Published in final edited form as:
Neurotoxicology. 2012 October ; 33(5): 1291–1297. doi:10.1016/j.neuro.2012.08.001.

Dental Composite Restorations and Neuropsychological Development in Children: Treatment Level Analysis from a Randomized Clinical Trial

Nancy N. Maserejian, ScD[a], **Felicia L. Trachtenberg, PhD**[a], **Russ Hauser, MD, ScD, MPH**[b,c,d], **Sonja McKinlay, PhD**[a], **Peter Shrader, MS**[a], and **David C. Bellinger, PhD, MSc**[b,e,f]

Nancy N. Maserejian: nmaserejian@neriscience.com; Felicia L. Trachtenberg: ftrachtenberg@neriscience.com; Russ Hauser: rhauser@hohp.harvard.edu; Sonja McKinlay: smckinlay@neriscience.com; Peter Shrader: pshrader@neriscience.com; David C. Bellinger: David.Bellinger@childrens.harvard.edu

[a]New England Research Institutes, 9 Galen St., Watertown, MA 02472

[b]Department of Environmental Health, Harvard School of Public Health, 665 Huntington Ave., Building I, 14th Floor, Boston, MA 02115

[c]Department of Epidemiology, Harvard School of Public Health, 677 Huntington Ave., Boston MA 02115

[d]Vincent Obstetrics and Gynecology, 32 Fruit St., Massachusetts General Hospital, Boston, MA 02114

[e]Department of Neurology, Children's Hospital Boston, Boston MA 02115

[f]Harvard Medical School, 25 Shattuck St., Boston, MA 02115

Abstract

Background—Resin-based dental restorations may intra-orally release their components and bisphenol A. Gestational bisphenol A exposure has been associated with poorer executive functioning in children.

Objectives—To examine whether exposure to resin-based composite restorations is associated with neuropsychological development in children.

Methods—Secondary analysis of treatment level data from the New England Children's Amalgam Trial, a 2-group randomized safety trial conducted from 1997–2006. Children (N=534) aged 6–10 y with >2 posterior tooth caries were randomized to treatment with amalgam or resin-based composites (bisphenol-A-diglycidyl-dimethacrylate-composite for permanent teeth; urethane dimethacrylate-based polyacid-modified compomer for primary teeth). Neuropsychological function at 4- and 5-year follow-up (N=444) was measured by a battery of tests of executive function, intelligence, memory, visual-spatial skills, verbal fluency, and problem-solving. Multivariable generalized linear regression models were used to examine the association between composite exposure levels and changes in neuropsychological test scores

CORRESPONDING AUTHOR: Nancy Nairi Maserejian, ScD, New England Research Institutes, Inc., 9 Galen Street, Watertown, MA 02472, Direct Dial Tel: (01) 617.972.3229, FAX: (01) 617.926.0144, nmaserejian@neriscience.com.

Conflict of Interest Disclosures: Authors report no competing financial interests.

NIH-PA Author Manuscript
NIH-PA Author Manuscript

from baseline to follow-up. For comparison, data on children randomized to amalgam treatment were similarly analyzed.

Results—With greater exposure to either dental composite material, results were generally consistent in the direction of slightly poorer changes in tests of intelligence, achievement or memory, but there were no statistically significant associations. For the four primary measures of executive function, scores were slightly worse with greater total composite exposure, but statistically significant only for the test of Letter Fluency (10-surface-years $\beta = -0.8$, SE=0.4, $P=0.035$), and the subtest of color naming ($\beta = -1.5$, SE=0.5, $P=0.004$) in the Stroop Color-Word Interference Test. Multivariate analysis of variance confirmed that the negative associations between composite level and executive function were not statistically significant (MANOVA $P=0.18$). Results for greater amalgam exposure were mostly nonsignificant in the opposite direction of slightly improved scores over follow-up.

Conclusions—Dental composite restorations had statistically insignificant associations of small magnitude with impairments in neuropsychological test change scores over 4- or 5-years of follow-up in this trial.

MeSH Keywords

Composite dental resin; Composite resins; Bisphenol A-Glycidyl Methacrylate; Compomers; Child Development; Neuropsychological tests; Executive Function; Epidemiology; Prospective Studies

1. INTRODUCTION

Dental caries are present in over half of U.S. children, and by adolescence, 80% have decayed or filled teeth (USDHHS 2000). The popularity of dental amalgam for restoration treatment of caries has decreased due to concerns with mercury exposure and cosmetic preferences. Meanwhile, use of composite resin materials has risen rapidly, with over 10 million placed annually in U.S. children alone (Beazoglou et al., 2007).

However, components of materials such as epoxy resins and acrylic monomers also have potential for toxicity (Schweikl et al., 2006). Of particular concern has been the release of bisphenol A (BPA) (Fleisch et al., 2010), a chemical which has been shown in numerous studies to have adverse health effects in experimental animals (Richter et al., 2007). In dentistry, BPA is used in the synthesis of matrix monomers such as dimethacrylate monomers (e.g., bisphenol-A-diglycidyl-dimethacrylate, bisGMA) for composite restorations. Elution of BPA from composites may result from impurities left after resin synthesis or from resin degradation (Van Landuyt et al., 2011). Over time, composites undergo mechanical, hydrolytic, and enzymatic degradation processes, thereby potentially releasing polymeric breakdown products throughout the life of the restoration. Although numerous laboratory studies show release of resin monomers from dental materials (Van Landuyt et al., 2011), the extent to which they are released after restoration treatment in humans remains unclear. A recent saliva study in 10 adults found that treatment with a bisGMA-based filling led to increased bisGMA and other resin components in saliva shortly after treatment, but no detectable levels were found one week later (Michelsen et al., 2012). In a study of 20 children, urinary BPA levels increased after dental composite treatment and had not returned to baseline levels at the end of follow-up two weeks later (Martin et al., 2005). A cross-sectional study in South Korean children found significantly higher urinary BPA levels (2.67 μg/g creatinine) in children with more than ten composites and sealants than those with no fillings (Chung et al., 2012). However, causality cannot be determined in these observational studies, particularly considering the numerous possible exposure routes of BPA in the environment.

There is limited data on potential human health effects of BPA exposure, but rodent studies have shown that perinatal BPA affected neurological development, resulting in impaired learning of passive and active avoidance tasks and permanently influencing spatial and avoidance memory (Negishi et al., 2004, Palanza et al., 2008, Richter et al., 2007, Tian et al., 2010, Xu et al., 2010). In adolescent mice, long-term exposure to low levels of BPA altered exploration, spatial learning and memory, and passive avoidance memory through adulthood (Xu et al., 2011). These low doses of BPA administered in some recent animal studies (e.g., 10–100 microg/kg/day) reflect environmentally relevant doses for humans (vom Saal and Hughes, 2005, Welshons et al., 2006). However, of two human studies of gestational BPA exposure and neurobehavior, one found no associations among 5-week old infants (Yolton et al., 2011), whereas the other found associations with poorer emotional control and inhibition of behavioral responses at 3 years of age, with gestational, but not early childhood, BPA exposure (Braun et al., 2011).

Despite findings of release of BPA, as well as other monomers with potential toxicity (e.g., triethylene glycol dimethacrylate [TEGDMA], bisphenol A diglycidyl ether [BADGE] (Van Landuytet al., 2011), from dental resin materials, there is little data to inform the long-term safety of composite restorations in children. The New England Children's Amalgam Trial (NECAT) was an NIH-funded randomized clinical safety trial of dental amalgam, examining neuropsychological and renal effects in children over 5-years follow-up, with the comparison treatment of resin composites. Results showed no harmful neuropsychological effects among children randomized to the amalgam group (Bellinger et al., 2007a, Bellinger et al., 2006), and there were no associations between extent of amalgam exposure or urinary mercury excretion and neuropsychological function (Bellinger et al., 2007b). In contrast, children assigned to composites and with higher composites treatment levels had poorer self-reported behavioral measures (Bellinger et al., 2008, Maserejian et al., 2012). In fact, scores for most outcomes were consistently less favorable among children assigned to composites, and the consistent differences reached statistically significance for neurological function in secondary tests of spatial working memory and immediate memory span (Bellingeret al., 2007a). These findings were mirrored in a separate trial of amalgam vs. composites in Portuguese children, which found that children assigned to composites were statistically nonsignificantly more likely to have neurological hard signs (14.1% vs. 8.1%) or neurological soft signs (37.3% vs. 31.9%) at the 7-year final follow-up visit, as well as at most annual follow-up visits (Lauterbach et al., 2008). The consistency in the directions of these findings for composites from two separate randomized clinical trials in different pediatric populations suggests the possibility of harmful neurological effects of composite materials.

Given the previously published differences by assigned treatment group, the objective in this paper was to examine levels of treatment received, to test the hypothesis that greater composite treatment is associated with worse neurological function in children. We examine children's cumulative exposure levels to composites and changes in neuropsychological function over a 4-to−5 year follow-up interval.

2. METHODS

2.1 Study Design and Participants

NECAT, a randomized clinical safety trial of amalgam vs. composites, occurred from 1997–2005 at six community dental clinics in Boston and Maine. Although children were randomly assigned to a treatment plan of composites or amalgam, the level of exposure to restorative materials differed by individuals' treatment needs; thus, we applied methods typical for analysis of data from observational, prospective cohort studies for this analysis.

Of 5,116 children screened for eligibility, 598 were eligible and 534 had written parental consent and child assent. Eligibility criteria were: aged 6–10 y; English fluency; no amalgam restorations; >2 posterior teeth with caries requiring restoration on occlusal surfaces; and, by parent-report, no physician-diagnosed psychological, behavioral, neurological, immunosuppressive or renal disease. The study was approved by the institutional review boards of all participating sites. Details of the study design have been published (Children's Amalgam Trial 2003, Bellingeret al., 2007a, Bellingeret al., 2006).

2.2 Dental Materials and Interventions

Randomization was stratified by number of teeth with caries (2–4 vs. >5) and geographic location. In the composites treatment arm, a minifill composite (Z100, by 3M ESPE, St. Paul, Minn) containing bisGMA and TEGDMA for the resin matrix was used on permanent teeth, and compomer was used on primary teeth. Compomers are polyacid-modified composites that contain 72% (by weight) strontium-fluorosilicate-glass to allow fluoride release; the compomer used (Dyract, by Dentsply Caulk, Milford, Del.) contained urethane dimethacrylate and trimethacrylate resins. Composites were used in the amalgam arm to restore anterior tooth caries, per standard practice. Children had semiannual dental examinations and treatment visits as needed throughout the 5-year follow-up. Dental procedures were standardized across sites and clinicians.

2.3 Neuropsychological Assessment Measures

At baseline and again at pre-specified time points during the 5-year follow-up, children participated in two sessions of interviewer-administered neuropsychological testing. In one session (occurring at baseline, and post-baseline year 3 and year 5), the Wechsler Intelligence Scale for Children-Third Edition (WISC-III) (Wechsler, 1991) and the Wechsler Individual Achievement Test (WIAT) (Psychological Corporation, 1992) were administered. In the other session (occurring at baseline, and post-baseline years 1, 2, and 4), a battery of domain-focused tests were administered. These tests included the Wide Range Assessment of Memory and Learning (WRAML) (Sheslow and Adams, 1990), the Wide Range Test of Visual-Motor Ability (WRAVMA) (Adams and Sheslow, 1995), the Trail-Making Test (Spreen and Strauss, 1991), an ordered and unordered verbal cancellation task (Mesulam, 1985), category fluency (McCarthy, 1972), the Controlled Oral Word Association Test (letter fluency) (Spreen and Strauss, 1991), simple visual reaction time using the Standard Reaction Timer (Software Science, Cincinnati, OH), the Stroop Color-Word Interference Test (Trenerry et al., 1989), and the Wisconsin Card Sorting Test (Heaton et al., 1993).

For this analysis, primary and secondary outcomes of interest (listed in Table 3) were pre-specified as those measures that reflect global performance on the WISC-III, WIAT, and WRAML, derived by combining a child's performance on tasks that assess somewhat different abilities. Executive function, also of primary interest, was measured by the Trail-Making Test, Letter Fluency subtest of Verbal Fluency, Stroop Color-Word Interference Test, and the Wisconsin Card Sorting Test.

Quality control of the assessments was assured by having all examiners (n=19) trained and certified by one supervising psychologist (D.C.B.) and continuously monitored during the trial. Each testing session was completely re-scored by a second individual and errors corrected. Computerized algorithms were used to check the entered data for internal consistency.

2.4 Statistical Analysis

Multivariable generalized linear regression models were used to assess the association of continuous and categorical exposure measures with change in neuropsychological test scores from baseline to follow-up (5-year follow-up for WISC-III and WIAT; 4-year follow-up for all other tests). For the four primary tests of executive function, we also used multivariate analysis of variance (MANOVA) to examine the linear combination of their means simultaneously and to minimize possible problems with multiple testing (i.e., reduce the Type I error rate).

A total of 444 children had year 5 outcome data, and 409 had year 4 outcome data. Children missing outcome data were excluded from analyses; they were similar in age, sex, baseline caries and blood lead levels, but had lower baseline WISC-III full-scale IQ scores (92.9 ± 13.8 vs. 96.1 ± 13.2, P=0.046) compared to children with complete follow- up. The complete case analysis had 80% power at alpha=0.05 to detect a correlation of at least 0.14 between composites exposure level and changes in test scores.

Multivariable models were determined using directed acyclic graphs (Greenland et al., 1999) and included factors shown to be relevant in prior NECAT analyses and other studies of environmental toxicant-neurodevelopment associations (Bellingeret al., 2007b): age, sex, socioeconomic status, geographic site, and baseline blood lead level. Effect modification by age, sex, gum chewing, and toothbrushing frequency were investigated, but no interactions were found.

Exposure levels of compomer and composite were analyzed separately, given that differently manufactured composites have been shown to differ in release of their components (Joskow et al., 2006, Van Landuytet al., 2011). Where results were similar by material type, additional analyses combining all composites were conducted. Exposure levels were calculated using surface-years (each treated surface weighted by number years present in the mouth), which indicates cumulative exposure throughout the trial. Given our prior finding that cumulative treatment on posterior-occlusal surfaces was most strongly associated with biomarkers of amalgam restorations (Maserejian et al., 2008), presumably owing to chewing effects on degradation, posterior-occlusal surface-years were of primary interest. Exposure categories were none and, among the exposed, were divided into tertiles. Trend tests were conducted using the continuous measure. Sensitivity analyses examined two additional exposure metrics: total surface-years and number of extant filled surfaces. Lastly, to evaluate whether findings for composite treatment level were due to residual cofounding by factors related to severity of dental disease (rather than treatment material), we conducted additional analyses using the available data on randomization to amalgam, to compare associations between posterior-occlusal surface-years amalgam and outcomes. Analyses were conducted using SAS v.9.2 (Cary, NC).

3. RESULTS

Children assigned to the composites treatment plan had a mean (SD) of 6.2 (3.1) posterior-occlusal surfaces filled over the course of the trial, corresponding to 19.2 (10.8) posterior-occlusal surface-years (10.6 surface-years compomer, 8.7 surface-years composite). Among all children in this analysis, combining those in the composites or amalgam arm (who may have received composites on anterior teeth), mean (SD) posterior-occlusal surface-years exposure was 5.5 (8.2) for compomer and 4.6 (8.2) for composite (Table 1). Most children had mixed dentition at baseline, and over two-thirds of children who received composites were treated with both compomer and composite materials during the course of the study. Cumulative exposure to composites by the end of the trial was not associated with characteristics such as age, sex, or bottled vs. tap water use (Table 2).

With increasing compomer or composite exposure, adjusted mean neuropsychological test change scores between baseline and 4- or 5-year follow-up were generally consistent in the direction of increasing impairment (Table 3), but there were few statistically significant associations. In secondary analyses combining total posterior-occlusal composites exposures, WISC-III Full-scale IQ, WIAT, and WRAML test scores had no significant associations with surface-years exposure. Children with greater exposure to either compomer or composite had poorer change scores on Letter Fluency; an additional 10 posterior-occlusal surface-years was associated with a decreased mean change score by 0.8 (SE=0.4, P=0.035). Worse change scores with higher total exposure to compomer/composite were also found for other measures of executive function: perseverative errors in the Wisconsin Card Sorting Test (β=1.4, SE=0.8, P=0.08) and the Trail-Making Test Part B-Part A (β= −3.0, SE=2.5, P=0.23), but results were not statistically significant. For the Stroop Color-Word Interference Test, only the change scores for the Color naming trial were significantly associated with greater exposure to composites (10 posterior-occlusal surface-years total composites β= −1.5, SE=0.5, P=0.004), indicating poorer ability to name colors. Amalgam posterior-occlusal surface-years exposure was not associated with scores on these executive function tests; in fact, all mean change scores were in the direction of improvement (10 surface-years, Letter Fluency β=0.7, SE=0.4, P=0.10; perseverative errors β= −2.0, SE=0.9, P=0.02; Trail-Making β=1.0, SE=3.0, P=0.70; Color naming β=0.05, SE=0.6, P=0.9). In the multivariate analysis of variance, the association between composite and impairments in tests of executive function was not statistically significant (*P*=0.18). Results were similar in sensitivity analyses of total surface-years exposure and the number of extant filled surfaces at follow-up (data not shown).

4. DISCUSSION

Using exposure-response analyses from a randomized trial, this study found consistent but not statistically significant associations between UDMA-based polyacid-modified (compomer) or standard minifill bisGMA-based dental composite and neuropsychological health in children. Overall, most change scores were slightly poorer among children with greater compomer or composite exposure, which is in contrast to the findings for amalgam exposure levels (Bellingeret al., 2007b). However, of 4 primary tests of executive function, scores on only one, the test of Letter Fluency, were statistically significantly related to compomer/composite exposure, and the results for other general tests of intelligence, learning, memory, and visual-spatial skills indicate that chance cannot be ruled out as an explanation for these findings.

A strength of this study is that the data were obtained as part of a randomized clinical trial. For this analysis of composite treatment level, the previously reported intent-to-treat and amalgam level analyses are available to evaluate the possibility of confounding by factors related to severity of dental disease, or disease on primary teeth vs. permanent teeth. Of note, the current finding of poorer change scores with higher composite exposure is in contrast to findings from analyses of amalgam exposure-response, where change scores tended to improve (Bellingeret al., 2007b). Thus, confounding by factors related to severity of dental disease is unlikely. Furthermore, the current findings are consistent with the intent-to-treat results, which showed that children randomized to amalgam fared better on the 3 primary neuropsychological endpoints of the trial (WISC-II full-scale intelligence, General memory index, and Visuomotor global score) (Bellingeret al., 2006). A possible explanation for these trends is that we are observing actual effects of composites, but the effects on neuropsychological health measures are indeed small, as reflected in both the original trial and these additional analyses, and that they are statistically insignificant due to insufficient power to detect differences of such small magnitude. This possibility would be definitively addressed only by additional randomized controlled trials designed specifically to assess smaller effect sizes with chronic exposure.

In advance of such data, given the lack of statistical significance in our results, associations between composites and worse neuropsychological outcomes may be spurious findings due to chance. A consequence of conducting multiple neuropsychological tests may be a compromise in the statistical significance threshold. The multivariate analysis of variance, which had the benefit of minimizing the likelihood of Type I errors due to multiple tests of executive function, confirmed that the impairment in change scores was not statistically significant.

The rationale for using multiple neuropsychological outcome measures was that various tests are often conducted in a neuropsychological assessment to enhance interpretation of results, particularly for complex constructs such as executive functioning (Golden et al., 2002). Executive functions include planning, directing and maintaining attention, organization, abstract reasoning and problem-solving, self-regulation, and motor control, and may be confounded by intelligence, memory, and language. Executive functioning was of particular interest given numerous rodent experiments showing effects of bisphenol A on executive function measures, and findings that gestational BPA exposure is associated with poorer executive functioning in girls (Braunet al., 2011). In the current study, children with greater exposure to compomer or composite fared worse on most tests, but the differences were statistically significant for only one test of executive function, Letter Fluency (sum of 3 trials from the Verbal Fluency test). This test required the child to combine processes related to verbal language within a set of constraints (e.g., to name words beginning with the letter ‘F’) which require the inhibition of inappropriate responses. For another executive function test, the Stroop Color-Word Interference Test, children with greater composites exposure performed worse only on the Color portion (naming the color of a bar). Poor performance on the Color portion alone may be affected by speech motor function, or the individual’s ability to name colors. In the absence of colorblindness, an impaired score on the Color trial may indicate brain dysfunction in the left (dominant) temporal-occipital or the right (non-dominant) posterior area (Goldenet al., 2002). We found no similar associations with greater amalgam exposure levels in this study.

Previous studies of maternal prenatal urinary BPA measures and child neuropsychological health or behavior have shown inconsistent results. Braun et al. (Braunet al., 2011, Braun et al., 2009) found adverse associations with executive functioning and social behavior particularly in girls. Perera et al. (Perera et al., 2012) found the reverse, whereby higher maternal prenatal BPA concentration was associated with worse parent-reported social behavior scores in boys, but not girls. In a study of 5-week old infants, maternal prenatal BPA levels were not associated with neurobehavioral scores (Yoltonet al., 2011). Lacking consistency across studies, firm conclusions cannot yet be drawn regarding the role of BPA in human neuropsychological behavior.

In this study, no data were available to evaluate BPA levels, or whether levels of other chemicals that may leach from dental composites, such as bisGMA, UDMA, or TEGDMA (Van Landuytet al., 2011), increased with greater composite exposure. Prior in vitro and in vivo studies have shown that the minifill composite (Z100) used in NECAT released BPA, bisGMA, bisDMA, and BADGE (Al-Hiyasat et al., 2004, Martinet al., 2005, Ortengren et al., 2004, Pulgar et al., 2000, Sasaki et al., 2005, Yap et al., 2004). For the polyacid-modified composite (Dyract compomer), no detectable BPA or bisGMA were found in eluates from filled tooth samples in one study (Hamid et al., 1998). For both composites, numerous studies have reported cytotoxic effects (Milhem et al., 2008, Schweikl et al., 2005, Sletten and Dahl, 1999, Wataha et al., 1999). Resin-composite restorations have comparatively high failure rates (Soncini et al., 2007). As they undergo degradation, resin components are released, presumably throughout the life of the restoration. Additional studies are needed to measure the long-term release of components of resin-based dental

NIH-PA Author Manuscript

NIH-PA Author Manuscript

materials and whether the levels absorbed or excreted are associated with adverse health effects.

In conclusion, consistent but not statistically significant associations were observed between methacrylate-based dental composites and small impairments in neuropsychological test score changes over 4- or 5-years of follow-up among children in this randomized clinical trial. Although findings were not statistically significant, they were consistent in the direction suggesting small adverse effects with greater composite exposure. Furthermore, this consistency was not observed for the randomly-assigned amalgam treatment. In light of the previously-reported differences in behavioral outcomes (Bellingeret al., 2008, Maserejianet al., 2012), and the non-significant tendency for composites exposure to be associated with poorer neuropsychological test scores both in the present study and in a separate randomized study of children (Bellingeret al., 2006, DeRouen et al., 2006), further studies on the safety of methacrylate-based dental composite materials are warranted. Newly-developed dental materials (e.g., ormocer-based, silorane-based) exist, and because they may have distinct properties in chemical composition, biocomptability, and wear (Ilie and Hickel, 2011, Polydorou et al., 2009), their potential for toxicity should also be thoroughly tested. In the meantime, well-established factors such as the durability of amalgam, technique-sensitivity needed for composite vs. amalgam, preservation of sound tooth structure, cosmetic preferences of the patient, and differing financial costs should remain among the primary determinants of a decision regarding choice of dental restorative materials.

Acknowledgments

Funding/Support: The analyses presented in this paper were funded by Award Number R01ES019155 from the National Institute of Environmental Health Sciences (NIEHS). The NIEHS had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript. The data collection was supported by a cooperative agreement (U01 DE11886) between the New England Research Institutes and the National Institute of Dental and Craniofacial Research (NIDCR), both of which participated in the design and conduct of the New England Children's Amalgam Trial, including collection and management of data. The NIDCR had no role in the analyses or interpretation of data for this manuscript, or in the preparation, review, or approval of the manuscript. The content of this work is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Environmental Health Sciences, the National Institute of Dental and Craniofacial Research, or the National Institutes of Health. Trial Registration: clinicaltrials.gov Identifier: NCT00065988

Abbreviations

BADGE	Bisphenol A diglycidyl ether
bisGMA	Bisphenol A-Glycidyl Methacrylate
BPA	Bisphenol A
MANOVA	Multivariate analysis of variance
NECAT	New England Children's Amalgam Trial
TEGDMA	Triethylene glycol dimethacrylate
WISC-III	Wechsler Intelligence Scale for Children-Third Edition
WIAT	Wechsler Individual Achievement Test
WRAML	Wide Range Assessment of Memory and Learning
WRAVMA	Wide Range Test of Visual-Motor Ability

References

Adams, W.; Sheslow, D. WRAVMA. Wide Range Assessment of Visual Motor Abilities. Wilmington, DE: Wide Range, Inc; 1995.

Al-Hiyasat AS, Darmani H, Elbetieha AM. Leached components from dental composites and their effects on fertility of female mice. Eur J Oral Sci. 2004; 112:267–72. [PubMed: 15154926]

Beazoglou T, Eklund S, Heffley D, Meiers J, Brown LJ, Bailit H. Economic impact of regulating the use of amalgam restorations. Public Health Rep. 2007; 122:657–63. [PubMed: 17877313]

Bellinger DC, Daniel D, Trachtenberg F, Tavares M, McKinlay S. Dental amalgam restorations and children's neuropsychological function: the New England Children's Amalgam Trial. Environmental health perspectives. 2007a; 115:440–6. [PubMed: 17431496]

Bellinger DC, Trachtenberg F, Barregard L, Tavares M, Cernichiari E, Daniel D, et al. Neuropsychological and renal effects of dental amalgam in children: a randomized clinical trial. JAMA. 2006; 295:1775–83. [PubMed: 16622139]

Bellinger DC, Trachtenberg F, Daniel D, Zhang A, Tavares MA, McKinlay S. A dose-effect analysis of children's exposure to dental amalgam and neuropsychological function: the New England Children's Amalgam Trial. J Am Dent Assoc. 2007b; 138:1210–6. [PubMed: 17785386]

Bellinger DC, Trachtenberg F, Zhang A, Tavares M, Daniel D, McKinlay S. Dental amalgam and psychosocial status: the New England Children's Amalgam Trial. J Dent Res. 2008; 87:470–4. [PubMed: 18434579]

Braun JM, Kalkbrenner AE, Calafat AM, Yolton K, Ye X, Dietrich KN, et al. Impact of early-life bisphenol A exposure on behavior and executive function in children. Pediatrics. 2011; 128:873–82. [PubMed: 22025598]

Braun JM, Yolton K, Dietrich KN, Hornung R, Ye X, Calafat AM, et al. Prenatal bisphenol A exposure and early childhood behavior. Environmental health perspectives. 2009; 117:1945–52. [PubMed: 20049216]

Children's Amalgam Trial: design and methods. Control Clin Trials. 2003; 24:795–814. [PubMed: 14662283]

Chung SY, Kwon H, Choi YH, Karmaus W, Merchant AT, Song KB, et al. Dental composite fillings and bisphenol A among children: a survey in South Korea. Int Dent J. 2012; 62:65–9. [PubMed: 22420473]

DeRouen TA, Martin MD, Leroux BG, Townes BD, Woods JS, Leitao J, et al. Neurobehavioral effects of dental amalgam in children: a randomized clinical trial. Jama. 2006; 295:1784–92. [PubMed: 16622140]

Fleisch AF, Sheffield PE, Chinn C, Edelstein BL, Landrigan PJ. Bisphenol A and related compounds in dental materials. Pediatrics. 2010; 126:760–8. [PubMed: 20819896]

Golden, CJ.; Espe-Pfeifer, P.; Wachsler-Felder, J. Neuropsychological Interpretation of Objective Psychological Tests. New York: Kluwer Academic Publishers; 2002.

Green LW. Manual for scoring socioeconomic status for research on health behavior. Public Health Rep. 1970; 85:815–27. [PubMed: 4989476]

Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology. 1999; 10:37–48. [PubMed: 9888278]

Hamid A, Okamoto A, Iwaku M, Hume WR. Component release from light-activated glass ionomer and compomer cements. J Oral Rehabil. 1998; 25:94–9. [PubMed: 9576591]

Heaton, RK.; Chelune, GJ.; Talley, JL.; Kay, GG.; Curtiss, G. Wisconsin Card Sorting Test Manual. Odessa, FL: Psychological Assessment Resources; 1993.

Ilie N, Hickel R. Resin composite restorative materials. Aust Dent J. 2011; 56 (Suppl 1):59–66. [PubMed: 21564116]

Joskow R, Barr DB, Barr JR, Calafat AM, Needham LL, Rubin C. Exposure to bisphenol A from bis-glycidyl dimethacrylate-based dental sealants. J Am Dent Assoc. 2006; 137:353–62. [PubMed: 16570469]

Lauterbach M, Martins IP, Castro-Caldas A, Bernardo M, Luis H, Amaral H, et al. Neurological outcomes in children with and without amalgam-related mercury exposure: seven years of longitudinal observations in a randomized trial. J Am Dent Assoc. 2008; 139:138–45. [PubMed: 18245680]

Martin MD, Bajet D, Woods JS, Dills RL, Poulten EJ. Detection of dental composite and sealant resin components in urine. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005; 99:429.

Maserejian NN, Trachtenberg FL, Assmann SF, Barregard L. Dental amalgam exposure and urinary mercury levels in children: the New England Children's Amalgam Trial. Environmental health perspectives. 2008; 116:256–62. [PubMed: 18288327]

Maserejian NN, Trachtenberg FL, Hauser R, McKinlay S, Shrader P, Tavares M, et al. Dental composite restorations and psychosocial function in children. Pediatrics. Jul 16.2012 [Epub ahead of print].

McCarthy, D. McCarthy Scales of Children's Abilities. New York: Psychological Corporation; 1972.

Mesulam, M. Principles of Behavioral Neurology. Philadelphia: F.A. Davis; 1985.

Michelsen VB, Kopperud HB, Lygre GB, Bjorkman L, Jensen E, Kleven IS, et al. Detection and quantification of monomers in unstimulated whole saliva after treatment with resin-based composite fillings in vivo. Eur J Oral Sci. 2012; 120:89–95. [PubMed: 22288926]

Milhem MM, Al-Hiyasat AS, Darmani H. Toxicity testing of restorative dental materials using brine shrimp larvae (Artemia salina). J Appl Oral Sci. 2008; 16:297–301. [PubMed: 19089264]

Negishi T, Kawasaki K, Suzaki S, Maeda H, Ishii Y, Kyuwa S, et al. Behavioral alterations in response to fear-provoking stimuli and tranylcypromine induced by perinatal exposure to bisphenol A and nonylphenol in male rats. Environmental health perspectives. 2004; 112:1159–64. [PubMed: 15289160]

Ortengren U, Langer S, Goransson A, Lundgren T. Influence of pH and time on organic substance release from a model dental composite: a fluorescence spectrophotometry and gas chromatography/mass spectrometry analysis. Eur J Oral Sci. 2004; 112:530–7. [PubMed: 15560837]

Palanza P, Gioiosa L, vom Saal FS, Parmigiani S. Effects of developmental exposure to bisphenol A on brain and behavior in mice. Environ Res. 2008; 108:150–7. [PubMed: 18949834]

Perera F, Vishnevetsky J, Herbstman JB, Calafat AM, Xiong W, Rauh V, et al. Prenatal Bisphenol A Exposure and Child Behavior in an Inner City Cohort. Environmental health perspectives. 2012

Polydorou O, Konig A, Hellwig E, Kummerer K. Long-term release of monomers from modern dental-composite materials. Eur J Oral Sci. 2009; 117:68–75. [PubMed: 19196321]

Psychological Corporation. Wechsler Individual Achievement Test. San Antonio, TX: Psychological Corporation; 1992.

Pulgar R, Olea-Serrano MF, Novillo-Fertrell A, Rivas A, Pazos P, Pedraza V, et al. Determination of bisphenol A and related aromatic compounds released from bis-GMA-based composites and sealants by high performance liquid chromatography. Environmental health perspectives. 2000; 108:21–7. [PubMed: 10620520]

Richter CA, Birnbaum LS, Farabollini F, Newbold RR, Rubin BS, Talsness CE, et al. In vivo effects of bisphenol A in laboratory rodent studies. Reprod Toxicol. 2007; 24:199–224. [PubMed: 17683900]

Sasaki N, Okuda K, Kato T, Kakishima H, Okuma H, Abe K, et al. Salivary bisphenol-A levels detected by ELISA after restoration with composite resin. J Mater Sci Mater Med. 2005; 16:297–300. [PubMed: 15803273]

Schweikl H, Hiller KA, Bolay C, Kreissl M, Kreismann W, Nusser A, et al. Cytotoxic and mutagenic effects of dental composite materials. Biomaterials. 2005; 26:1713–9. [PubMed: 15576145]

Schweikl H, Spagnuolo G, Schmalz G. Genetic and cellular toxicology of dental resin monomers. J Dent Res. 2006; 85:870–7. [PubMed: 16998124]

Sheslow, D.; Adams, W. WRAML. Wide Range Assessment of Memory and Learning. Wilmington, DE: Wide Range, Inc; 1990.

Sletten GB, Dahl JE. Cytotoxic effects of extracts of compomers. Acta Odontol Scand. 1999; 57:316–22. [PubMed: 10777134]

Soncini JA, Maserejian NN, Trachtenberg F, Tavares M, Hayes C. The longevity of amalgam versus compomer/composite restorations in posterior primary and permanent teeth: findings From the

New England Children's Amalgam Trial. J Am Dent Assoc. 2007; 138:763–72. [PubMed: 17545265]

Spreen, O.; Strauss, E. A Compendium of Neuropsychological Tests. New York: Oxford University Press; 1991.

Tian YH, Baek JH, Lee SY, Jang CG. Prenatal and postnatal exposure to bisphenol a induces anxiolytic behaviors and cognitive deficits in mice. Synapse. 2010; 64:432–9. [PubMed: 20169576]

Trenerry, MR.; Crosson, B.; DeBoe, J.; Leber, WR. Stroop Neuropsychological Screening Test Manual. Odessa, FL: Psychological Assessment Resources; 1989.

U.S. Department of Health and Human Services (USDHHS). Oral Health in America: A Report of the Surgeon General. Rockville, MD: HHS, National Institutes of Health, National Institute of Dental and Craniofacial Research; 2000.

Van Landuyt KL, Nawrot T, Geebelen B, De Munck J, Snauwaert J, Yoshihara K, et al. How much do resin-based dental materials release? A meta-analytical approach. Dent Mater. 2011; 27:723–47. [PubMed: 21664675]

vom Saal FS, Hughes C. An extensive new literature concerning low-dose effects of bisphenol A shows the need for a new risk assessment. Environmental health perspectives. 2005; 113:926–33. [PubMed: 16079060]

Wataha JC, Rueggeberg FA, Lapp CA, Lewis JB, Lockwood PE, Ergle JW, et al. In vitro cytotoxicity of resin-containing restorative materials after aging in artificial saliva. Clin Oral Investig. 1999; 3:144–9.

Wechsler, D. Wechsler Intelligence Scale for Children. 3. San Antonio: The Psychological Corporation; 1991.

Welshons WV, Nagel SC, vom Saal FS. Large effects from small exposures. III. Endocrine mechanisms mediating effects of bisphenol A at levels of human exposure. Endocrinology. 2006; 147:S56–69. [PubMed: 16690810]

Xu X, Tian D, Hong X, Chen L, Xie L. Sex-specific influence of exposure to bisphenol-A between adolescence and young adulthood on mouse behaviors. Neuropharmacology. 2011; 61:565–73. [PubMed: 21570416]

Xu XH, Zhang J, Wang YM, Ye YP, Luo QQ. Perinatal exposure to bisphenol-A impairs learning-memory by concomitant down-regulation of N-methyl-D-aspartate receptors of hippocampus in male offspring mice. Horm Behav. 2010; 58:326–33. [PubMed: 20206181]

Yap AU, Han VT, Soh MS, Siow KS. Elution of leachable components from composites after LED and halogen light irradiation. Oper Dent. 2004; 29:448–53. [PubMed: 15279486]

Yolton K, Xu Y, Strauss D, Altaye M, Calafat AM, Khoury J. Prenatal exposure to bisphenol A and phthalates and infant neurobehavior. Neurotoxicol Teratol. 2011; 33:558–66. [PubMed: 21854843]

Highlights

- Secondary analysis of randomized trial data
- 534 Children randomly assigned to dental treatment of amalgam or resin composites
- Analyzed treatment levels of composites and neuropsychological test scores
- Consistent but not statistically significant associations observed

Table 1

Dental Composite Restoration Treatment Levels and 5-Year Cumulative Exposure during the 5-Year Trial among 444 Children in this Analysis[a]

	Compomer	Composite	Total Composites
Number of Teeth Ever Filled	2.3 (2.7)	1.7 (2.5)	4.0 (4.1)
Number of Posterior Occlusal Surfaces Ever Filled	2.0 (2.5)	1.3 (2.1)	3.3 (3.7)
Surface-Years of Exposure	11.8 (17.9)	10.3 (17.2)	22.2 (25.3)
Posterior Occlusal Surface-Years of Exposure	5.5 (8.2)	4.6 (8.2)	10.1 (12.1)

[a]Columns present mean (SD) for children who received any restoration treatment on posterior or anterior teeth with each specific material, and are not mutually exclusive. “Total composites” includes both compomer and composite restorations. Among children randomized to the composites treatment plan (n=224), compomer was used for primary dentition and composite for permanent dentition. Among children randomized to amalgam treatment (n=220), compomer or composite was used for anterior tooth surfaces per NECAT protocol and standard clinical practice. Materials applied were Dyract compomer and Z100 composite.

Table 2

Baseline Characteristics of Children, Overall and by Cumulative Exposure to Composites during the 5-Year Study

	Overall	5-Year Cumulative Exposure Level[a] (surface-years category)			
		0	0.1–16.0	16.1–40.0	>40.0
N	444	136	102	104	102
Age, mean (SD)	8.1 (1.4)	8.2 (1.3)	7.9 (1.4)	8.1 (1.3)	7.9 (1.5)
Sex, n (%)					
Female	237 (53.4%)	73 (53.7%)	42 (52.9%)	49 (47.1%)	61 (59.8%)
Male	207 (46.6%)	63 (46.3%)	48 (47.1%)	55 (52.9%)	41 (40.2%)
Race/ethnicity, n (%)[b]					
Non-Hispanic White	290 (65.3%)	83 (61.0%)	76 (74.5%)	63 (60.6%)	68 (66.7%)
Non-Hispanic Black	88 (19.8%)	36 (26.5%)	14 (13.7%)	21 (20.2%)	17 (17.7%)
Hispanic (non-mixed)	30 (6.8%)	8 (5.9%)	4 (3.9%)	12 (11.5%)	6 (5.9%)
Other	36 (8.1%)	9 (6.6%)	8 (7.8%)	8 (7.7%)	11 (10.8%)
Socioeconomic status, n (%)[c]					
Low	136 (30.6%)	51 (37.5%)	26 (25.5%)	41 (39.4%)	18 (17.7%)
Medium	153 (34.5%)	44 (32.4%)	40 (39.2%)	29 (27.9%)	40 (39.2%)
High	155 (34.9%)	41 (30.2%)	36 (35.3%)	34 (32.7%)	44 (43.1%)
Geographic location, n (%)					
Urban (Boston, MA)	229 (51.6%)	81 (56.6%)	38 (37.3%)	57 (54.8%)	53 (52.0%)
Rural (Farmington, ME)	215 (48.4%)	55 (40.4%)	64 (62.8%)	47 (45.2%)	49 (48.0%)
Drinking water source, n (%)					
Bottled	127 (31.1%)	39 (31.7%)	28 (29.5%)	29 (29.9%)	31 (33.0%)
Tap	158 (38.6%)	46 (37.4%)	40 (42.1%)	38 (39.2%)	34 (36.2%)
Mixed	116 (28.4%)	36 (29.3%)	24 (25.3%)	28 (28.9%)	28 (29.8%)
Don't Know	8 (2.0%)	2 (1.6%)	3 (3.2%)	2 (2.1%)	1 (1.1%)
Blood lead level, mean (SD) µg/dL	2.3 (1.8)	2.5 (1.9)	2.3 (1.9)	1.9 (1.2)	2.5 (1.7)
Birth weight, mean (SD) g	3360 (542)	3333 (515)	3353 (554)	3371 (595)	3390 (514)

[a]Composites exposure included exposure to both polyacid-modified compomer and traditional composite.

[b]Race/ethnicity was self-reported by the parent of the child. The "other" category included individuals who identified themselves as Asian, Native American, multiracial (specified) or other (specified).

[c]Socioeconomic status index was calculated using household income and education level of the primary caregiver and standardized to the U.S. population .(Green, 1970)

Table 3

Changes in Neuropsychological Test Scores between Baseline and 4-or 5-Year Follow-up, by Cumulative Exposure to Dental Compomer or Composite on Posterior-Occlusal Surfaces, Multivariable-Adjusted Coefficients for Mean (SE) Change Scores[a]

	Compomer (Primary Teeth)						**Composite (Permanent Teeth)**					
	5-Year Exposure Category				**Each additional 10 Surface- Years Exposure**		**5-Year Exposure Category**				**Each additional 10 Surface- Years Exposure**	
	0	**0.1–6.0**	**6.1–13.0**	**>13.0**	**Beta**	***P***	**0**	**0.1–6.0**	**4.1–14.0**	**>14.0**	**Beta**	***P***
Median surface-years	0.0	3.1	9.5	19.4			0.0	2.5	10.3	19.5		
N	*219*	*70*	*75*	*66*			*255*	*67*	*49*	*59*		
WISC-III Full-Scale IQ	3.2 (0.6)	1.7 (1.0)	1.2 (1.0)	3.7 (1.1)	−0.2 (0.5)	0.68	2.9 (0.5)	1.9 (1.1)	3.6 (1.2)	1.8 (1.2)	−0.4 (0.5)	0.44
Factors:												
Verbal Comprehension	2.0 (0.7)	1.4 (1.2)	1.2 (1.1)	2.8 (1.2)	0.2 (0.6)	0.70	1.6 (0.6)	2.3 (1.2)	2.1 (1.4)	2.7 (1.3)	0.2 (0.6)	0.79
Perceptual Organization	3.9 (0.7)	3.0 (1.3)	1.5 (1.2)	3.5 (1.3)	−0.6 (0.7)	0.37	3.9 (0.7)	1.6 (1.3)	4.5 (1.5)	1.6 (1.4)	−0.4 (0.7)	0.52
Freedom from Distractibility	3.8 (0.8)	−0.2 (1.4)	2.9 (1.3)	4.1 (1.5)	−0.1 (0.7)	0.91	2.8 (0.7)	2.3 (1.4)	4.6 (1.6)	3.4 (1.6)	0.1 (0.7)	0.85
Processing Speed	7.0 (0.9)	5.1 (1.6)	4.7 (1.5)	6.0 (1.7)	−0.8 (0.8)	0.33	6.8 (0.8)	5.9 (1.7)	6.7 (1.9)	3.4 (1.8)	−1.2 (0.8)	0.17
WIAT												
Reading	−1.7 (0.7)	0.6 (1.3)	−2.5 (1.2)	−2.6 (1.4)	−0.6 (0.7)	0.36	−1.3 (0.7)	−3.9 (1.3)	−2.0 (1.5)	−0.2 (1.5)	0.2 (0.7)	0.76
Mathematics	−1.9 (0.8)	−1.7 (1.4)	−2.9 (1.3)	−4.7 (1.5)	−1.0 (0.7)	0.15	−2.2 (0.7)	−4.5 (1.4)	−3.1 (1.7)	−0.9 (1.6)	0.1 (0.7)	0.90
	4-Year Exposure Category						**4-Year Exposure Category**					
	0	**0.1–6.0**	**6.1–12.0**	**>12.0**			**0**	**0.1–4.0**	**4.1–10.0**	**>10.0**		
Median surface-years	0.0	3.0	9.1	19.0			0.0	2.8	7.5	13.6		
WRAML, *N*	*201*	*68*	*70*	*63*			*255*	*48*	*46*	*53*		
General Memory Index	8.0 (0.7)	9.1 (1.2)	6.1 (1.2)	7.1 (1.3)	−0.7 (0.7)	0.31	7.5 (0.6)	8 (1.5)	7.4 (1.5)	8.6 (1.4)	0.2 (0.9)	0.82
Individual Index:												
Verbal Memory	2.7 (0.7)	3.2 (1.2)	1.0 (1.2)	2.4 (1.3)	−0.5 (0.7)	0.43	2.2 (0.6)	3.2 (1.4)	2.4 (1.4)	3.2 (1.4)	0.6 (0.9)	0.50
Visual Memory	6.5 (0.9)	6.7 (1.6)	4.6 (1.6)	5.0 (1.7)	−0.7 (0.9)	0.47	5.7 (0.8)	6.9 (1.9)	4.9 (1.9)	7.0 (1.9)	−0.1 (1.2)	0.95
Learning	9.9 (0.8)	12.0 (1.5)	10 (1.4)	9.3 (1.6)	−0.5 (0.8)	0.57	10.1 (0.8)	9.5 (1.7)	11.5 (1.8)	10.2 (1.7)	−0.1 (1.1)	0.95
WRAVMA												
Visual Motor Composite	3.3 (0.9)	4.6 (1.5)	3.5 (1.4)	5.3 (1.6)	0.5 (0.9)	0.55	4.0 (0.8)	4.1 (1.7)	5.9 (1.8)	1.6 (1.7)	−0.8 (1.1)	0.45
Trail-Making Test												

	Compomer (Primary Teeth)						Composite (Permanent Teeth)					
	5-Year Exposure Category				Each additional 10 Surface- Years Exposure		5-Year Exposure Category				Each additional 10 Surface- Years Exposure	
	0	**0.1–6.0**	**6.1–13.0**	**>13.0**	**Beta**	***P***	**0**	**0.1–6.0**	**4.1–14.0**	**>14.0**	**Beta**	***P***
Part B-Part A	−27.4 (3.5)	−42.0 (6.0)	−30.2 (5.8)	−40.1 (6.5)	−5.8 (3.4)	0.09	−31.4 (3.1)	−29.5 (7.0)	−41.8 (7.1)	−30.6 (7.1)	−0.2 (0.4)	0.97
Verbal Cancellation												
Ordered trial: no. of errors	−19.1 (0.5)	−19.6 (0.9)	−19.0 (0.9)	−20.7 (1.0)	−0.8 (0.5)	0.15	−19.3 (0.5)	−19.4 (1.0)	−19.8 (1.1)	−19.7 (1.1)	0.1 (0.7)	0.93
Verbal Fluency[b]												
Category fluency	9.6 (0.4)	10.4 (0.8)	9.7 (0.7)	8.6 (0.8)	−0.3 (0.4)	0.51	9.5 (0.4)	9.0 (0.9)	10.8 (0.9)	9.6 (0.9)	0.1 (0.6)	0.93
Letter fluency	13.8 (0.6)	13.0 (1.0)	12.4 (0.9)	11.8 (1.0)	−1.1 (0.6)	0.05	13.2 (0.5)	13.0 (1.1)	12.9 (1.2)	12.9 (1.1)	−0.9 (0.7)	0.19
Stroop Color-Word Interference												
Word	25.9 (0.9)	24.7 (1.5)	23.4 (1.4)	25.8 (1.8)	−0.3 (0.9)	0.71	25.4 (0.8)	25.4 (1.7)	24.4 (1.8)	24.9 (1.6)	−0.5 (1.0)	0.60
Color	19.7 (0.7)	20.6 (1.2)	16.5 (1.2)	17.7 (1.5)	−1.9 (0.8)	0.02	19.7 (0.7)	18.1 (1.5)	19.9 (1.6)	16.3 (1.3)	−1.9 (0.9)	0.03
Color-Word	13.1 (0.6)	13.1 (1.0)	12.3 (0.9)	13.1 (1.2)	−0.1 (0.6)	0.89	12.9 (0.5)	12.7 (1.2)	14.7 (1.2)	12.1 (1.1)	−0.5 (0.7)	0.50
Wisconsin Card Sorting												
No. of categories achieved	1.1 (0.1)	1.0 (0.2)	1.1 (0.2)	1.1 (0.2)	0.01 (0.1)	0.93	1.1 (0.1)	1.1 (0.2)	0.8 (0.2)	1.2 (0.2)	−0.01 (0.1)	0.97
Total perseverative errors	17.6 (1.1)	20.6 (2.0)	19.4 (1.9)	21.5 (2.2)	1.5 (1.1)	0.19	18.5 (1.0)	18.7 (2.4)	20.1 (2.4)	21.0 (2.3)	2.2 (1.5)	0.12
Total errors	15.9 (1.1)	18.5 (2.0)	16.4 (1.9)	17.8 (2.2)	0.7 (1.1)	0.54	16.6 (1.0)	16.4 (2.4)	15.5 (2.4)	18.5 (2.3)	1.5 (1.5)	0.30

[a]Means are adjusted for age, sex, socioeconomic status, geographic study site, and baseline blood lead level. Compomer and Composite were not mutually exclusive. The *N* provided is for the WISC-III or WRAML.

[b]Category fluency test mean is the sum of 4 trials. Letter fluency test mean is the sum of 3 trials.