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A dose–effect analysis of children's exposure to dental amalgam and neuropsychological function

The New England Children's Amalgam Trial

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The New England Children's Amalgam Trial (NECAT) is one of the first two trials to use the random-assignment-to-treatment method to assess the health effects associated with the use of dental amalgam—which contains elemental mercury—to restore dental caries in children.[1,2] In a previous article, we reported that no adverse effects on the primary and secondary neuropsychological endpoints of NECAT were detected by analyses in which exposure to amalgam was characterized on the basis of treatment group assignment (that is, amalgam versus mercury-free resin-based composite).[1]

A limitation of the intention-to-treat analyses was that they did not factor in the varying dental needs of the children in the amalgam group and, thus, the differing amounts of amalgam exposure they experienced. For the purposes of the analyses, all of the children randomized to the amalgam group were considered to have had equivalent exposures to amalgam-related mercury vapor. However, children in the amalgam group had varying numbers of carious lesions requiring restoration over the course of the trial. The total number of tooth surfaces restored with amalgam over the five-year follow-up interval among the children in this group

ABSTRACT

Background. The New England Children's Amalgam Trial (NECAT) was a five-year randomized trial of 534 6- to 10-year-old children that compared the neuropsychological outcomes of those whose caries were restored using dental amalgam with the outcomes of those those whose caries were restored using mercury-free resin-based composite. The primary intention-to-treat analyses did not reveal significant differences between the treatment groups on the primary or secondary outcomes of the administered psychological tests: Full-Scale IQ score on the Wechsler Intelligence Scale for Children-Third Edition, General Memory Index of the Wide Range Assessment of Memory and Learning, and Visual-Motor Composite of the Wide Range Assessment of Visual Motor Abilities.

Methods. To determine whether treatment group assignment, a dichotomous measure of exposure, was sufficiently sensitive to detect associations between mercury exposure and these outcomes, the authors conducted analyses to evaluate the associations between the primary and secondary outcomes and two continuously distributed indexes of potential exposure, surface-years of amalgam and urinary mercury excretion.

Results. Neither index of mercury exposure was significantly associated with any of the three outcomes.

Conclusions. The authors found no evidence that exposure to mercury from dental amalgam was associated with any adverse neuropsychological effects over the five-year period after placement of amalgam restorations.

Clinical Implications. Analyses of the outcomes of the NECAT study indicate that use of dental amalgam was not associated with an increase in children's risk of experiencing neuropsychological dysfunction.

Key Words. Dental amalgam; children; mercury; neuropsychology.

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ranged from 0 to 35, and urinary mercury excretions at the end of follow-up ranged from 0.1 to 5.7 micrograms per gram creatinine (Cr). Therefore, a form of exposure misclassification, resulting from the presumed equivalence of the exposure to mercury experienced by the children in the amalgam group, might explain the absence of significant treatment group differences between the amalgam group and the resin-based composite group on the primary and secondary outcomes.

In this article, we present additional analyses of the primary and secondary neuropsychological outcomes in which we used two continuously distributed indexes to characterize children's exposure to mercury from amalgam. The surface-years of amalgam index characterized how many tooth surfaces were restored with amalgam, as well as the duration of each (in years). The urinary mercury excretion index was a biomarker of absorbed dose, which is associated positively with number of amalgam restorations in children and adults.[3-5]

For each subject, we calculated surface-years of amalgam exposure using dates of amalgam placement, the number of tooth surfaces involved in the restoration and the timing of loss of primary teeth containing amalgam restorations.

SUBJECTS AND METHODS

Trial design. The design of the NECAT has been described in detail elsewhere.[1,6] In brief, 534 children from Boston; Cambridge, Mass.; and Farmington, Maine, were enrolled and followed between September 1997 and March 2005. Children were eligible for the study if they were 6 to 10 years of age, fluent in English, had no known prior or existing amalgam restorations, had two or more posterior teeth with dental caries on the occlusal surface, and did not have a physician-diagnosed psychological, behavioral, neurological, immunosuppressive or renal disorder.

At the baseline visits, the subjects received a dental examination by study dentists (including M.A.T.), bitewing radiographs and standard preventive dental care. Study staff members collected blood and urine samples; took anthropometric measurements of height, weight, and body fat; completed neuropsychological testing of the child and guardian; and conducted a health interview with the subject's parent or guardian.

After the baseline visits, we randomized the subjects to one of two treatment groups; they received restorations of dental amalgam or mercury-free resin-based composite. We stratified the randomization by geographic location (Massachusetts versus Maine) and number of teeth with caries (two to four versus five or more), using randomly permuted blocks within each of the four strata.

The subjects received semiannual dental care throughout the five-year trial period. For subjects in the amalgam group, we used a dispersed-phase amalgam to restore all posterior teeth with caries at baseline and to restore incident caries. For subjects in the composite group, we used a resin-based composite material for all restorations in permanent posterior teeth and a compomer in primary posterior teeth. Regardless of which treatment group subjects were assigned, we used resin-based composite to restore caries in the subject's anterior teeth, per standard clinical practice. We placed stainless steel crowns in primary teeth with extensive lesions that could not otherwise be restored.

Data collection. The subjects underwent annual neuropsychological evaluations. The primary outcome of the trial was a change in the Full-Scale IQ score on the Wechsler Intelligence Scale for Children-Third Edition (WISC-III)[7] between the baseline evaluation and an evaluation conducted five years after a subject's enrollment. The secondary outcomes were the scores on the General Memory Index (GMI) from the Wide Range Assessment of Memory and Learning[8] and the Visual-Motor Composite (VMC) from the Wide Range Assessment of Visual Motor Abilities.[9] We assessed these secondary outcomes for the last time as part of the evaluation conducted four years after the subjects enrolled in the study; therefore, the critical scores were the changes between the baseline evaluation and the year four evaluation.

We collected urine samples from the subjects

ABBREVIATION KEY. Cr: Creatinine. **GMI:** General Memory Index. **NECAT:** New England Children's Amalgam Trial. **VMC:** Visual-Motor Composite. **WISC-III:** Wechsler Intelligence Scale for Children-Third Edition.

TABLE 1

Baseline characteristics of subjects, by group.

CHARACTERISTIC	AMALGAM (N = 267)	COMPOSITE (N = 267)
Site (N [%])		
Massachusetts	144 (53.9)	147 (55.1)
Maine	123 (46.1)	120 (44.9)
No. of Carious Surfaces (Mean, SD,* Range)	9.8, 6.9, 2-39	9.3, 6.2, 2-36
Age in Years (Mean, SD, Range)	7.9, 1.3, 5.9-11.4	7.9, 1.4, 5.9-11.5
Sex (N [%])		
Female	131 (49.1)	156 (58.4)
Male	136 (50.9)	111 (41.6)
Race (N [%])†		
Non-Hispanic White	165 (64.0)	158 (60.3)
Non-Hispanic Black	49 (19.0)	49 (18.7)
Hispanic	15 (5.8)	23 (8.8)
Other	29 (11.2)	32 (12.2)
Household Income (N [%])		
$20,000	74 (29.2)	86 (33.1)
$20,000-40,000	113 (44.7)	109 (41.9)
> $40,000	66 (26.1)	65 (25.0)
Education of Primary Caretaker (N [%])		
< High school	34 (13.2)	38 (14.6)
High school graduate	197 (76.4)	194 (74.3)
College graduate	18 (7.9)	17 (6.5)
Postcollege degree	9 (3.5)	12 (4.6)
Wechsler Intelligence Scale for Children-Third Edition Full-Scale IQ Score (Mean, SD, Range)	95.1, 14.5, 65-141	96.1, 12.1, 62-123
Urinary Mercury (≥ 1.5 Nanograms per Milliliter) (N [%])	21 (8.4)	11(4.5)
Hair Mercury (Micrograms per Gram) (Mean, SD, Range)	0.4, 0.5, 0.1-4.4	0.4, 0.5, 0.1-4.5
Blood Lead (Micrograms per Deciliter) (Mean, SD, Range)	2.4, 1.9, 1-13	2.3, 1.5, 1-11

* SD: Standard deviation.
† Race was self-reported by parents or guardians.

annually and tested them for elemental mercury using cold vapor atomic absorption. Values were expressed as micrograms of mercury per gram of Cr. The detection limit, 1.5 nanograms of mercury per milliliter at baseline, was reduced to 0.45 ng/mL after Feb. 1, 2000, as a result of our increasing the volume of sample collected. Therefore, for comparability, the analyses reported urinary mercury concentrations in samples collected only at three, four and five years. We estimated that children with levels below the detection limit (< 0.45 ng/mL) had a urinary excretion level of 0.45 divided by 1.41 (the square root of 2).[10]

The institutional review boards of the New England Research Institutes, The Forsyth Institute and the clinics from which the subjects were recruited approved the NECAT trial. All parents or guardians provided informed consent, and all children provided assent.

Statistical analyses. For each subject, we calculated surface-years of amalgam exposure (number of amalgam surfaces weighted by number of years present in mouth) using the information in his or her dental clinic records regarding dates of amalgam placement, the number of tooth surfaces involved in the restoration and the timing of loss of primary teeth containing amalgam restorations. To analyze the change in WISC-III Full-Scale IQ score in relation to amalgam exposure, we used surface-years of amalgam between baseline and the five-year follow-up evaluation. To analyze the changes in GMI and VMC scores in relation to amalgam exposure, we used surface-years of amalgam between baseline and four-year follow-up evaluation.

For each subject, we computed mean urinary mercury excretion. To analyze the change in WISC-III Full-Scale IQ score in relation to urinary mercury excretion, we used the mean of available urinary mercury excretions at the three-, four- and five-year follow-up. To analyze the changes in GMI and VMC scores in relation to urinary mercury excretion, we use the mean of available excretions at years three and four of follow-up.

We used analysis of covariance (ANCOVA) to evaluate the associations between the two continuously distributed indexes of mercury dose and the change in scores for the three neuropsychological tests. We made adjustments for the following baseline covariates: test score, randomization stratum, age, sex, family socioeconomic

TABLE 2

Distribution of dental treatment, amalgam exposure and urinary mercury excretion, by treatment group.

DENTAL TREATMENT	AMALGAM (MEAN, SD,* RANGE)	COMPOSITE (MEAN, SD, RANGE)
No. of Restored Surfaces in Mouth at End of Trial Period†	5.3, 5.2, 0-36	6.1, 6.0, 0-36
No. of Restored Amalgam Surfaces at End of Trial Period‡	4.0, 4.0, 0-21	0.05, 0.6, 0-9
Cumulative No. of Surfaces Restored (Over Five Years)§¶	14.6, 9.6, 0-55	15.8, 9.9, 0-51
Cumulative No. of Surfaces Restored Over Five Years With Amalgam¶	11.5, 7.1, 0-35	0.04, 0.6, 0-9
Surface-Years of Amalgam **Baseline to year 5** **Baseline to year 4**	 31.7, 20.9, 0-94.1 27.2, 17.8, 0-78.9	 0.14, 1.87, 0-27.4 0.10, 1.46, 0-20.9
Urinary Mercury Excretion (Micrograms of Creatinine per Gram) **Mean of years 3-5** **Mean of years 3-4**	 0.99, 0.79, 0.16-5.07 1.03, 0.92, 0.16-5.75	 0.61, 0.69, 0.17-8.77 0.60, 0.75, 0.10-8.77

* SD: Standard deviation.
† P = .16 for difference between amalgam and composite groups.
‡ Two subjects in the composite group received amalgam restorations from a nonstudy dentist.
§ P = .10 for the difference between amalgam and composite groups.
¶ Cumulative numbers do not include subjects who withdrew from the study.

TABLE 3

Associations between neuropsychological test change scores and two indexes of exposure (surface-years of amalgam and urinary mercury excretion).*

TEST SCORE	SURFACE-YEARS OF AMALGAM				URINARY MERCURY EXCRETION			
	n	COEFFICIENT†‡	STANDARD ERROR	*P* VALUE	n	COEFFICIENT†‡	STANDARD ERROR	*P* VALUE
Full-Scale IQ§	434	0.01	0.02	.48	433	0.46	0.53	.38
General Memory Index¶	407	0.03	0.03	.20	401	0.74	0.55	.18
Visual-Motor Composite#	406	-0.01	0.03	.67	400	0.20	0.65	.76

* Regression coefficients in analyses of covariance.
† Adjusted for the following baseline covariates: test score, randomization stratum, age, sex, family socioeconomic status, hair mercury concentration, blood lead level.
‡ Coefficients represent the slope of the association between test change score and surface-years of amalgam or urinary mercury excretion (that is, a coefficient with a negative sign indicates that the score declined with greater surface-years of amalgam or greater urinary mercury excretion).
§ Full-Scale IQ score on the Wechsler Intelligence Scale for Children-Third Edition.[7]
¶ General Memory Index from the Wide Range Assessment of Memory and Learning.
# Visual-Motor Composite (VMC) from the Wide Range Assessment of Visual Motor Abilities.

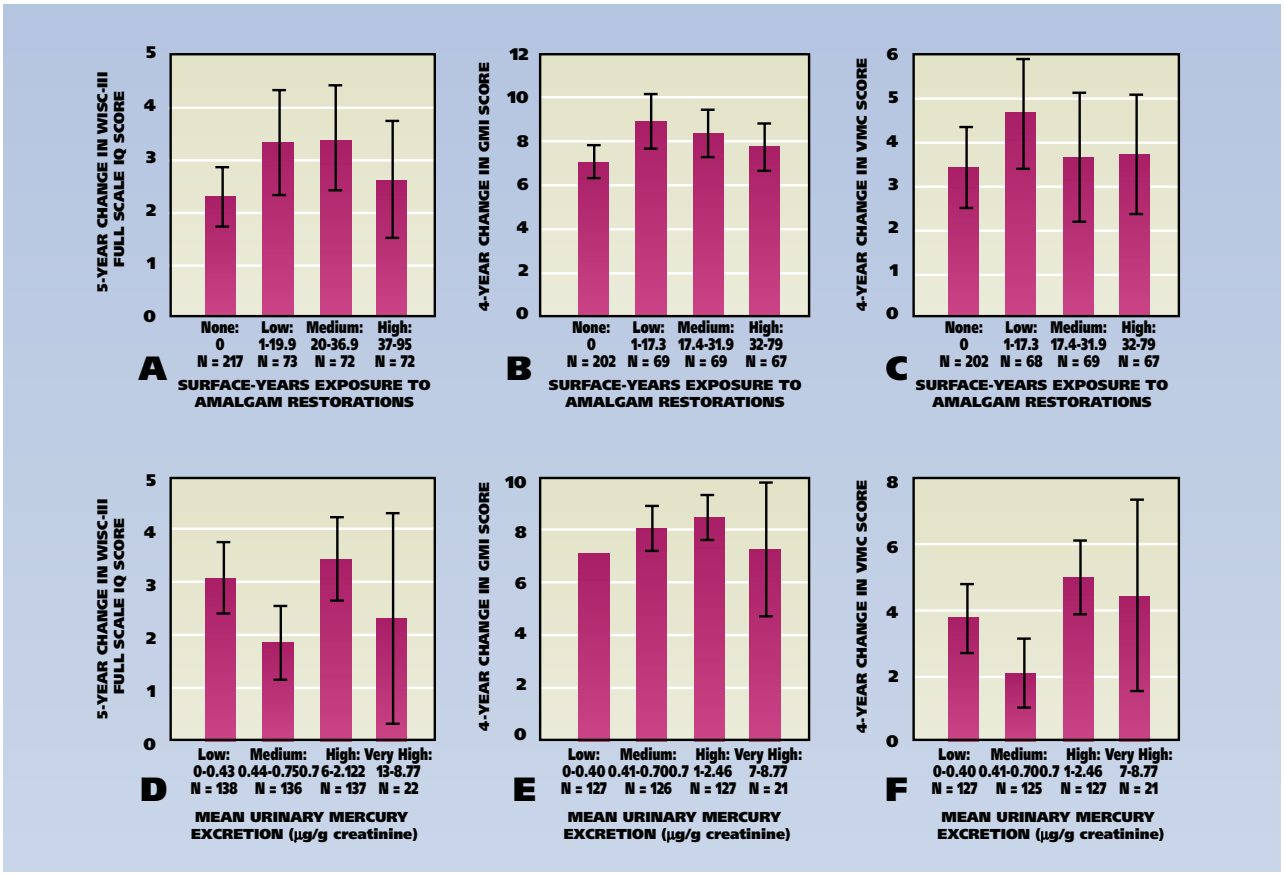

Figure. Histograms of changes in neuropsychological test scores, stratified by exposure category. **A.** Five-year change in Wechsler Intelligence Scale for Children-Third Edition (WISC-III) Full-Scale IQ score and surface-years of amalgam at year five. **B.** Four-year change in General Memory Index (GMI) from the Wide Range Assessment of Memory and Learning score and surface-years of amalgam at year four. **C.** Four-year change in Visual Motor Composite (VMC) from the Wide Range Assessment of Visual Motor Abilities score and surface-years of amalgam at year four. **D.** Five-year change in WISC-III Full-Scale IQ score and urinary mercury excretion, years three through five. **E.** Four-year change in GMI score and urinary mercury excretion, years three through four. **F.** Four-year change in VMC score and urinary mercury excretion, years three through four. µg/g: Microgram per gram.

status, hair mercury concentration and blood lead level.

We evaluated the likelihood of nonlinearity in the associations by constructing histograms of test scores and by stratifying subjects by surface-years of amalgam or by urinary mercury excretion. For surface-years of amalgam, 217 subjects had none, and we classified the other 217 subjects into three groups equal in size: low (1.00-19.99 surface-years; n = 73), middle (20.00-36.99 surface-years; n = 72) and high (37.00-95.00 surface-years; n = 72). (Although we enrolled 534 children in the trial, we did not include some subjects in these analyses because they dropped out of the study before the end or because we were unable to collect complete data on exposures and outcomes.) For urinary mercury excretion, we classified subjects into groups based on the mean level between years three and five for analyses of Full-Scale IQ scores or years three and four for analyses of GMI and VCM scores.

RESULTS

The baseline characteristics of the subjects enrolled in the NECAT, stratified by treatment group assignment, are provided in Table 1. Groups were similar in all respects except for sex. Whereas males and females were represented almost equally in the amalgam group, the number of girls exceeded the number of boys in the composite group.

Descriptive statistics for distribution of dental treatment by surface-years of amalgam and urinary mercury excretion are provided in Table 2. Treatment needs, as reflected by the number of restored surfaces, were similar in both treatment groups. The mean urinary mercury excretion level was significantly higher among subjects in the

amalgam group compared with those in the composite group. Two subjects in the composite group received amalgam restorations from nonstudy dentists.

Using ANCOVA, we found that none of the three neuropsychological test scores—WISC-III Full-Scale IQ, GMI or VMC—was associated significantly with either continuously distributed index of mercury dose (Table 3). Histograms of mean change in scores for subjects, stratified by surface-years of amalgam and by urinary mercury excretion, did not reveal a consistent pattern in the dose-effect relationships (Figure).

DISCUSSION

These data, as well as those from other NECAT analyses,[1,11] provide no evidence that exposure to mercury from dental amalgam was associated with any adverse neuropsychological effects in subjects across the five-year period after the subjects' first amalgam restorations were placed. We saw no significant associations between use of amalgam and the subject's scores on the primary and secondary neuropsychological outcomes, whether exposure was characterized dichotomously (that is, amalgam versus composite treatment group) or continuously (that is, surface-years of amalgam and urinary mercury excretion). Another large randomized trial of dental amalgam in children, which included a seven-year follow-up interval, also provided no evidence of adverse neuropsychological effects.[2]

The inferences drawn about the safety of amalgam should be tempered by the following considerations. It is possible that the follow-up period of five years was too brief for adverse neuropsychological effects of the chronic release of mercury vapor to be expressed. An amalgam restoration generally remains in place and releases mercury for a considerably longer period. However, observational studies of adults have not found significant associations between neuropsychological function and indexes of cumulative amalgam exposure over many years,[12] although studies of dental professionals with greater urinary mercury excretion levels than those we observed in NECAT have been associated with neurobehavioral deficits.[13,14]

Vulnerability to mercury from amalgam might vary with developmental stage, but our findings pertain only to exposure incurred after the age of six years. It is possible that fetal development is a period of particular sensitivity to elemental mercury, as it is for methylmercury.[15] Moreover, just as some people experience an allergic hypersensitivity to amalgam, it is possible that only a small subgroup of children experience neuropsychological injury from the mercury vapor released by amalgam. For example, two genetic polymorphisms that might confer increased risk of experiencing neurotoxic effects from exposure to elemental mercury have been identified.[16,17] We did not characterize the NECAT subject's genotypes, but we were unable to identify a subgroup of those who were particularly sensitive using methods that examined the shapes of the distributions of individual responses in the amalgam and composite treatment groups.[11]

We assessed neuropsychological function using standardized instruments that commonly are used clinically and in research. In an additional analysis of the NECAT, we found that children with higher baseline blood lead levels had significantly lower scores on many of the administered tests.[18] This suggests that our methods were sensitive enough that we likely would have detected adverse effects of the amalgam exposure had any been present. Nevertheless, it is possible that we would have detected significant associations between amalgam exposure and the subject's outcomes had we used different tests and measured different outcomes.

CONCLUSIONS

In a sample of children with substantial unmet dental needs, we found that dose-effect analyses showed no significant associations between neuropsychological outcomes and either of two continuous indexes of mercury exposure. These more sensitive analyses confirm the null results of the original dichotomous comparison of treatment groups reported earlier[1] and of a similar, contemporaneous randomized trial.[2] Under the conditions in which amalgam was used in the NECAT, there appear to be no detectable adverse neuropsychological outcomes in children that are attributable to the use of amalgam dental restorations. ■

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