

Reported asthma and dental amalgam exposure among adults in the United States: An assessment of the National Health and Nutrition Examination Survey

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Abstract

Objective: Mercury (Hg)-based amalgam is a dental restorative material in common use. This hypothesis-testing study evaluated the relationship between dental amalgam exposure and the risk of reported asthma diagnoses in American adults. **Methods:** A total of 97,861,577 weighted-persons with one or more dental amalgam surfaces (exposed group) and 31,716,558 weighted-persons with one or more other dental surfaces (no dental amalgams, unexposed group) were examined in the 2015–2016 National Health and Nutrition Examination Survey. All persons were 20–80 years old and with known reported asthma status (only newly diagnosed asthma cases were examined). Survey logistic regression and survey frequency modeling in SAS were employed to evaluate the relative incidence rate of reported asthma diagnoses among those in the exposed group compared to the unexposed group. Covariates of gender, race, socioeconomic status, educational status, country of birth, and tobacco exposure were considered. **Results:** Survey logistic modeling revealed a significantly increased incidence rate of reported asthma in the exposed group as compared to the unexposed group in unadjusted (4.46-fold) and adjusted (4.84-fold) models. A dose–response relationship was observed for the risk of reported asthma per dental amalgam filling surface in unadjusted (1.073) and adjusted (1.076) models. Survey frequency modeling revealed that the frequency of reported asthma (per 10,000 weighted-person years) was 3.66-fold significantly increased in the exposed group (2.06) as compared to the unexposed group (0.56). **Conclusion:** Increased dental amalgam exposure was associated with an increased risk of reported asthma diagnoses in American adults, but future studies should further evaluate this relationship.

Keywords

Asthma, cross-sectional, dental amalgam, mercury

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Introduction

Dental amalgam fillings are a mixture of mercury (Hg), silver (Ag), tin (Sn), copper (Cu), as well as several other metals. On a weight basis, dental amalgam fillings are about 50% Hg. Of particular concern, Hg⁰ vapor at body temperature is continuously released from dental amalgam fillings. Hg⁰ vapor is easily absorbed into the human body through mucus membranes and the lungs where it is rapidly oxidized to other forms. It was estimated that Hg⁰ vapor exposure from dental amalgam fillings would result in a significant number of persons exceeding the chronic Hg vapor inhalation safety guidelines established by the California Environmental Protection Agency (EPA) and US EPA.¹

On 29 September 2020, the US Food and Drug Administration (FDA)² issued new recommendations after

two decades of reviewing studies about the uncertainties of the effects of Hg exposure from dental amalgam fillings, the acceptable exposure levels for Hg vapor, the potential for Hg to collect in the body, and whether the degree of accumulation of Hg from dental amalgam fillings results in adverse health outcomes. The US FDA concluded that the majority of evidence shows exposure to Hg from dental amalgam fillings does not lead to negative health effects in the general population, but exposure to Hg may pose a greater health

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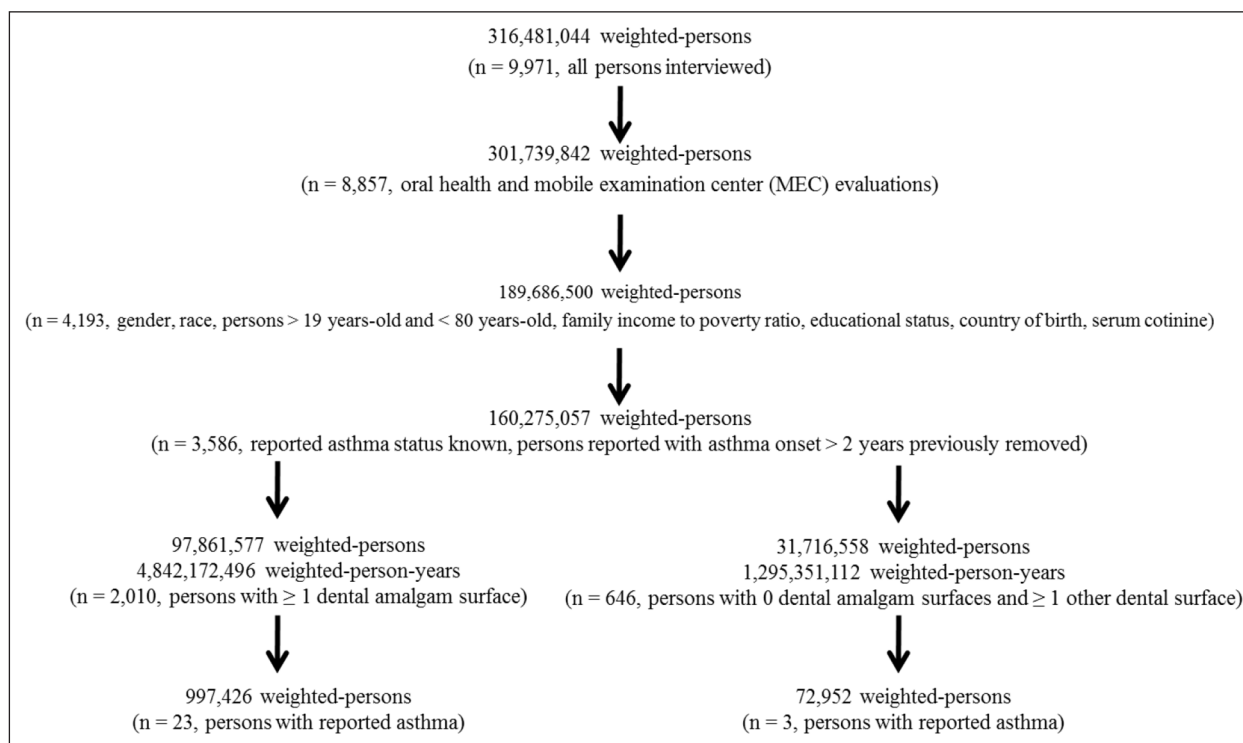


Figure 1. A schematic flowchart of the data examined in this study.

risk in certain groups of people, who may be more susceptible to potential adverse effects generally associated with Hg. As a result, the US FDA strongly encourages the use of non-dental amalgam fillings in high-risk populations, including pregnant women and their developing fetuses; women who are planning to become pregnant; children, especially those younger than 6 years; people with pre-existing neurological disease; people with impaired kidney function; and people with heightened sensitivity (allergy) to Hg or other components of dental amalgam fillings.

It was recently postulated that most researchers examining the adverse effects of Hg exposure were focused on systemic conditions of the human body, in which, Hg is oxidized to Hg-complex and dissolved in body fluids/tissues. However, this is a secondary effect, and investigators have ignored the primary effect in the organ systems that first come into contact with Hg.³ The respiratory organs are particularly important because they are a primary location for the initial interaction between the human body and Hg⁰ vapor. For this reason, the examination of the respiratory system becomes an urgent aspect that needs to be evaluated in the context of potential Hg toxicity in the human body following Hg⁰ vapor exposure from dental amalgam fillings.

Asthma is a chronic disorder of the lungs that negatively impacts people of all ages. Asthma is associated with chronic symptoms that include difficulty breathing, wheezing, chest tightness, and coughing.⁴ Several recent epidemiological studies suggest that in the etiology of asthma, there is an important interaction between genetic variation/susceptibility and environmental exposures.^{5,6}

It was hypothesized that Hg⁰ vapor exposure from dental amalgam fillings may negatively impact the respiratory system by inducing asthma. The purpose of the present hypothesis-testing cross-sectional epidemiological study was to evaluate the potential relationship between dental amalgam fillings and the incidence rate of asthma in adults.

Methods

The SAS system for Windows, version 9.4 (Cary, NC, USA), was used to examine the National Health and Nutrition Examination Survey (NHANES) data. This study integrated the 2015–2016 NHANES data from demographic survey questions, oral health examinations, and medical diagnoses. The 2015–2016 NHANES data collection methods were approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board (ERB) (Protocol#2011-17). Each study subject provided informed consent to participate in the NHANES program. The health information collected in the NHANES program is kept in strictest confidence, and is only used for stated purposes. Figure 1 presents a schematic flowchart of the data examined in this study.

Study participants

An overall population of 160,275,057 weighted-persons >20 years old with non-missing values for the demographic survey questions, oral health examinations, tobacco smoke exposure, and asthma diagnosis (all persons diagnosed with

asthma more than 2 years prior to the NHANES survey were eliminated) were examined in this study. The number of weighted-persons was derived by applying the full sample 2-year mobile examination weight variable (WTMEC2YR) to each person examined in this study. The WTMEC2YR variable was created by the NHANES program. The WTMEC2YR is a measure of the number of persons in the general population that a sampled individual represents and is needed to obtain unbiased estimates of population parameters when sample participants are chosen with unequal probabilities. The demographic variables for the population were identified from within the NHANES demographic dataset. The variables examined were as follows: gender, age in years at examination, race (non-Hispanic White, non-Hispanic Black, non-Hispanic Asian, Hispanic, or other), educational level (less than 9th grade, 9–11th grade, high school graduate/general equivalence degree, some college or associates degree, or college graduate or above), country of birth, and socioeconomic status (poverty income ratio (PIR)—a ratio of family income to poverty threshold). The PIR variable was created by the NHANES program. To examine tobacco smoke exposure, serum cotinine (ng/mL) measures were examined for each person from the cotinine and hydroxycotinine—serum dataset. Serum cotinine, a nicotine metabolite, is a well-established measure of tobacco use and exposure.⁷

Exposures

The dental amalgam filling surface exposure variable was determined by examining the NHANES oral health—dentition dataset. For each person, the oral health examination was conducted by dental examiners, who were dentists (D.D.S./D.M.D.) licensed in at least one US state. A health technician assisted in entering all examiner observations directly into a computerized data collection system. All oral health assessments took place in a designated room at the mobile examination center (MEC) that included a portable dental chair, light, and compressed air.

For all survey participants aged 1 year and older, the oral health examination began with a tooth count assessment. Next, their teeth were assessed for coronal caries, including untreated dental decay and teeth treated or extracted due to caries. The 2015–2016 coronal caries assessment was similar to the protocols used in 1999–2004 and 2011–2014, with the following exception: filled surfaces were assessed by restoration type (amalgam or other). The cumulative numbers of dental amalgam filling or other dental filling surfaces were computed for each person examined in this study. The exposed group consisted of a total of 97,861,577 weighted-persons with ≥ 1 dental amalgam filling surface and ≥ 0 other dental filling surfaces. The unexposed group consisted of a total of 31,716,558 weighted-persons with 0 dental amalgam filling surfaces and ≥ 1 other dental filling surface. All persons without any dental filled surfaces (dental amalgam or other) were not examined.

Outcomes

The medical condition NHANES dataset was examined to determine the incidence rate of reported asthma. Among the persons examined, asthma was determined based upon each person reporting whether a doctor ever said they had asthma and the age at which they were told they had asthma (the age of onset of asthma). Among those reported with asthma, only persons reported with onset of asthma within 2 years of NHANES data collection were included in this study. Persons with onset of asthma previous to that period were not examined.

Statistical analyses

In all statistical analyses, the statistical package in SAS was utilized, and a two-sided p value < 0.05 was considered statistically significant. The number of persons examined in this study was sufficient to allow for adequate statistical power for the analyses undertaken. The null hypothesis was that there would be no difference in the incidence rate of reported asthma in the dental amalgam filling surface group as compared to other filling surface group.

Survey logistic regression modeling was utilized to evaluate the incidence rate of reported asthma among those persons in the dental amalgam filling surface group as compared to the other filling surface group. The covariates of race, gender, socioeconomic status, country of birth, age, education level, and serum cotinine were considered in adjusted models. In addition, survey frequency modeling was employed to evaluate the incidence rate of reported asthma in the dental amalgam filling surface group as compared to the other filling surface group. To adjust for differences in age between the two groups examined, the total number of weighted-person years (age of person at the time of the NHANES survey multiplied by WTMEC2YR) were examined.

Additional analyses were undertaken to evaluate the potential dose-dependent relationship between the incidence rate of reported asthma and the number of dental amalgam filling surfaces using survey logistic modeling. The covariates of race, gender, socioeconomic status, country of birth, age, education level, and serum cotinine were considered in adjusted models. Further, analyses were undertaken to determine, what, if any, threshold existed between the incidence rate of reported asthma and the number of dental amalgam filling surfaces.

Results

Table 1 displays the demographic characteristics of the population of persons examined in the NHANES database. The mean age in the dental amalgam filling surface group (49.5 years old) was older than the mean age in the other dental filling surface group (40.8 years old) and the male/female ratio was greater in the dental amalgam filling surface group (1.03) as compared to the other dental filling surface group

Table 1. Demographic characteristics of the dental amalgam filling group^a and the other dental filling exposed group^b examined in the NHANES database.

Parameter examined	Dental amalgam filling surface group	Other dental filling surface group
Age		
Mean age \pm std (age range: 20–80)	49.5 \pm 14.3	40.8 \pm 16.4
Gender (%)		
Male	49,623,180 (50.7%)	12,886,314 (40.6%)
Female	48,238,397 (49.3%)	18,830,243 (59.4%)
Race (%)		
Non-Hispanic White	68,446,836 (70.0%)	20,689,828 (65.2%)
Non-Hispanic Black	8,556,883 (8.7%)	3,045,288 (9.6%)
Non-Hispanic Asian	4,432,152 (4.5%)	2,401,620 (7.6%)
Hispanic	13,118,512 (13.4%)	4,755,022 (15.0%)
Other ^c	3,307,194 (3.4%)	824,799 (2.6%)
Country of birth (%)		
Born in 50 US states or Washington, DC	83,410,620 (85.2%)	24,698,794 (77.9%)
Others	14,450,957 (14.8%)	7,017,764 (22.1%)
Education level (%)		
Less than 9th grade	3,842,160 (3.9%)	1,216,557 (3.8%)
9–11th grade (includes 12 grade with no diploma)	6,458,284 (6.6%)	1,783,426 (5.6%)
High school graduate/GED or equivalent	20,457,952 (20.9%)	4,781,175 (15.1%)
Some college or AA degree	33,205,541 (33.9%)	10,806,527 (34.1%)
College graduate or above	33,897,639 (34.7%)	13,128,872 (41.4%)
Socioeconomic status (score range: 0–5)		
Mean PIR score \pm std	3.2 \pm 1.6	3.2 \pm 1.6
Exposure status		
Mean number of dental amalgam filling surfaces \pm std	7.5 \pm 6.5	0 \pm 0
Mean number of other dental filling surfaces \pm std	4.1 \pm 5.2	6.5 \pm 5.4
Cigarette smoking exposure (ng/mL)		
Mean serum cotinine \pm std	53.9 \pm 126	27.1 \pm 82.4
Period of examination		
Total weighted-person years	4,842,172,496	1,295,351,112
Reported to be diagnosed with asthma		
Frequency per 10,000 weighted-person years (n)	2.06 (23)	0.56 (3)

NHANES: National Health and Nutrition Examination Survey; std: standard deviation of the mean; GED: general education development; AA: associate degree; PIR: poverty income ratio.

^aThose weighted-persons with ≥ 1 amalgam filling surfaces.

^bThose weighted-persons with ≥ 1 other dental filling surfaces and 0 dental amalgam filling surfaces.

^cPersons of mixed race.

(0.68). When comparing the dental amalgam filling surface group to the other dental filling surface group, the racial distribution revealed more non-Hispanic White persons (70.0% vs 65.2%) and fewer non-Hispanic Asian persons (4.5% vs 7.6%) and the country of birth distribution revealed more born in the 50 US states or Washington, DC (85.2% vs 77.9%). The education level distribution revealed that there were more high school graduates in the dental amalgam filling surface group (20.9%) as compared to the other dental filling surface group (15.1%) and fewer persons were at least college graduates in the dental amalgam filling surface group (34.7%) as compared to the other dental filling surface group (41.4%). The socioeconomic status measurements were similar in the dental amalgam filling surface and other dental filling surface groups.

Table 2 shows the results of survey logistic regression models examining the incidence rate of reported asthma in the dental amalgam filling surface group in comparison to the other dental filling surface group. The risk of reported asthma was significantly increased by 4.46-fold in the unadjusted and 4.84-fold in the adjusted models when comparing the dental amalgam filling surface group to the other dental filling surface group.

Table 3 reveals the results of survey frequency modeling evaluating the incidence rate of reported asthma (per 10,000 weighted-person years) in the dental amalgam filling surface group as compared to the other dental filling surface group. The rate ratio=3.66 was significantly increased with an attributable rate difference=1.50 per 10,000 weighted-person years.

Table 2. Survey logistic regression models^a examining the incidence rate of reported asthma in the dental amalgam filling surfaces group as compared to the other dental filling surfaces group in the NHANES database.

Outcomes	Variables	Odds ratio	95% Confidence interval	p value
Asthma ^b	Dental amalgam filling surfaces group vs other dental filling surfaces group	4.46	1.25–16.0	0.021
	Dental amalgam filling surfaces group vs other dental filling surfaces group	4.84	1.33–17.6	0.017
	Non-Hispanic Asian vs non-Hispanic White	4.02	1.46–11.1	0.026
	Non-Hispanic Black vs non-Hispanic White	2.41	0.79–7.36	0.41
	Hispanic vs non-Hispanic White	1.20	0.35–4.19	0.60
	Other race vs non-Hispanic White	1.14	0.14–9.25	0.67
	Female vs male	2.68	0.67–10.7	0.16
	Socioeconomic status	1.01	0.56–1.82	0.97
	Born outside the USA vs born in the USA	0.44	0.16–1.19	0.11
	Age	1.01	0.97–1.06	0.59
	Less than 9th grade vs some college or associates degree	0.29	0.025–3.45	0.80
	9–12th grade (no diploma) vs some college or associates degree	0.44	0.10–1.89	0.86
	High school graduate/GED or equivalent vs some college or associates degree	0.10	0.02–0.54	0.034
	College graduate or above vs some college or associates degree	0.63	0.17–2.28	0.41
	Serum cotinine levels	0.99	0.98–1.00	0.05

NHANES: National Health and Nutrition Examination Survey; GED: general education development.

Bold-italicized values are statistically significant.

^aThe survey logistic model employed used stratum, cluster, and weight variables. The incidence rate of reported asthma within 2 years of the NHANES survey was evaluated among those weighted-persons with ≥ 1 amalgam filling surfaces (dental amalgam filling surfaces group) in comparison to those weighted-persons with ≥ 1 other dental filling surfaces and 0 dental amalgam filling surfaces (other dental filling surfaces group).

^bThe incidence rate of reported asthma was derived from NHANES survey data among those persons with reported asthma within 2 years of the NHANES survey collection. Those persons with reported asthma at any time prior to within 2 years of the NHANES survey collection were eliminated from the analyses.

Table 3. A summary of survey frequency modeling^a to evaluate the incidence rate of reported asthma in the dental amalgam filling surfaces group as compared to the other dental filling surfaces group in the NHANES database.

Exposure group examined	Total weighted-persons reported to be diagnosed with asthma ^b	Total weighted-person years	Outcome measurements
Dental amalgam filling surfaces group	997,426	4,842,172,496	
Other dental filling surfaces group	72,952	1,295,351,112	
Rate ratio (95% CI)			3.66 (1–14)
p value			<0.05
Attributable rate difference per 10,000 weighted-person years			1.50

NHANES: National Health and Nutrition Examination Survey; CI= confidence interval.

Bold-italicized values are statistically significant.

^aThe survey logistic model employed used stratum, cluster, and weight variables. The incidence rate of reported asthma within 2 years of the NHANES survey was evaluated among those weighted-persons with ≥ 1 amalgam filling surfaces (dental amalgam filling surfaces group) in comparison to those weighted-persons with ≥ 1 other dental filling surfaces and 0 dental amalgam filling surfaces (other dental filling surfaces group).

^bThe incidence rate of reported asthma was derived from NHANES survey data among those persons with reported asthma within 2 years of the NHANES survey collection. Those persons with reported asthma at any time prior were eliminated from the analyses.

Table 4 shows the results of survey logistic regression models examining the incidence rate of reported asthma in relation to the total number of dental amalgam filling surfaces for each person examined in the NHANES database. Overall, a significant dose-dependent relationship was observed between increasing total number of dental amalgam filling surfaces and the incidence rate of reported asthma in unadjusted (1.073-fold per dental amalgam filling surface)

and adjusted (1.076-fold per dental amalgam filling surface) models.

Table 5 further examines the relationship between the incidence rate of reported asthma (per 10,000 weighted-person years) and the total number of dental amalgam filling surfaces (the range of exposure was from 0 to 41 dental amalgam filling surfaces). The incidence rate of reported asthma was 0.56 among those persons examined with no

Table 4. Survey logistic regression models^a examining the incidence rate of reported asthma in relationship to the total number of dental filling surfaces for each person examined in the NHANES database.

Outcome	Variables	Odds ratio	95% Confidence interval	p value
Asthma ^b	Total number of dental amalgam filling surfaces	1.073	1.02–1.13	0.0036
	Total number of dental amalgam filling surfaces	1.076	1.03–1.12	0.0006
	Total number of other dental filling surfaces	0.97	0.89–1.05	0.44
	Non-Hispanic Asian vs non-Hispanic White	4.32	1.47–12.7	0.036
	Non-Hispanic Black vs non-Hispanic White	2.81	0.99–7.93	0.27
	Hispanic vs non-Hispanic White	1.30	0.38–4.49	0.60
	Other race vs non-Hispanic White	1.22	0.16–9.26	0.66
	Female vs male	2.88	0.68–12.2	0.15
	Socioeconomic status	1.07	0.66–1.74	0.79
	Born outside the USA vs born in the USA	0.48	0.18–1.29	0.14
	Age	1.02	0.97–1.06	0.49
	Less than 9th grade vs some college or associates degree	0.30	0.029–3.14	0.80
	9–12th grade (no diploma) vs some college or associates degree	0.51	0.15–1.75	0.71
	High school graduate/GED or equivalent vs some college or associates degree	0.11	0.02–0.53	0.030
	College graduate or above vs some college or associates degree	0.57	0.17–1.97	0.46
Serum cotinine levels	0.99	0.98–1.00	0.05	

NHANES: National Health and Nutrition Examination Survey; GED: general education development.

Bold-italicized values are statistically significant.

^aThe survey logistic model employed used stratum, cluster, and weight variables. The incidence rate of reported asthma within 2 years of the NHANES survey was evaluated in relation to the total number of dental filling surfaces for each person. The population examined included those persons in the dental amalgam filling surfaces group plus the other dental filling surfaces group.

^bThe incidence rate of reported asthma was derived from NHANES survey data among those persons with reported asthma within 2 years of the NHANES survey collection. Those persons with reported asthma at any time prior to within 2 years of the NHANES survey collection were eliminated from the analyses.

Table 5. A summary of survey frequency modeling to evaluate the incidence rate of reported asthma as compared to the total number of dental amalgam filling surfaces per person in the NHANES database.

Number of dental amalgam filling surfaces ^a (percentile)	Total weighted-persons with reported asthma ^b	Total weighted-person years	Incidence rate of persons with reported asthma (per 10,000 weighted-person years)
0 (0–28)	72,952	1,295,235,112	0.56
1 (29–37)	0	531,166,969	0.0
2 (37–45)	69,880	534,544,454	1.31
3 (46–52)	82,630	452,849,177	1.82
4 (53–58)	48,451	476,266,478	1.02
5 (59–63)	37,479	303,463,635	1.24
6 (64–68)	124,118	330,091,588	3.76
>6 (69–100)	634,869	2,213,790,195	2.87
>13 (90–100)	234,268	728,088,856	3.22

NHANES: National Health and Nutrition Examination Survey.

^aThe range of dental amalgam filling surfaces was from 0 to 41.

^bThe incidence rate of reported asthma was derived from NHANES survey data among those persons with reported asthma within 2 years of the NHANES survey collection. Those persons with reported asthma at any time prior to within 2 years of the NHANES survey collection were eliminated from the analyses.

dental amalgam filling surfaces. As the number of dental amalgam filling surfaces increased, the incidence rate of reported asthma increased from 0 among those with 1 dental amalgam filling to a maximum of 3.76 among those with 6 dental amalgam filling surfaces. The incidence rate of

reported asthma remained relatively similarly increased among those with 6 dental amalgam filling surfaces (3.76) as compared to those with >6 dental amalgam filling surfaces (2.87) or those with >13 dental amalgam filling surfaces (3.22).

Discussion

The present hypothesis-testing study is the first epidemiological study to evaluate the relationship between exposure to dental amalgam filling surfaces and reported asthma in American adults. The results revealed that the incidence rate of reported asthma was significantly increased among those persons in the dental amalgam filling surface group in comparison to those persons in the other dental filling surfaces group. The association between dental amalgam filling surfaces and the increased risk of reported asthma was observed to remain significant in statistical modeling even when considering multiple covariates. Finally, it was observed that there was a dose-dependent association between increasing number of dental amalgam filling surfaces and an increasing incidence rate of reported asthma.

The results from this study help to provide important considerations regarding the societal impacts of the association between dental amalgam filling surfaces and the increased risk of asthma. Survey frequency modeling revealed that the attributable rate difference per 10,000 weighted-person years for reported asthma was 1.50 among those in the dental amalgam filling surfaces group as compared to those in the other dental filling surfaces group. Since, there were a total of 97,861,577 weighted-persons in the dental amalgam filling surface group, this means that 14,679 weighted-persons ($97,861,577 \text{ weighted-persons} \times 0.00015 \text{ weighted-person years}$) were reported to be newly diagnosed with asthma associated with their dental amalgam filling surface exposure.

Unfortunately, asthma is known to have significant economic, personal, and societal impacts. It was previously reported in a detailed analysis of the cost of the asthma in the United States that the direct cost of asthma was US\$3259 per person per year.⁴ Therefore, the annual cost to the United States of asthma associated with dental amalgam fillings exposure from this study would be US\$47,838,861, and assuming that such persons lived an additional 25 years, this would mean that the costs over the 25-year period of such persons to the United States would be US\$1,195,971,525.

The results observed in this study need to be evaluated in the context of a number of previous studies. There are several previous studies suggesting an association between dental amalgam fillings and asthma. One study evaluated the impact of dental amalgam removal on clinical symptoms among 86 persons examined on average 10 months post-dental amalgam filling removal.⁸ Of the 86 persons examined, it was described that three persons were reported to have asthma and that among this group, 67% reported significant improvements in their asthma symptoms. A second study reported a case of a patient that showed significant improvement in her exercise-induced asthma following the removal of her dental amalgam fillings.⁹ A third study reported a case of a 15-year-old girl that developed severe asthma at 5 years.¹⁰ The girl received her first amalgam filling at 3 years. Four months prior to the onset of her severe asthma

at 5 years, the girl had a couple of deep cavities that were filled with dental amalgams. By the time the girl was 15 years old, she had 11 amalgam surfaces filled in her mouth with no other restorations present. The girl subsequently underwent dental amalgam filling removal. It was described by the investigators 6 weeks after her last dental amalgam fillings were removed that the patient was able to stop using asthma medication for the first time, since 5 years old. Seven months later, the patient was still without symptoms of asthma. At final examination 8 years later, she still had no asthma symptoms. Similar case reports of significant improvements in asthma following removal of dental amalgam fillings were described by other investigators.^{11,12}

By contrast, other investigators observed no association between dental amalgam fillings and the risk of asthma. For example, investigators undertook a cross-sectional survey with a questionnaire asking for symptoms of allergic disease during the previous year combined with current dental status of 348 students between the ages of 13 and 15 years.¹³ The investigators observed the students with dental amalgam fillings reported significantly fewer cases of asthma as compared to a group without dental amalgam fillings. The significant inverse relationship remained consistent when considering hereditary factors and parental smoking habits. The investigators in considering their results described that there are no reports on any biological mechanism that might explain a protective role of dental amalgam fillings on the risk of asthma. The investigators considered that systematic biases may be present in their study population with respect to materials used in various dental fillings.

In comparing the aforementioned studies to this study, there are a number of important limitations. First, most of the aforementioned studies examined persons undergoing dental amalgam filling removal. As a result, there may be selection biases present in those persons wanting to undergo dental amalgam filling removal. Namely, the persons examined by the investigators maybe more or less healthy than the general population and they may have preconceived perceptions regarding the risk/benefits of various dental filling materials. This study examined a representative sample of the US population that participated in NHANES independent of their health status or their dental filling status. It is the aim of NHANES to help determine the prevalence of major diseases and risk factors for diseases, and then, from such data, help to develop sound public health policy. Second, the aforementioned studies examined persons with various health complaints. It is not clear, what, if any, relationship existed between the health complaints examined and dental filling status (i.e. the health complaints may have started prior to the placement of dental amalgam fillings). This study examined persons with newly diagnosed asthma within 2 years of their dental filling status being determined. Further, a comparison was made between groups with dental amalgam filling surfaces and other dental filling surfaces. The groups assessed in this study were examined at the same

time and under the same circumstances with consideration of multiple other covariates. Thus, this study was able to isolate differences in material utilized in filling teeth and its relationship with newly diagnosed asthma. Third, this study, unlike the previous studies, was able to evaluate a potential dose–response relationship between exposure to increasing numbers of dental amalgam filling surfaces and the risk of asthma.

The results observed in this study are supported by biological plausibility data. Investigators previously evaluated Hg distribution in primates 1 year after placement of dental amalgam fillings as compared to untreated primates.¹⁴ They demonstrated significantly increased Hg concentrations within the respiratory tissues of primates with dental amalgam fillings as compared to untreated controls. Similar results were observed in adult sheep following placement of dental amalgam fillings.¹⁵ A subsequent study evaluated the genomic response in rat respiratory tissues following Hg vapor exposure.¹⁶ These researchers observed significant increases in the expression of genes encoding inflammatory responses, such as those for tumor necrosis factor (TNF)- α , TNF-receptor-1, interleukin (IL)-2, IL-7, prostaglandin E2 receptor, and heat-shock proteins. A recent epidemiological study observed a significant association between dental amalgam filling surface exposures and an increased risk of arthritis.¹⁷ These investigators suggested that the biological mechanism for dental amalgam adverse immunological effects in humans may involve an immune-mediated allergic-type reaction to metals, especially among immunologically susceptible persons, with the consequence that minute concentrations of an allergen can induce systemic reactions in sensitized individuals.

Study limitations

A potential limitation of this observational cross-sectional study is that study participants were not followed on a prospective longitudinal basis to evaluate the relationship between exposures and outcomes overtime. Furthermore, dental amalgam filling surface exposure was cumulative over many potential years of exposure, whereas the incidence rate of asthma was counted within the previous 2 years of the NHANES data collection. As a result, as with any observational cohort study, it was not possible to assign a direct causal relationship between exposures and outcomes.

There are several factors employed in this study that help to minimize this potential limitation. First, dental amalgam filling surface exposures and reported asthma diagnostic status were collected on an independent and contemporaneous basis. Second, time lapses between exposure and outcomes were minimized because reported new asthma diagnoses within 2 years of their dental filling status being assessed. Third, recall biases between exposures and outcomes were minimized in this study because these two variables were collected independent of one another, and

independent of the study design. Fourth, in support of the associations observed in this study, the results, as described previously, are biologically plausible and are supported by previous epidemiological studies. It is recommended that future studies further explore the phenomenon observed in this study within other populations examined on a prospective longitudinal cohort basis.

Another potential limitation of the data examined in this study is that the NHANES program uses the questionnaire method of data collection and participants may recall information wrongly or report information inaccurately. In considering this potential limitation, the NHANES employs highly trained study personnel to interview NHANES participants using detailed and consistent questions. Importantly, the observations made in this study regarding reported asthma are consistent with observations made in previous Centers for Disease Control and Prevention (CDC) asthma studies.¹⁸

Also, it was presumed that whatever limitations or errors may occur utilizing the NHANES questionnaire method of data collection, that such phenomena would have occurred with equal likelihood among dental amalgam filling surfaces and other dental filling surfaces groups examined. The impact on this study would have been to reduce the statistical power of this study. Despite this potential limitation, significant associations were observed between dental amalgam filling surfaces and the outcome of asthma. It is recommended that future studies employ other tests and measurements of asthma to more fully evaluate dental amalgam surface-associated effects on asthma.

The exclusion of persons with no dental filling surfaces was a further potential limitation of this study. It was hypothesized that there may be social and medical attributes associated with avoidance of dental filling surface placement. Therefore, by including only persons with at least one dental amalgam filling surface, it was attempted in this study to minimize potential confounding associated with lack of dental care.

Another potential limitation of this study is that the results observed could have occurred as a consequence of statistical chance. In considering this potential limitation, it is unlikely to explain the results observed in this study. First, a limited number of statistical tests were conducted, and all yield highly statistically significant results with similar directions and magnitudes of the results. Second, the results observed were biologically plausible. Third, several different types of statistical models with consideration of covariates all yielded similar statistically significant results.

Another potential limitation of this study is persons diagnosed with asthma may visit dental professionals differently than the general population. Specifically, a population-based study revealed that persons diagnosed with asthma were significantly less likely to receive dental care than the general population.¹⁹ This study attempted to address this phenomenon by analyzing reported cases of newly diagnosed asthma

within 2 years of the NHANES survey, when data were collected regarding the dental filling status of persons. As a result, it is assumed that more long-term trends in differential dental care among persons diagnosed with asthma versus the general population would be minimized.

Finally, while this study observed a significant association between dental amalgam filling surfaces with reported asthma diagnoses, this study did not examine the impact of many potential environmental and genetic susceptibility risk factors for asthma.²⁰ For example, a previous study in the 2005–2006 NHANES data revealed that several types of food allergies were significantly associated with an increased risk of asthma.²¹ Unfortunately, such data were not available for consideration in the 2015–2016 NHANES data examined. It would be worthwhile in future studies to further examine how various different environmental exposures and genetic susceptibility factors may work independently or synergistically with exposure to dental amalgam filling surfaces to induce asthma.

Conclusion

This cross-sectional study provides the first epidemiological evidence linking increasing dental amalgam filling surface exposures with reported asthma among adult Americans. It was observed that the association remained significant when considering multiple other covariates and different statistical models. Overall, it was estimated that 14,679 weighted-persons were reported to be newly diagnosed with asthma associated with their dental amalgam filling surface exposure with an additional annual total cost of US\$47,838,861. It is recommended that future longitudinal cohort studies be conducted for consistency with the observations made in this study and to further determine the association between dental amalgam filling surfaces and asthma in other populations. It is also recommended that dental amalgam fillings be eliminated from use in the routine practice of dentistry.

Authors' contributions

M.R.G. and D.A.G. contributed to the conception, analysis, and drafting of the article.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: M.R.G. and D.A.G. are directors of the non-profit Institute of Chronic Illnesses, Inc. and CoMeD, Inc. M.R.G. and D.A.G. own shares in EmeraMed Limited, a private company developing compounds to treat mercury toxicity.

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Ethics approval

The 2015–2016 National Health and Nutrition Examination Survey (NHANES) data collection methods were approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board (ERB) (Protocol#2011-17).

Informed consent

Each study subject provided written informed consent to participate in the National Health and Nutrition Examination Survey (NHANES) program.

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