Bayley, 1993), Clinical Evaluation of Language Fundamentals-Preschool (CELF-P; Wiig, Secord, & Semel, 2004), MacArthur-Bates Communicative Development Inventories (MCDI; Fenson et al., 1993) Mullen Scales of Early Learning (MSEL; Mullen, 1995), Reynell Developmental Language Scales (RDLS; Reynell & Grubber, 1990), and Vineland Adaptive Behavior Scales-2nd Edition (VABS; Sparrow, Cicchetti, & Balla, 2005).

Given the assumption of independence in meta-analysis, we could only select one dependent measure for each ability and sample at each point. We selected the measure most widely used across the included studies in order to decrease variance between studies. The majority of articles used the MSEL (71% for language and 100% for motor skills), so whenever multiple instruments were used, we selected scores from the MSEL. The MSEL is an extensive standardized assessment of expressive language, receptive language, fine motor, and gross motor skills and provides age equivalent and standard scores from birth to 68 months old. The CELF-P Scale evaluates expressive and receptive language in children aged between 36 and 72 months. The VABS Scale is a parent report measure of communication, daily living, and motor and social skills, used from birth to adulthood. The MCDI Scale is also a parent questionnaire measure of language development used for children aged between 8 and 37 months.

Differences in language skills

Detailed results from the three meta-analyses on expressive language skills are shown in Figures S1, S2, and S3. Relative to LR children, HR children showed worse expressive language skills at all ages. The size of the effect was moderate at 12 months

(SMD=-.40, 95% CI [-.57, -.23], n=2044, k=18), at 24 months (SMD=-.34, 95% CI [-.45, -.23], n=3590, k=18) and at 36 months (SMD=-.44, 95% CI [-.58, -.30], n=3422, k=12).

Detailed results from the three meta-analyses on receptive language skills are found in Figures S4, S5, and S6. Similar to the results on expressive language, relative to LR children, HR children showed worse receptive language skills at all ages. The size of the effect was moderate at 12 months (SMD=-.44, 95% CI [-.53, -.34], n=1694, k=15) at 24 months (SMD=-.52, 95% CI [-.68, -.37], n=3243, k=15) and at 36 months (SMD=-.48, 95% CI [-.60, -.36], n=3422, k=12).

Differences in motor skills

Figures S7, S8, and S9 provide detailed results from the three meta-analyses on fine motor skills. Relative to LR children, HR children showed significantly worse fine motor skills. The size of the effect was small at 12 months (SMD=-.21, 95% CI [-.39, -.04], n= 1542, k=12), and small-to-moderate at 24 months (SMD=-.35, 95% CI [-.46, -.24], n=3177, k=11), and at 36 months (SMD=-.36, 95% CI [-.54, -.17], n=2906, k=6).

Only one study assessed differences in gross motor skills between HR and LR children at 36 months, so we could only conduct meta-analyses at 12 and 24 months. Detailed results of these are shown in Figures S10 and S11. Relative to LR children, HR children showed significantly worse gross motor skills at 12 months, with a small effect size (SMD=-.22, 95% CI [-.40, -.04], n=738 , k=7). Only four studies assessed gross motor skills at 24 months. On average, HR children tended to show worse gross motor skills at 24 months; however, this effect was not statistically significant (SMD=-.57, 95% CI [-1.20, .05], n=377, k=4). The one study that assessed differences in gross

motor skills between HR and LR children at 36 months showed significant differences between the groups (SMD=-.44, 95% CI [-.83, -.04], n=101, k=1).

Moderators

We investigated if the year of publication, the average age of participants in months, and the type of test used (i.e., parent-report or not) influenced the effect size by fitting mixed-effects models and testing for moderation where applicable. For instance, due to the relationship between motor and language skills, it is possible that children with poor language skills may show poor motor skills partially due to failure to understand motor task instructions. We did not find effects of clinician- vs. parent-report measures on language skill differences ($p>.05$). Because motor skills were measured with the MSEL in all studies, we were not able to compare clinician- vs. parent-report measures of motor skills, leaving us unable to fully address the question of whether parents would report different levels of motor skills based on observations outside of a testing context.

Moderator tests indicated that for the interval 25-36 months, smaller effects were observed in younger versus older children for expressive language ($QM(1)=9$, $p=.003$) and receptive language ($QM(1)=12$, $p=.001$). These differences were driven by the study by Herlihy and colleagues (2013). This was the only study in the sample in which the assessment was performed at 25 and not at 36 months and it found no significant effects (see Figures S3 and S6). There was another effect of age on fine motor skills in the 3-12 months interval, such that larger differences were found in younger children ($QM(1)=7$, $p=.008$, see Figure S7). Finally, studies published later found larger differences in expressive language at 24 months ($QM(1)=5$, $p=.026$, see Figure S2).

Comparisons of effects

Figure 2 gives an overview of the estimated effect sizes and results from the tests for heterogeneity for each dependent variable (expressive language, receptive language, fine motor, and gross motor skill). In this figure we can compare the effect sizes by age, and observe that differences in both language and motor skills are reliably detected as early as 12 months of age. The figure further suggests that the differences in language are somewhat larger compared to differences in motor skills. For instance, at 12 months differences in language are about twice as large as differences in motor skills. Finally, there is a tendency such that larger differences in fine motor skills are detected at a later age.

Publication bias

Figure 3 shows contour-enhanced funnel plots for the eleven mini meta-analyses, in which publication bias is signaled if studies appear to be missing in the white regions of statistical non-significance. Generally we observed no signs of publication bias, with the exception of receptive language at 36 months where studies appear to be missing in the regions of non-significance, despite a non-significant asymmetry test ($p>.05$).

INSERT FIGURES 2 AND 3 ABOUT HERE

Discussion

After a systematic search and review, we examined the 34 eligible studies providing data on linguistic and/or motor skills in siblings of children with ASD (HR children) and siblings of children with TD (LR children). Our goal was to estimate to what extent HR children show differences in these skills relative to LR children in the first three years of life, and to compare the performance of HR children on motor versus

language development. The collection of mini meta-analyses presented here demonstrates that, compared to children who have older siblings with TD, children who have older siblings with ASD have worse linguistic and fine motor skills, and these differences are detectable during the first three years of life. Our results accord with those from other authors (e.g. Ozonoff et al., 2010), who report that the first ASD symptoms can already be seen at 12 or 24 months in infants who are later diagnosed with ASD. Our results show that infants at heightened genetic risk for ASD as a group show patterns of lower performance similar to those found in HR infants later diagnosed with ASD. Consistent with our target population being at risk for ASD, but not necessarily developing ASD, we found small to moderate differences between HR and LR children. Importantly, this meta-analysis demonstrated that on average, detectable differences in language and motor skills based only on genetic risk can be expected already during the first three years of life. Differences in language were about twice as big as differences in motor skills as early as 12 months of age. This suggests that at an early age language assessment might be more useful than motor skills assessment at detecting risk of subsequent development delays.

Expressive and receptive language in siblings of children with ASD

Our analyses show significant differences in language skills between siblings of children with ASD and siblings of children with TD. For both receptive and expressive language skills effect sizes are moderate already at 12 months and remain so at 36 months. These results are interpreted as additional support for previous findings (e.g. Zwaigenbaum et al., 2005; Landa & Garrett-Mayer, 2006) showing significant differences in expressive and receptive language in HR compared to LR children. They suggest that potential deficits in HR children can be reliably identified already during

the first year of age. In the current data, we do not see evidence that these differences in language increase or decrease from the first to the third year.

If we compare both language aspects, we find somewhat stronger differences in receptive language than expressive language at 12, 24, and 36 months. Assuming that language deficits increase with age, these results suggest that differences in comprehension between HR and LR children are detectable earlier than differences in expression, similar to what is found in children with ASD (e.g. Landa & Garrett-Mayer, 2006; Snyder, 2007; Goodwin, Fein, & Naigles, 2012). This finding is in line with the idea that language development in children with ASD follows a similar pattern to that of TD children. In other words, infants (both with ASD and TD) understand words before they begin saying them.

Fine and gross motor skills in siblings of children with ASD

Our analyses show that there are significant differences between HR and LR infants in fine motor skills at 12, 24 and 36 months. Looking at the longitudinal trajectory, we see some evidence that differences in fine motor development between HR and LR children become larger from the first to the third year. This finding is consistent with Ozonoff and colleagues (2015), who found that HR children could show additional symptoms warranting an ASD diagnosis at three years despite not meeting criteria for the diagnosis at earlier ages. Additionally, our results are in line with those of Leonard et al. (2015), who found much larger differences in gross motor skills between HR and LR children at 36 compared to 7 months of age (see Figures S10 and S11).

Overall, compared to linguistic skills, differences in fine motor skills are smaller, especially during the first year of life. This suggests that, contrary to what some previous studies have suggested (see Iverson, 2010), instead of difficulties in movement

contributing to language delays, language delays at a very early age could be contributing to fine movement differences that become evident or more pronounced later. For instance, language delays and lack of (successful) communication attempts could be limiting the experiences of some HR children that would support the normal trajectory of development of fine motor skills. It is also possible that there is a bidirectional process, such that language and motor skills influence each other. Longitudinal studies assessing both abilities could clarify the developmental trajectory (e.g., Leonard et al. 2015).

The finding that HR children show less proficient fine and gross motor skills than LR children supports outcomes from studies that illustrated differences and/or deficiencies in movement between siblings of children with ASD and siblings of children with TD (e.g. John et al., 2016; Landa & Garrett-Mayer, 2006; Ozonoff et al., 2010; Flanagan et al., 2012). The current review also highlights the need for studies comparing gross motor skills in HR and LR children, especially in two and three-year old infants. Such studies can give us further insight into the developmental trajectory of children at high risk.

It is also important to keep in mind that all studies that met the inclusion criteria used the MSEL to assess motor skills. This means that the extent of the detected differences between HR and LR children is limited by the sensitivity of this particular test. For instance, HR children may be experiencing motor difficulties that are not reliably detected by the MSEL, in which case differences in motor skills may actually be larger than the results reported here suggest.

Limitations

This meta-analysis was based on mean differences unadjusted for important demographic covariates, as these were not reported in the selected studies. None of the studies compared groups that were matched based on important demographic characteristics. This limitation potentially introduces heterogeneity and reduces the precision of the effect sizes estimated here, as adjusting for covariates can either increase or decrease the obtained effect size, depending on the relationship of the covariate to the outcome of interest (Voils, Crandell, Chang, Leeman, & Sandelowski, 2011). Future studies should take into account factors like gender, severity of the sibling's ASD diagnosis, and diagnostic outcome, as these variables could be potential moderators. We did not find any important moderators that had consistent influence on effect sizes across all mini meta-analyses. However, given that there was small variability between studies on some of the parameters tested (e.g., only a few studies used parent-based measures), more studies are needed to draw definitive conclusions regarding possible moderators.

Implications for future research and practice

We would like to encourage further research into language and motor skills development in populations at high risk for ASD identified on the basis of familial (genetic) risk. Knowing the specific language and motor difficulties those children at risk for ASD may experience, at what age these start to appear, and what tests are best at detecting them, can help health professionals intervene in families with children at high risk. For instance, further research along these lines would help us identify at a very early age the risk of specific later diagnoses (e.g., ASD vs. TD vs. language delay) and would increase the possibility for early intervention not only for HR children who will

later be diagnosed with ASD but also for those who will later manifest other developmental problems.

Future research on HR children should focus on answering the following questions: what happens when HR children grow up? It seems that differences in motor and language development would continue to be heterogeneous and not only apparent at earlier ages (e.g. Gamliel et al. 2009). Do differences between HR and LR children increase incrementally with age into adulthood, or do differences dissipate over time? If the HR children who go on to be diagnosed with ASD are removed from the comparisons, what are the effect sizes for differences in linguistic and motor skills of HR children not ever diagnosed with ASD compared to LR children? Answers to these questions could provide a better understanding of the potential value of implementing interventions for HR infants before the time a definitive diagnosis of ASD can be made. That is, if in the natural course of development, differences dissipate with time in any of these areas, then prodromal interventions may not be cost-effective, given that only about 20% of infant siblings of children with ASD will eventually receive a diagnosis of ASD themselves (Ozonoff et al., 2011). On the other hand, if differences between HR and LR children increase over time, and especially if this pattern is evident for the 11-38% of HR children who will not ever meet criteria for an ASD diagnosis but who will meet criteria for other diagnoses and/or exhibit cognitive or language delays (Charman et al., 2016; Elsabbagh & Johnson, 2010; Miller et al., 2016; Zwaigenbaum et al., 2005), this would offer stronger support for early intervention with all infant siblings of children with ASD.

The results of our meta-analysis reflect the heterogeneity of the available studies of children with ASD and related populations. As mentioned before, there are mixed

results concerning specific deficits observed in younger siblings of children with ASD (e.g., see Gamliel, Yirmiya, & Sigman, 2007; Hudry et al., 2014 for findings on language skills and Hilton et al., 2012; Mulligan & White, 2012 for findings on motor skills). The findings of our meta-analyses support the idea that whereas there is not a stable or homogeneous pattern of altered linguistic and motor skills in siblings of children with ASD, there certainly are atypical aspects of language and motor skills among HR children that yield differences in group comparisons between HR and LR children already during the first three years of life (Georgiades et al., 2013; Ozonoff et al., 2014 Gammer et al., 2015).

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Note. References marked with an asterisk indicate studies included in the meta-analysis.

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Figure 1. Searching process and articles selected

Figure 2. Estimated effects sizes and tests for heterogeneity from random effects models for each of 11 mini meta-analyses

Note. SDM=standardized mean difference: A negative value indicates lower scores for the HR vs LR group. The observed effects are drawn proportional to the precision of the estimates. LLCI/UPLL=Lower/Upper level 95% confidence intervals. Confidence intervals not crossing 0 (i.e., the reference line) indicate a significant effect. I^2=Estimated % of the total variability in effect size estimates that can be attributed to variability among the true effects.

*Based on 4 studies

**Based on 1 study

Figure 3. Contour-enhanced funnel plots.

Note. The unshaded (i.e., white) region in the middle corresponds to p-value>.10, the gray-shaded region to p-values between .10 and .05, the dark gray-shaded region to p-values between .05 and .01, and the region outside of the funnel corresponds to p-values<.01. If studies appear to be missing in areas of statistical non-significance (i.e., white areas), publication bias is likely (Peters et al., 2008).

Figure S1. Forest plot for expressive language abilities at 12 months

Note. SMD= Standardized mean differences and 95% confidence intervals. A negative value indicates lower scores for the high risk vs. low risk group. The observed effects are drawn proportional to the precision of the estimates.

Figure S2. Forest plot for expressive language abilities at 24 months

Note. SMD= Standardized mean differences and 95% confidence intervals. A negative value indicates lower scores for the high risk vs. low risk group. The observed effects are drawn proportional to the precision of the estimates.

Figure S3. Forest plot for expressive language abilities at 36 months

Note. SMD= Standardized mean differences and 95% confidence intervals. A negative value indicates lower scores for the high risk vs. low risk group. The observed effects are drawn proportional to the precision of the estimates.

Figure S4. Forest plot for receptive language abilities at 12 months

Note. SMD= Standardized mean differences and 95% confidence intervals. A negative value indicates lower scores for the high risk vs. low risk group. The observed effects are drawn proportional to the precision of the estimates.

Figure S5. Forest plot for receptive language abilities at 24 months

Note. SMD= Standardized mean differences and 95% confidence intervals. A negative value indicates lower scores for the high risk vs. low risk group. The observed effects are drawn proportional to the precision of the estimates.

Figure S6. Forest plot for receptive language abilities at 36 months

Note. SMD= Standardized mean differences and 95% confidence intervals. A negative value indicates lower scores for the high risk vs. low risk group. The observed effects are drawn proportional to the precision of the estimates.

Figure S7. Forest plot for fine motor skills at 12 months

Note. SMD= Standardized mean differences and 95% confidence intervals. A negative value indicates lower scores for the high risk vs. low risk group. The observed effects are drawn proportional to the precision of the estimates.

Figure S8. Forest plot for fine motor skills at 24 months

Note. SMD= Standardized mean differences and 95% confidence intervals. A negative value indicates lower scores for the high risk vs. low risk group. The observed effects are drawn proportional to the precision of the estimates.

Figure S9. Forest plot for fine motor skills at 36 months

Note. SMD= Standardized mean differences and 95% confidence intervals. A negative value indicates lower scores for the high risk vs. low risk group. The observed effects are drawn proportional to the precision of the estimates.

Figure S10. Forest plot for gross motor skills at 12 months

Note. SMD= Standardized mean differences and 95% confidence intervals. A negative value indicates lower scores for the high risk vs. low risk group. The observed effects are drawn proportional to the precision of the estimates.

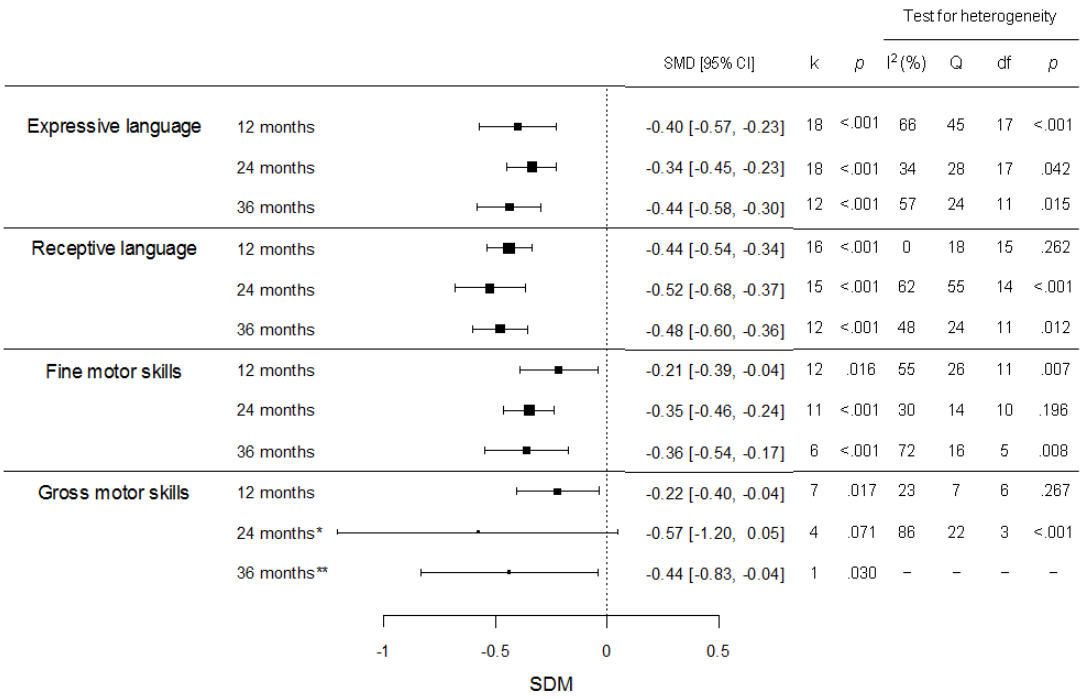
Figure S11. Forest plot for gross motor skills at 24 months

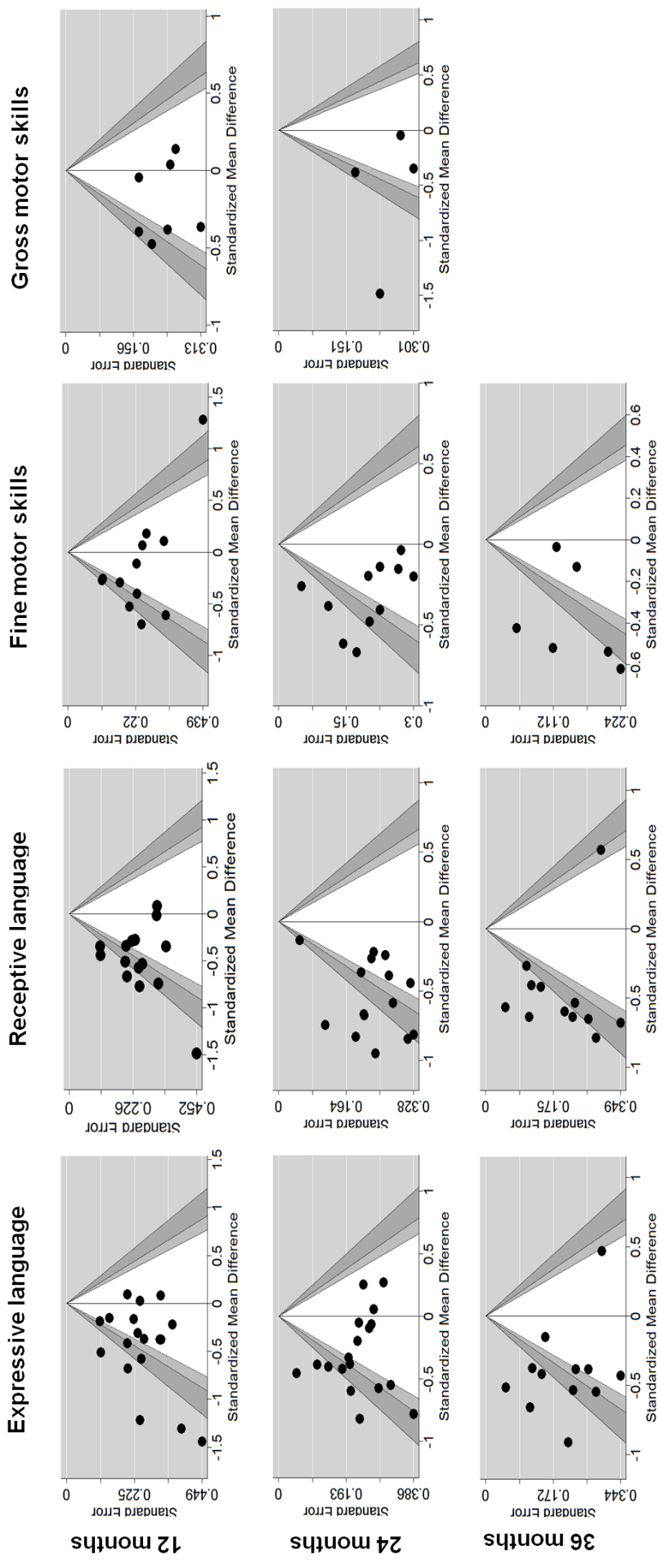
Note. SMD= Standardized mean differences and 95% confidence intervals. A negative value indicates lower scores for the high risk vs. low risk group. The observed effects are drawn proportional to the precision of the estimates.

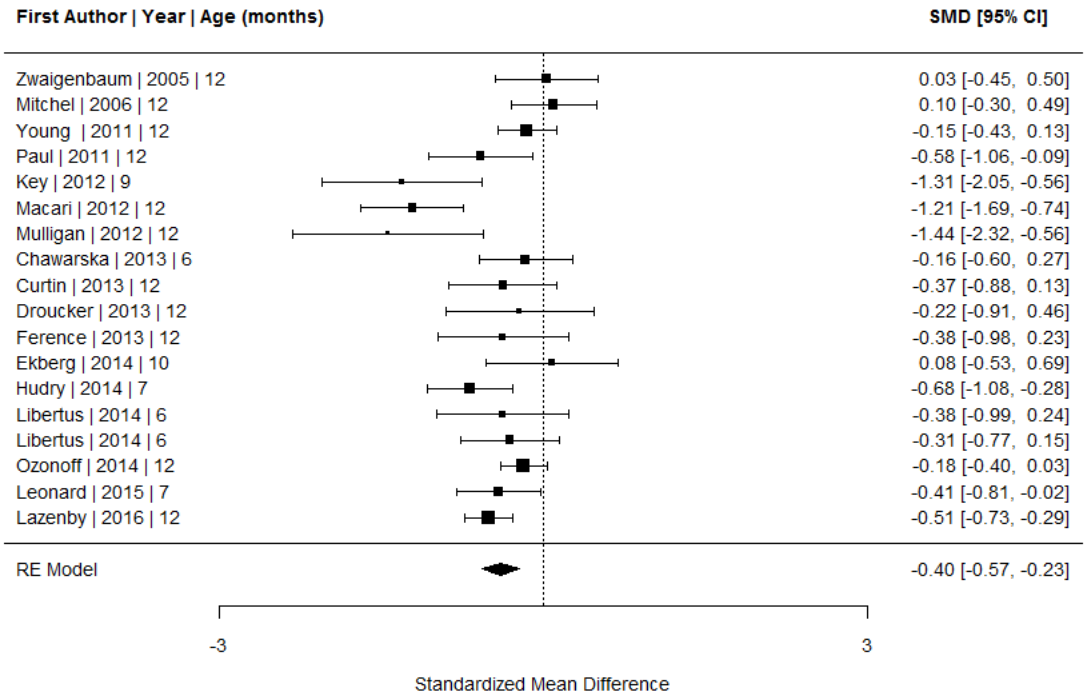
Authors	HR Siblings		LR Siblings		Scales	
	N	Age: months	N	Age: months	Language	Motor
Zwaigenbaum et al. (2005)	65	12	23	12	**MSEL**	
Mitchell et al. (2006)	74 95	12 24	37 46	12 24	**MSEL**	
Gamliel et al. (2007)	38 39	24 36	38 39	24 36	**RDLS** **CELF-P**	
Presmanes et al. (2007)	46	15	35	15	**MSEL**	**MSE**
Stone et al. (2007)	64	16	42	16	**MSEL**	**MSE**
Toth et al. (2007)	42	20	20	22	**MSEL**	**MSE**
Yirmiya et al. (2007)	30 30	24 36	30 30	24 36	**RDLS** **CELF-P**	
Young et al. (2009)	33	24	25	24	**MSEL**	**MSE L**
Young et al. (2011)	157 157 157	12 24 36	75 75 75	12 24 36	**MSEL**	**MSE L**
Paul et al. (2011)	38 24	12 24	31 21	12 24	**MSEL**	**MSE L**
Key et al. (2012)	15	9	20	9	**VABS**	
Macari et al. (2012)	50 50	12 24	34 34	12 24	**MSEL**	**MSE L**
Mulligan et al. (2012)	13	12	12	12	**MSEL**	**MSE**
Chawarska et al. (2013)	49	6	35	6	**MSEL**	**MSE**
Curtin et al. (2013)	31 25	12 18	31 26	12 18	**MCDI**	**MSE L**
Droucker et al. (2013)	14 11	12 18	20 21	12 18	**MCDI**	
Ference et al. (2013)	20	12	23	12	**MCDI**	
Herlihy et al. (2013)	21	25	27	25	**MSEL**	
Ibañez et al. (2013)	26	36	13	36	**MSEL**	
Schwichtenberg et al.	104	36	76	36	**MSEL**	**MSE**

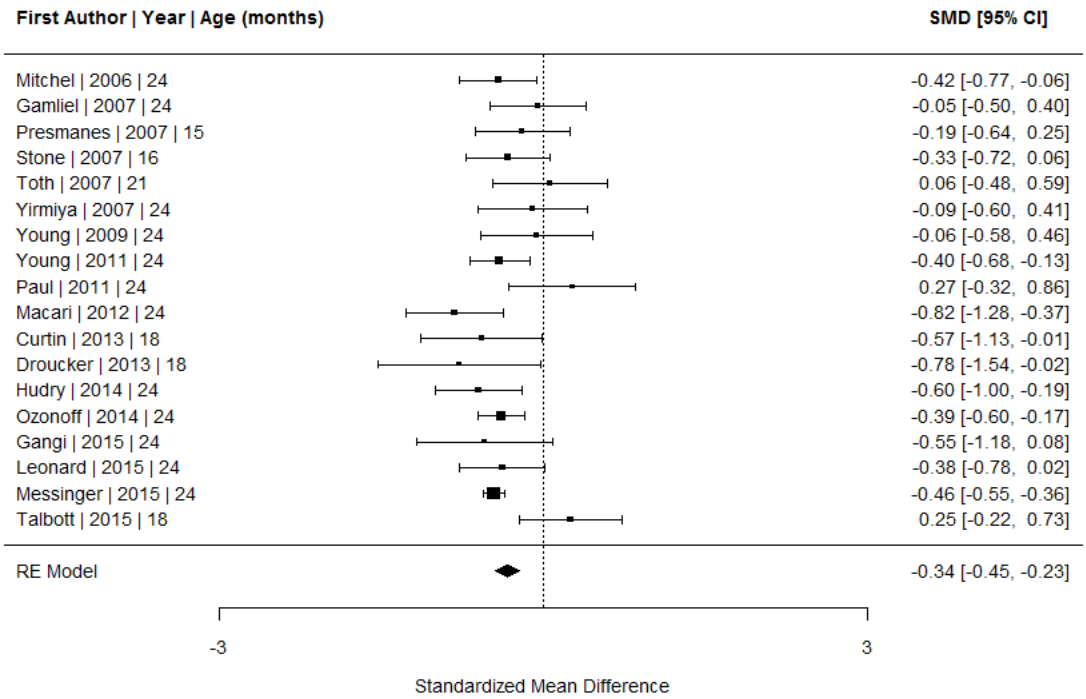
Ekberg et al. (2014)	29	10	16	10	**MSEL**	
Elison et al. (2014)	105	12	53	12		**MSE**
Hudry et al. (2014)	54	7	50	7	**MSEL**	
	52	24	47	24		
Klerk et al. (2014)	44	36	40	36	**MSEL**	**MSE**
Libertus et al. (2014)	23	6	19	6	**MSEL**	**MSE**
Libertus et al. (2014)	107	6	22	6	**MSEL**	**L**
Miller et al. (2014)	119	36	188	36	**MSEL**	**MSE**
Ozonoff et al (2014)	294	12	116	12	**MSEL**	**MSE**
	294	24	116	24		**L**
	294	36	116	36		
Gangi et al. (2015)	43	24	13	24	**MSEL**	
	39	36	20	36		
Leonard et al. (2015)	53	7	48	7	**VABS**	**MSE**
	52	24	47	24		**L**
	53	36	48	36		
Messinger et al. (2015)	124	24	583	24	**MSEL**	**MSE**
	1	36	583	36		**L**
Talbott et al. (2015)	47	18	27	18	**MCDI**	
Lazenby et al. (2016)	213	12	133	12	**MSEL**	
StJohn et al. (2016)	124	12	50	12		**MSE**
	125	24	49	24		**L**

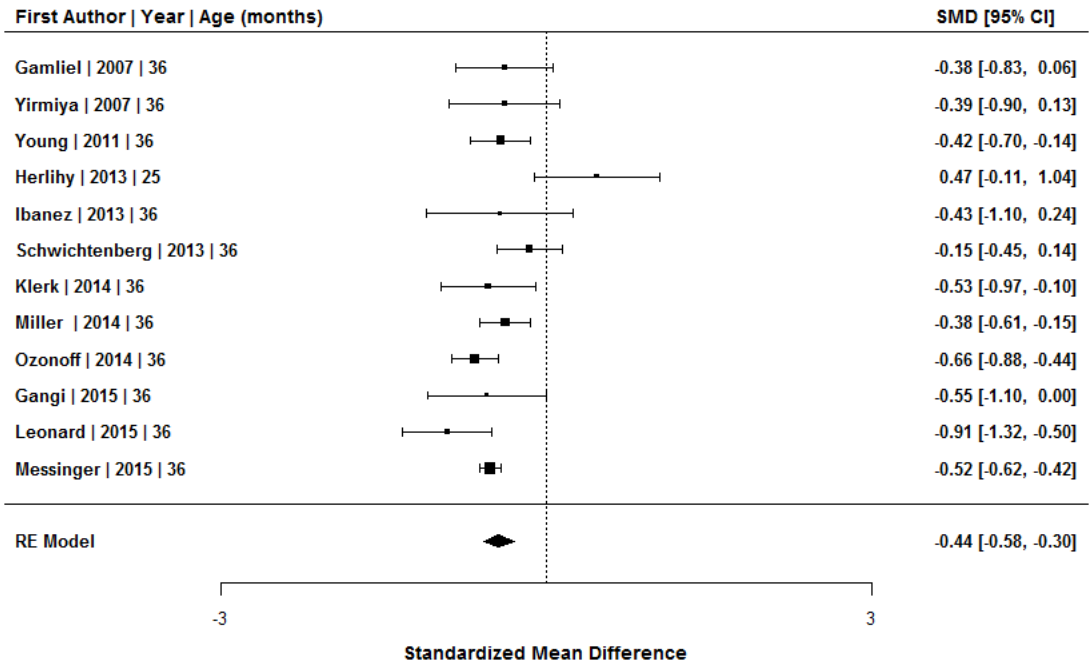
Note: Scales in bold were selected to be included in the meta-analysis. BSID-II (Bayley ´s Scales of Infant Development; Bayley, 1993), CELF-P (Clinical Evaluation of Language Fundamentals-Preschool; Wiig, Secord, & Semel, 2004), RDLS (Reynell Developmental Language Scales; Reynell and Grubber, 1990), MSEL (Mullen Scales of Early Learning; Mullen, 1995), MCDI (MacArthur-Bates Communicative Development Inventories; Fenson et al., 1993), y VABS (Vineland Adaptative Behaviour Scales-2nd Edition; Sparrow, Cicchetti, & Balla, 2005).

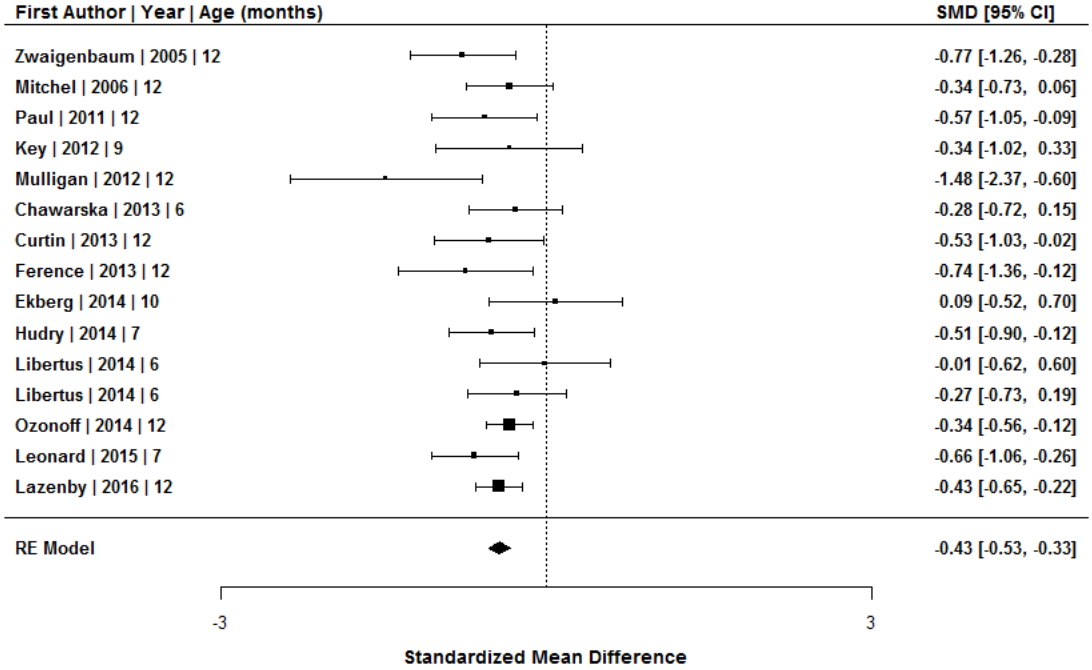

Test for heterogeneity
SMD [95% CI] k p I^2 (%) Q df p
Expressive language
12 months -0.40 [-0.57, -0.23] 18 <.001 66 45 17 <.001
24 months -0.34 [-0.45, -0.23] 18 <.001 34 28 17 .042
36 months -0.44 [-0.58, -0.30] 12 <.001 57 24 11 .015
Receptive language
12 months -0.44 [-0.54, -0.34] 16 <.001 0 18 15 .262
24 months -0.52 [-0.68, -0.37] 15 <.001 62 55 14 <.001
36 months -0.48 [-0.60, -0.36] 12 <.001 48 24 11 .012
Fine motor skills
12 months -0.21 [-0.39, -0.04] 12 .016 55 26 11 .007
24 months -0.35 [-0.46, -0.24] 11 <.001 30 14 10 .196
36 months -0.36 [-0.54, -0.17] 6 <.001 72 16 5 .008
Gross motor skills
12 months -0.22 [-0.40, -0.04] 7 .017 23 7 6 .267
24 months* -0.57 [-1.20, 0.05] 4 .071 86 22 3 <.001
36 months** -0.44 [-0.83, -0.04] 1 .030 – – – –
-1
-0.5
0
0.5
SDM

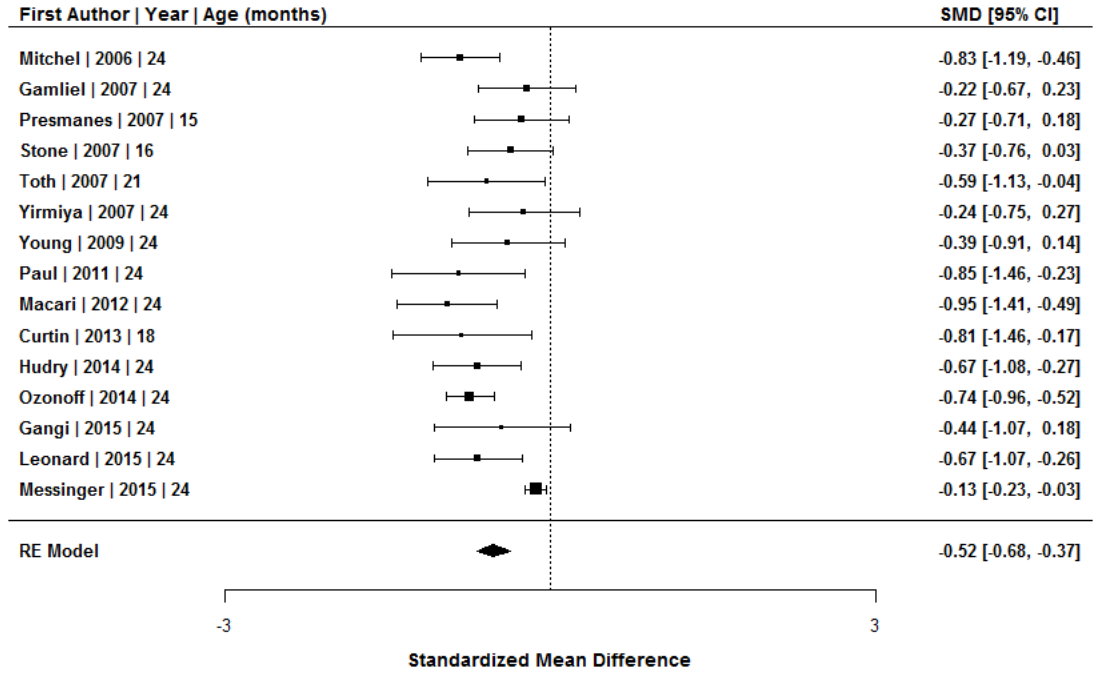

Expressive language
Receptive language
Fine motor skills
Gross motor skills
12 months
24 months
36 months
Standard Error
Standardized Mean Difference

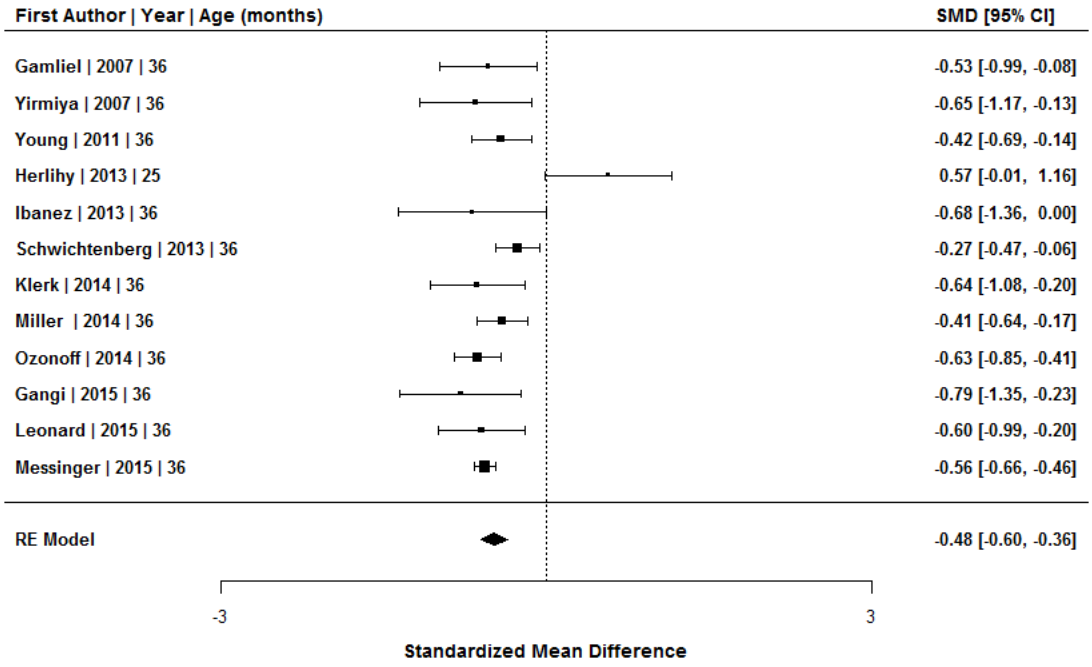

First Author | Year | Age (months)
SMD [95% CI]
Zwaigenbaum | 2005 | 12
0.03 [-0.45, 0.50]
Mitchel | 2006 | 12
0.10 [-0.30, 0.49]
Young | 2011 | 12
-0.15 [-0.43, 0.13]
Paul | 2011 | 12
-0.58 [-1.06, -0.09]
Key | 2012 | 9
-1.31 [-2.05, -0.56]
Macari | 2012 | 12
-1.21 [-1.69, -0.74]
Mulligan | 2012 | 12
-1.44 [-2.32, -0.56]
Chawarska | 2013 | 6
-0.16 [-0.60, 0.27]
Curtin | 2013 | 12
-0.37 [-0.88, 0.13]
Droucker | 2013 | 12
-0.22 [-0.91, 0.46]
Ference | 2013 | 12
-0.38 [-0.98, 0.23]
Ekberg | 2014 | 10
0.08 [-0.53, 0.69]
Hudry | 2014 | 7
-0.68 [-1.08, -0.28]
Libertus | 2014 | 6
-0.38 [-0.99, 0.24]
Libertus | 2014 | 6
-0.31 [-0.77, 0.15]
Ozonoff | 2014 | 12
-0.18 [-0.40, 0.03]
Leonard | 2015 | 7
-0.41 [-0.81, -0.02]
Lazenby | 2016 | 12
-0.51 [-0.73, -0.29]
RE Model
-0.40 [-0.57, -0.23]
-3
3
Standardized Mean Difference

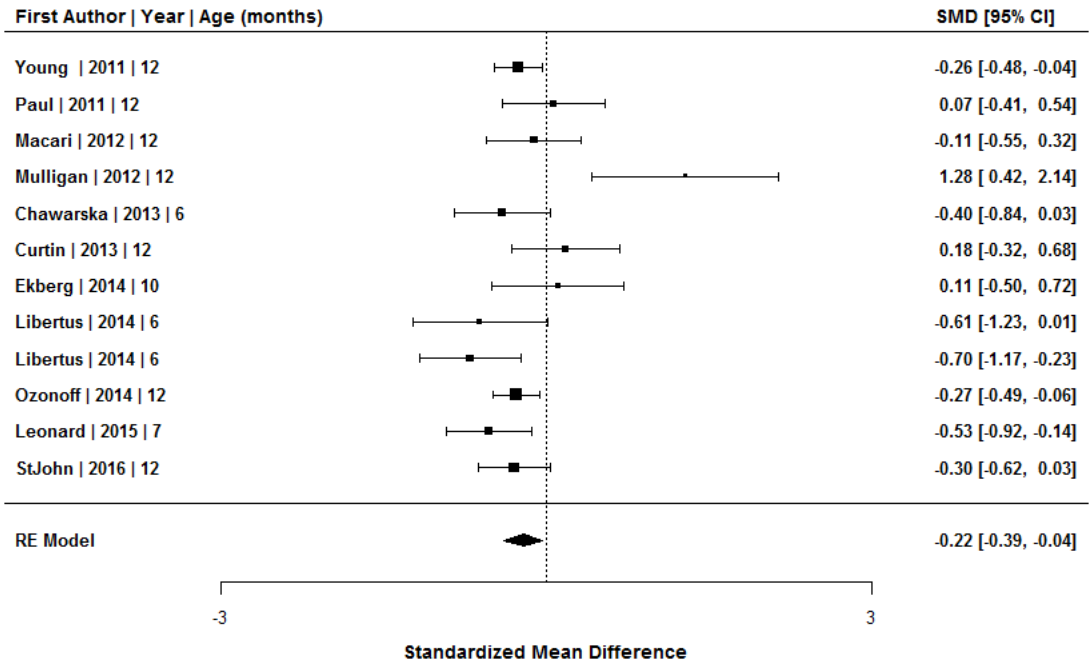

First Author | Year | Age (months)
SMD [95% CI]
Mitchel | 2006 | 24
-0.42 [-0.77, -0.06]
Gamliel | 2007 | 24
-0.05 [-0.50, 0.40]
Presmanes | 2007 | 15
-0.19 [-0.64, 0.25]
Stone | 2007 | 16
-0.33 [-0.72, 0.06]
Toth | 2007 | 21
0.06 [-0.48, 0.59]
Yirmiya | 2007 | 24
-0.09 [-0.60, 0.41]
Young | 2009 | 24
-0.06 [-0.58, 0.46]
Young | 2011 | 24
-0.40 [-0.68, -0.13]
Paul | 2011 | 24
0.27 [-0.32, 0.86]
Macari | 2012 | 24
-0.82 [-1.28, -0.37]
Curtin | 2013 | 18
-0.57 [-1.13, -0.01]
Droucker | 2013 | 18
-0.78 [-1.54, -0.02]
Hudry | 2014 | 24
-0.60 [-1.00, -0.19]
Ozonoff | 2014 | 24
-0.39 [-0.60, -0.17]
Gangi | 2015 | 24
-0.55 [-1.18, 0.08]
Leonard | 2015 | 24
-0.38 [-0.78, 0.02]
Messinger | 2015 | 24
-0.46 [-0.55, -0.36]
Talbott | 2015 | 18
0.25 [-0.22, 0.73]
RE Model
-0.34 [-0.45, -0.23]
-3
3
Standardized Mean Difference

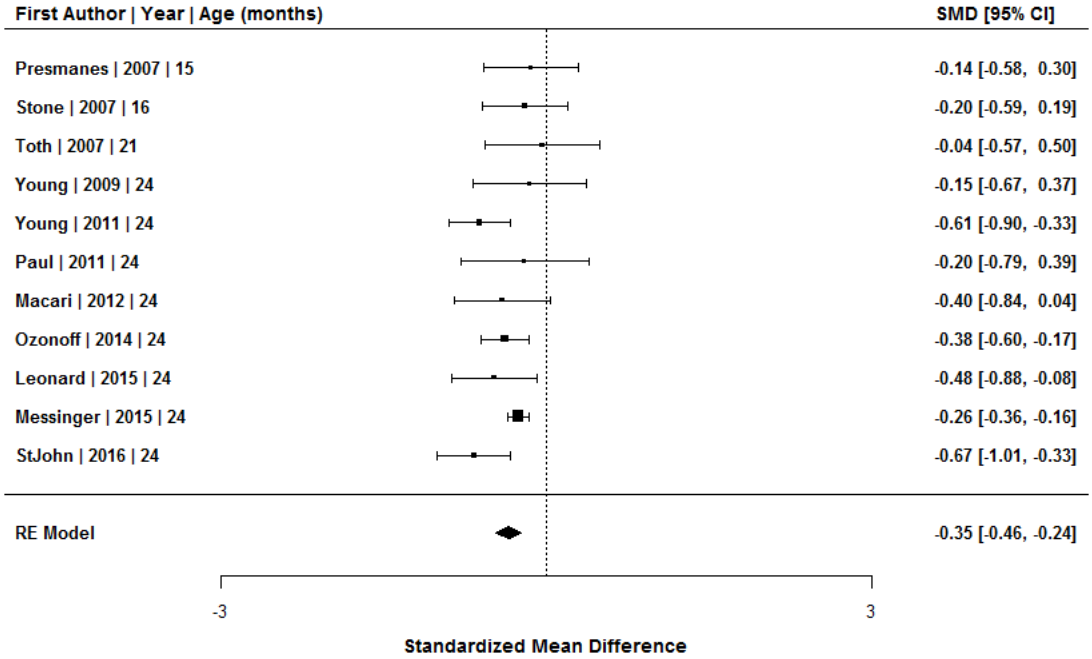

First Author | Year | Age (months)
SMD [95% CI]
Gamliel | 2007 | 36
-0.38 [-0.83, 0.06]
Yirmiya | 2007 | 36
-0.39 [-0.90, 0.13]
Young | 2011 | 36
-0.42 [-0.70, -0.14]
Herlihy | 2013 | 25
0.47 [-0.11, 1.04]
Ibanez | 2013 | 36
-0.43 [-1.10, 0.24]
Schwichtenberg | 2013 | 36
-0.15 [-0.45, 0.14]
Klerk | 2014 | 36
-0.53 [-0.97, -0.10]
Miller | 2014 | 36
-0.38 [-0.61, -0.15]
Ozonoff | 2014 | 36
-0.66 [-0.88, -0.44]
Gangi | 2015 | 36
-0.55 [-1.10, 0.00]
Leonard | 2015 | 36
-0.91 [-1.32, -0.50]
Messinger | 2015 | 36
-0.52 [-0.62, -0.42]
RE Model
-0.44 [-0.58, -0.30]
-3
3
Standardized Mean Difference

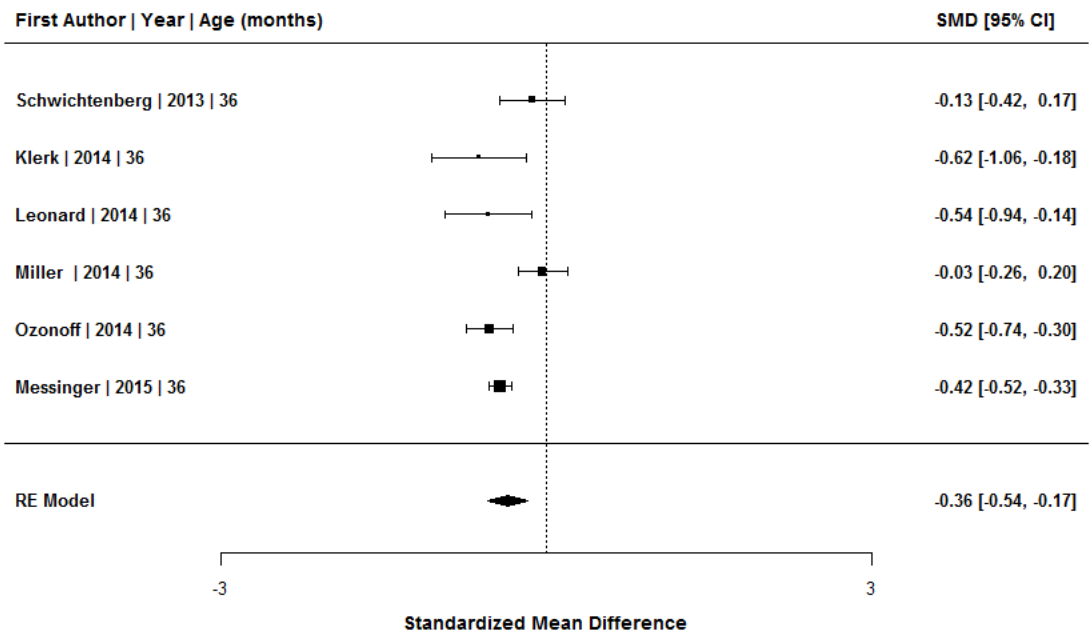

First Author | Year | Age (months)
SMD [95% CI]
Zwaigenbaum | 2005 | 12
-0.77 [-1.26, -0.28]
Mitchel | 2006 | 12
-0.34 [-0.73, 0.06]
Paul | 2011 | 12
-0.57 [-1.05, -0.09]
Key | 2012 | 9
-0.34 [-1.02, 0.33]
Mulligan | 2012 | 12
-1.48 [-2.37, -0.60]
Chawarska | 2013 | 6
-0.28 [-0.72, 0.15]
Curtin | 2013 | 12
-0.53 [-1.03, -0.02]
Ference | 2013 | 12
-0.74 [-1.36, -0.12]
Ekberg | 2014 | 10
0.09 [-0.52, 0.70]
Hudry | 2014 | 7
-0.51 [-0.90, -0.12]
Libertus | 2014 | 6
-0.01 [-0.62, 0.60]
Libertus | 2014 | 6
-0.27 [-0.73, 0.19]
Ozonoff | 2014 | 12
-0.34 [-0.56, -0.12]
Leonard | 2015 | 7
-0.66 [-1.06, -0.26]
Lazenby | 2016 | 12
-0.43 [-0.65, -0.22]
RE Model
-0.43 [-0.53, -0.33]
-3
3
Standardized Mean Difference

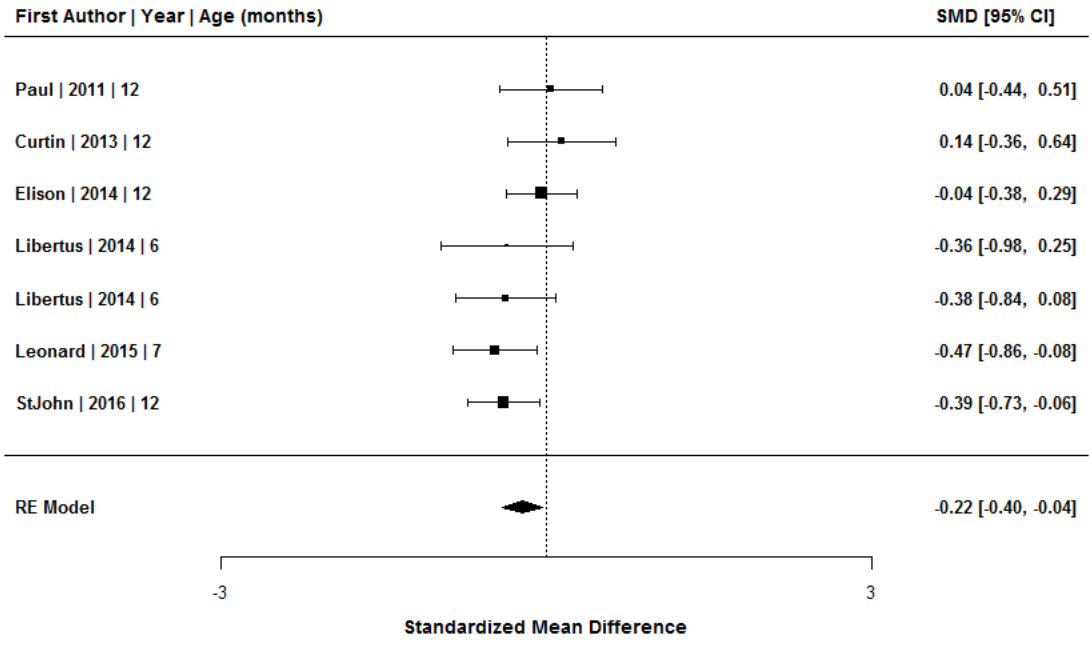

First Author | Year | Age (months)
SMD [95% CI]
Mitchel | 2006 | 24
-0.83 [-1.19, -0.46]
Gamliel | 2007 | 24
-0.22 [-0.67, 0.23]
Presmanes | 2007 | 15
-0.27 [-0.71, 0.18]
Stone | 2007 | 16
-0.37 [-0.76, 0.03]
Toth | 2007 | 21
-0.59 [-1.13, -0.04]
Yirmiya | 2007 | 24
-0.24 [-0.75, 0.27]
Young | 2009 | 24
-0.39 [-0.91, 0.14]
Paul | 2011 | 24
-0.85 [-1.46, -0.23]
Macari | 2012 | 24
-0.95 [-1.41, -0.49]
Curtin | 2013 | 18
-0.81 [-1.46, -0.17]
Hudry | 2014 | 24
-0.67 [-1.08, -0.27]
Ozonoff | 2014 | 24
-0.74 [-0.96, -0.52]
Gangi | 2015 | 24
-0.44 [-1.07, 0.18]
Leonard | 2015 | 24
-0.67 [-1.07, -0.26]
Messinger | 2015 | 24
-0.13 [-0.23, -0.03]
RE Model
-0.52 [-0.68, -0.37]
-3
3
Standardized Mean Difference

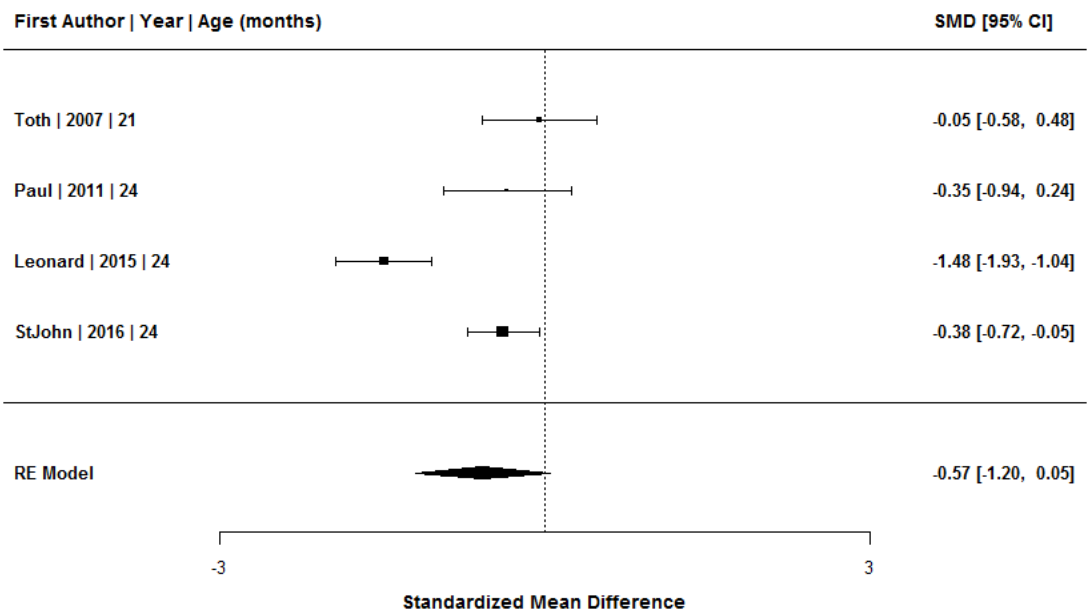

First Author | Year | Age (months)
SMD [95% CI]
Gamliel | 2007 | 36
-0.53 [-0.99, -0.08]
Yirmiya | 2007 | 36
-0.65 [-1.17, -0.13]
Young | 2011 | 36
-0.42 [-0.69, -0.14]
Herlihy | 2013 | 25
0.57 [-0.01, 1.16]
Ibanez | 2013 | 36
-0.68 [-1.36, 0.00]
Schwichtenberg | 2013 | 36
-0.27 [-0.47, -0.06]
Klerk | 2014 | 36
-0.64 [-1.08, -0.20]
Miller | 2014 | 36
-0.41 [-0.64, -0.17]
Ozonoff | 2014 | 36
-0.63 [-0.85, -0.41]
Gangi | 2015 | 36
-0.79 [-1.35, -0.23]
Leonard | 2015 | 36
-0.60 [-0.99, -0.20]
Messinger | 2015 | 36
-0.56 [-0.66, -0.46]
RE Model
-0.48 [-0.60, -0.36]
-3
3
Standardized Mean Difference

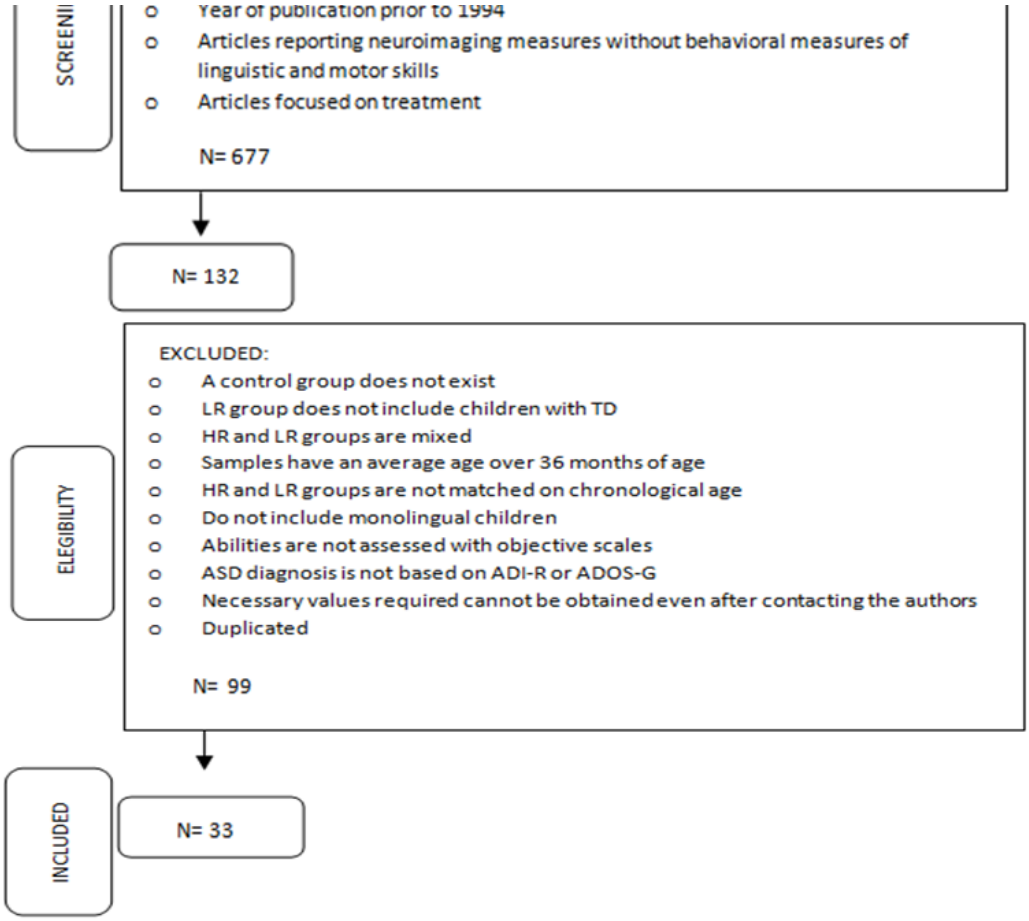

First Author | Year | Age (months)
SMD [95% CI]
Young | 2011 | 12
-0.26 [-0.48, -0.04]
Paul | 2011 | 12
0.07 [-0.41, 0.54]
Macari | 2012 | 12
-0.11 [-0.55, 0.32]
Mulligan | 2012 | 12
1.28 [0.42, 2.14]
Chawarska | 2013 | 6
-0.40 [-0.84, 0.03]
Curtin | 2013 | 12
0.18 [-0.32, 0.68]
Ekberg | 2014 | 10
0.11 [-0.50, 0.72]
Libertus | 2014 | 6
-0.61 [-1.23, 0.01]
Libertus | 2014 | 6
-0.70 [-1.17, -0.23]
Ozonoff | 2014 | 12
-0.27 [-0.49, -0.06]
Leonard | 2015 | 7
-0.53 [-0.92, -0.14]
StJohn | 2016 | 12
-0.30 [-0.62, 0.03]
RE Model
-0.22 [-0.39, -0.04]
-3
3
Standardized Mean Difference


First Author | Year | Age (months)
SMD [95% CI]
Presmanes | 2007 | 15
-0.14 [-0.58, 0.30]
Stone | 2007 | 16
-0.20 [-0.59, 0.19]
Toth | 2007 | 21
-0.04 [-0.57, 0.50]
Young | 2009 | 24
-0.15 [-0.67, 0.37]
Young | 2011 | 24
-0.61 [-0.90, -0.33]
Paul | 2011 | 24
-0.20 [-0.79, 0.39]
Macari | 2012 | 24
-0.40 [-0.84, 0.04]
Ozonoff | 2014 | 24
-0.38 [-0.60, -0.17]
Leonard | 2015 | 24
-0.48 [-0.88, -0.08]
Messinger | 2015 | 24
-0.26 [-0.36, -0.16]
StJohn | 2016 | 24
-0.67 [-1.01, -0.33]
RE Model
-0.35 [-0.46, -0.24]
-3
3
Standardized Mean Difference


First Author | Year | Age (months)
SMD [95% CI]
Schwichtenberg | 2013 | 36
-0.13 [-0.42, 0.17]
Klerk | 2014 | 36
-0.62 [-1.06, -0.18]
Leonard | 2014 | 36
-0.54 [-0.94, -0.14]
Miller | 2014 | 36
-0.03 [-0.26, 0.20]
Ozonoff | 2014 | 36
-0.52 [-0.74, -0.30]
Messinger | 2015 | 36
-0.42 [-0.52, -0.33]
RE Model
-0.36 [-0.54, -0.17]
-3
3
Standardized Mean Difference


First Author | Year | Age (months)
SMD [95% CI]
Paul | 2011 | 12
0.04 [-0.44, 0.51]
Curtin | 2013 | 12
0.14 [-0.36, 0.64]
Elison | 2014 | 12
-0.04 [-0.38, 0.29]
Libertus | 2014 | 6
-0.36 [-0.98, 0.25]
Libertus | 2014 | 6
-0.38 [-0.84, 0.08]
Leonard | 2015 | 7
-0.47 [-0.86, -0.08]
StJohn | 2016 | 12
-0.39 [-0.73, -0.06]
RE Model
-0.22 [-0.40, -0.04]
-3
3
Standardized Mean Difference


First Author | Year | Age (months)
SMD [95% CI]
Toth | 2007 | 21
-0.05 [-0.58, 0.48]
Paul | 2011 | 24
-0.35 [-0.94, 0.24]
Leonard | 2015 | 24
-1.48 [-1.93, -1.04]
StJohn | 2016 | 24
-0.38 [-0.72, -0.05]
RE Model
-0.57 [-1.20, 0.05]
-3
3
Standardized Mean Difference


SCREENI
Year of publication prior to 1994
Articles reporting neuroimaging measures without behavioral measures of linguistic and motor skills
Articles focused on treatment
N= 677
N= 132
ELEGIBILITY
EXCLUDED:
A control group does not exist
LR group does not include children with TD
HR and LR groups are mixed
Samples have an average age over 36 months of age
HR and LR groups are not matched on chronological age
Do not include monolingual children
Abilities are not assessed with objective scales
ASD diagnosis is not based on ADI-R or ADOS-G
Necessary values required cannot be obtained even after contacting the authors
Duplicated
N= 99
INCLUDED
N= 33