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ORIGINAL ARTICLE

Long term changes in health complaints after removal of amalgam restorations

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ABSTRACT

Objective: Concerns over adverse effects of mercury released from dental amalgam sometimes lead patients to request removal of their amalgam restorations. Several studies report improvement of subjective health after removal of amalgam restorations, but the mechanisms are unclear. The aim of this paper is to present data on long term changes in intensity of health complaints after amalgam removal in a group of patients with health complaints self-attributed to dental amalgam. Data from the five years follow-up in a clinical trial are presented and related to potential determinants of change.

Materials and methods: Patients previously referred to a specialty unit for health complaints attributed to amalgam restorations were included in the study. The 20 participants who were allocated to the treatment group had all amalgam restorations removed and replaced with other dental restorative materials. Intensity of health complaints was calculated from questionnaire data and personality variables were measured by MMPI-2.

Results: At the follow-up five years after the amalgam removal was completed, intensity of general health complaints was significantly reduced (p=.001), but the symptom load was still high. The reduction was significantly correlated with concentration of mercury in urine at pre-treatment. There were no significant correlations with personality variables.

Conclusions: Removal of amalgam restorations was followed by a long term reduction of general health complaints, which was associated with mercury concentration in urine before amalgam removal. Additional studies are needed to confirm the potential mechanisms for the observed reduction.

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Dental amalgam; mercury; personality tests; subjective health complaint

Introduction

The last century dental amalgam has been extensively used in the treatment of caries lesions. Dental amalgam contains mercury (about 50% by weight), silver, tin and copper. In addition, some other elements may be included (e.g. zinc) [1]. Mercury is released from amalgam fillings in the mouth, both as elemental mercury vapour (Hg^0) and as mercury containing corrosion products [2–8]. After inhalation, elemental mercury vapour is absorbed in the lungs and distributed via blood. Elemental mercury can pass into the brain, where it is oxidized and stored [9]. Corrosion products from amalgam are dissolved in saliva and swallowed, causing local exposure of the oral and gastrointestinal mucosa [8,10–15]. A minor fraction of swallowed amalgam derived mercury is absorbed via the gastrointestinal mucosa into blood and distributed systemically [16].

All forms of mercury are toxic, and consequently there is a potential risk of both local and systemic adverse effects. Local allergic reactions to mercury released from amalgam restorations are well known and may result in lichenoid contact reactions in the oral mucosa [17]. Since the uptake of inorganic mercury in the gastrointestinal mucosa into blood is low [9], swallowed mercury released from amalgam has caught relatively limited attention.

The average daily dose of Hg^0 from amalgam fillings is estimated to be below 10 μg/day in subjects with an ordinary number of amalgam fillings [18,19], but can for some individuals be considerably higher [20]. After removal of all amalgam fillings and replacement with other dental restorative materials, mercury levels in plasma are significantly reduced [21–23]. Even though there is clear evidence that dental amalgam fillings contribute to the body burden of mercury, there is considerable debate as to whether mercury derived from amalgam causes systemic adverse effects. There are a few published case reports suggesting general allergic reactions to dental amalgam [24–26]. In addition, there are some reports suggesting that health complaints in individuals with elevated exposure to mercury released from dental amalgam can be reduced after amalgam removal [27–29].

Exposure to high levels of mercury vapour may cause a variety of effects. Since mercury can interfere with sulfhydryl groups in proteins, in principle all kinds of adverse effects are possible since almost any protein in the cell is a potential

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target for mercury [30]. It is generally accepted that exposure to high concentrations of elemental mercury vapour can cause tremor, stomatitis and erethism (i.e. irritability, excessive shyness, confidence loss and nervousness) [31]. In addition, gastrointestinal symptoms have been associated with occupational exposure to relatively high levels of mercury vapour [32] and with oral exposure to inorganic mercury compounds [30].

Questions have been raised about the safety of dental amalgam [33], and several expert reports on this topic have been funded by health authorities [34–40]. Reviews of the literature identify exposure to dental amalgam as a potential health risk due to the mercury content, but there is no convincing scientific evidence that dental amalgam is a causal factor for disease [41,42]. Nevertheless, some individuals have a high daily exposure to mercury from dental amalgam restorations which could result in slight effects on the kidneys and the central nervous system [20]. In addition, subclinical effects on the peripheral nervous system have been associated with exposure to amalgam fillings [43].

Multi-symptom conditions are common among patients in general clinical practice [44], and some patients attribute the health complaints to their amalgam restorations. These patients often have a number of unspecific symptoms; diffuse pain, general weakness, extreme fatigue, dizziness, memory problems and local complaints from the orofacial region (e.g. pain, taste disturbances, sore and dry mouth) [45,46]. Temporal relationships between dental treatment with amalgam and episodes of ill health may be one of several reasons for the attribution to amalgam [47]. The increased prevalence of both somatic and psychological complaints found in this group of patients indicates experience of ill health, and in a Norwegian study from 2003, the personality profiles showed several similarities with other groups of patients with long-lasting symptoms [48].

Many patients have concerns about their exposure to mercury from amalgam fillings and some have had their amalgam fillings removed due to existing health complaints. However, few prospective studies (with intensity of health complaints measured both before and after amalgam removal) have been conducted. Melchart et al. [49] conducted a randomized controlled trial on the effects on health from removal of amalgam restorations. Nerdrum et al. [50] used a quasi-experimental design and followed patients for seven years after amalgam removal. Stenman and Grans [28] followed patients with health complaints attributed to amalgam for one to three years. Statistically significant reductions of health complaints after amalgam removal were found in all studies [28,49,50].

In the present paper, results from a before-and-after study [51] on changes of health complaints after amalgam removal are reported. In the study, participants in the treatment group had all amalgam restorations replaced with other dental restorative materials. Participants were followed up three months, one year, three years and five years after amalgam removal. Sjursen et al. [51] have previously reported findings from the three years follow-up after amalgam removal. At the three year follow-up, the treatment group had a statistically significant decrease in intensity of general health complaints and intraoral health complaints compared with a reference group who was not offered amalgam removal. Several mechanisms for this were discussed including a placebo effect associated with the removal of amalgam fillings (or an effect from reduced nocebo) [51]. Several predictors associated with placebo responses have been described [52], and among other predictors personality variables (e.g. neuroticism) have been found to be associated with the likelihood of patients developing a placebo response [53].

Aim

The aim of the present project was to gain knowledge on long term changes of local and general health complaints, life satisfaction and personality variables after removal of all amalgam restorations in patients with health complaints attributed to dental amalgam. It was hypothesized that changes of health complaints could be related to personality variables. The association between change scores of health complaints and neuroticism was of specific interest, in addition to other potential predictors.

Materials and methods

Participants

All 20 participants in the treatment group of a before-and-after study [51] took part in the follow-up five years after completed amalgam removal. The participants (14 women and six men) had previously been referred to the Dental Biomaterials Adverse Reaction Unit in Bergen, Norway, for health complaints attributed to amalgam fillings. The inclusion and exclusion criteria are given in Table 1. Participants in the treatment group had all amalgam restorations replaced with other dental restorative materials by their own dentists according to clinical guidelines aiming at minimal exposure to mercury during removal sessions [54]. The treatment was covered by project funds. The treatment group was followed up at the Adverse Reaction Unit three months, one year, three years and five years after completed amalgam removal.

Table 1. Inclusion and exclusion criteria.

Inclusion criteria
Referred to the Norwegian Dental Biomaterials Adverse Reaction Unit for examination of health complaints attributed to amalgam fillings
Amalgam fillings still present
No diagnosed contact allergy to substances in resin-based dental materials
Health complaints from at least three different organ systems
Data on mercury in blood and urine from initial examination
Aged 25–55 at initial examination
Accepted to be contacted in a follow-up study
Exclusion criteria
Severe medical disorders (e.g. Multiple Sclerosis, ALS, severe rheumatoid arthritis)
Severe food allergies
Psychological difficulties or psychiatric disorders which could influence the dental treatment
Complicated therapy (severe periodontitis, high caries activity and/or need for complicated dental rehabilitation, e.g. bridges)
Inclusion criteria no longer fulfilled

Outcome variables

Primary outcome measures were (i) changes in self-reported health complaints, (ii) changes in personality variables and (iii) changes in life satisfaction. Health complaints were measured by numeric rating scales (using a scale from 0 to 10) for recently experienced local and general health complaints [55]. The questionnaires were administered prior to the study start (Q1), at pre-treatment before amalgam removal (Q Baseline), and at all follow-ups of the treatment group (Q 3 months, Q 1 year, Q 3 years, Q 5 years). Indices were calculated for local (i.e. intraoral and extraoral), and general health complaints [55]. In addition, the Subjective Health Complaint (SHC) Inventory [56] was used to measure health complaints at pre-treatment and all follow-ups of the treatment group. SHC consists of 29 items regarding common somatic and psychological complaints experienced during the last 30 days. A four-point scale is used to map the severity of each complaint. The categories are *none* (0), *some* (1), *much* (2) and *severe* (3).

Personality variables were measured by the Minnesota Multiphasic Personality Inventory-2 (MMPI-2) [57]. Both the 10 clinical scales (Hs, D, Hy, Pd, MF, Pa, Pt, Sc, Ma and Si) and the three validity scales (L, F, K) were calculated for all measure points. The PSY-5 scales (aggressiveness, psychoticism, disconstraint, negative emotionality/neuroticism and introversion/low positive emotionality) [58] were calculated from MMPI-2 data collected at pre-treatment.

As a global measure of life satisfaction (quality of life, well-being and happiness), the Cantril Ladder Scale was used [59]. The scale is displayed as a ladder with 10 steps. The instructions were 'Here is a figure representing the "Ladder of Life." The top of the ladder represents the best imaginable life for you. The bottom represents the worst imaginable life for you.' The participants were instructed to indicate on which step of the ladder (1–10) they felt they stood at present, 12 months ago and 12 months from now.

Follow-up examinations and questionnaires

Participants in the treatment group were examined by a dentist at three months, one year, three years and five years after removal of the amalgam restorations. Any revisions of the new restorations replacing the amalgam fillings were noted. At pre-treatment and at all follow-ups, the four questionnaires were used (the questionnaire covering self-reported health complaints, SHC, MMPI-2 and life satisfaction).

Determination of trace elements in serum and urine

Concentration of mercury, silver and tin in serum was determined in samples collected at pre-treatment examination and at three months, one and three years after amalgam removal by inductively coupled plasma-sector field mass spectrometry at ALS Scandinavia AB in Luleå, Sweden as described elsewhere [60,61]. Concentration of mercury in urine was determined in samples collected at pre-treatment examination and at the one year follow-up by cold vapour atomic absorption spectrometry [62].

Statistical methods

Mean change scores and 95% confidence intervals of the intensity of different health complaints were calculated by subtracting the value at pre-treatment from the value at the five-year follow-up. Within group changes over time were analysed by ANOVA for repeated measures. Greenhouse–Geisser correction was applied when the assumption of equal variances was violated. Standardized response means (SRM) were calculated by dividing the mean change by the standard deviation of the change scores. The significance of change over time for dichotomous variables within related samples was calculated by Cochran's *Q*-test. Associations between change scores for general index (follow-up score minus pre-treatment score) and potential predictors of the change scores were analysed with correlational analyses. For the statistical calculations, SPSS version 23.0 (IBM Corp., Armonk, NY) was used. p Values $<.05$ were considered significant.

Ethical approval and registration

The project protocol was approved by the Regional Committee for Medical Research Ethics in Western Norway (REK III no. 24.01) and registered at ClinicalTrials.gov (NCT00346944). Written informed consent was obtained from all participants.

Results

At study start the mean age of the treatment group was 48.9 years (SD 6.7). Education level, as estimated by number of years of education, was 11.5 (SD 3.6) years. At study start, 15 participants reported working full or part time, and four of these reported being on sick leave. Three participants had full time disability pensions, and two participants combined part time disability pension with working part time. Fifteen of the participants were married, two were cohabitants, one was unmarried and two were divorced. At pre-treatment, daily or almost daily use of analgesics the last 12 months was reported by 13 participants. There was no evidence of any significant change over time in the use of medication (Table 2). A detailed description of the group was given by Sjursen et al. [51]. During the treatment period, a total of 282 amalgam restorations were replaced with other dental restorative materials (Table 3). The majority of the new restorations were polymer-based composites (79%). In total, 18 (6.4%) of the new restorations had to be revised during the five year follow-up period. Fourteen of these were restorations with polymer-based composites. The main reason for revision was new caries lesions in conjunction with the restoration (secondary caries).

All participants ($n = 20$) were examined at the follow-up after five years. Some participants did not answer all questions in the questionnaires at all follow-ups, and thus, there are some missing data. Results from follow-ups after amalgam removal showed that there was a reduction of the general health complaints index from 44.6 at pre-treatment to 32.8 at the five year follow-up ($p=.001$; Table 4). Mean change scores

Table 2. Number of individuals with medication (daily or in short periods), the last 12 months registered in questionnaires at pre-treatment and one, three and five years after completed amalgam removal.

Type of medication	Pre-treatment ($n = 20$)	One year follow-up ($n = 20$)	Three year follow-up ($n = 19$)	Five year follow-up ($n = 19$)	p Value[a]
Analgesics	14	15	13	10	.274
Sedative medication	2	2	3	2	.500
Hypnotic medication	1	2	1	4	.250
Medication for heart diseases	1	1	4	2	.563
Blood pressure medication	3	4	6	4	.750
Asthma/allergy medication	6	8	6	4	.109
Antidepressants	3	2	3	2	1.00
Vitamins/dietary supplements	13	15	14	13	1.00
Complementary/alternative medication	10	10	6	10	.514
Medication for gastro-intestinal disorders	6	7	6	7	.927[b]
Medication for metabolism disorders	2	2	2	3	1.00[b]

[a]Significance for test of change over time (Cochran's Q; $n = 18$).
[b]$n = 17$.

Table 3. Restorative materials used to replace amalgam fillings. Number of restorations placed during the treatment period and number of revisions (and percent) during the five year follow-up period ($n = 20$).

Type of restoration	Number of restorations	Number of revisions	Revisions (%)
Gold inlays	3	0	0.0
Metalloceramic crowns	27	3	11.1
Metalloceramic bridges	1	0	0.0
Ceramic crowns	22	1	4.5
Ceramic inlays	3	0	0.0
Composite	224	14	6.3
Glass ionomer cements	2	0	0.0
SUM	**282**	**18**	**6.4**

for the general health complaints index were −11.3 (SD 14.3), −12.0 (SD 15.7) and −11.0 (SD 14.7) at follow-up after one, three and five years, respectively ($n = 18$). Negative numbers indicate improved health/reduction of health complaints. The effect sizes (SRM) were 0.79, 0.76 and 0.75. There were no significant changes of index scores for local (intraoral and extraoral) health complaints over time. The decrease of complaint intensity was most pronounced for pain from muscles and joints, gastrointestinal symptoms, fatigue and memory problems. Mean intensity of the separate health complaints at pre-treatment and at follow-ups at one, three and five years after amalgam removal is given in Figure 1. Analyses of changes of complaint intensity from pre-treatment to the five year follow-up showed that six items were significantly reduced (increased salivation, pain from muscles and joints, gastrointestinal symptoms, fatigue, memory problems and difficult to concentrate; Table 5). No items were significantly increased compared with the pre-treatment value.

The correlation between the general health complaints index score and the SHC total scale score was highly significant (Table 6). The total SHC score decreased from 22.7 at pre-treatment to 20.6 at the follow-up after five years (Table 7). However, the reduction of total SHC score was not statistically significant. Neither were there statistically significant changes of any of the SHC subscales over time (Table 7).

The mean values of the MMPI-2 subscales were stable over time (analysis of variance for repeated measures; $p > .05$). The scales Hypochondriasis ('Concern with bodily symptoms'; Hs), Depression ('Depressive Symptoms'; D) and Hysteria ('Awareness of problems and vulnerabilities'; Hy) were slightly elevated compared with the norm (mean T-score >65; Figure 2).

Current life satisfaction measured by the Cantril Ladder of Life Scale was higher at the five year follow-up than at pre-treatment (mean 6.9 vs mean 5.8; Table 8), but over time the mean values were not significantly different ($p = .166$). Generally, the mean value for current life satisfaction was higher than the mean value for the situation 12 months ago, and lower than the imagined situation 12 months ahead (Table 8).

Concentration of mercury and silver in serum was considerably reduced after amalgam removal. At follow-up after three months, the mean mercury concentration was reduced by 50% and the silver concentration was reduced by 70% (Table 9). Concentration of tin in serum was not reduced at follow-up at three months and one year after amalgam removal. However, at follow-up after three years the mean tin concentration was reduced by 90% ($p < .001$; Table 9). Urine samples were collected from 14 participants at pre-treatment (six patients left no urine sample at pre-treatment examination) and from 17 participants at the follow-up after one year (three patients left no urine sample at follow-up after one year). Concentration of mercury in urine was significantly reduced ($p = .004$; Table 9).

Correlational analysis was used in the search for predictors of change in intensity of general health complaints. Correlations between change scores for the general health complaints index at one, three and five years after amalgam removal, and pre-treatment values for index scores for general health complaints, age, number of amalgam surfaces, concentration of trace elements (Hg, Ag, Sn) in serum, concentration of mercury in urine, and scales from MMPI-2 were calculated. The results indicated that the correlations between general index scores at pre-treatment and change scores after one, three and five years, as well as the mean change score, were statistically significant (Table 10). Individuals with high scores at pre-treatment had, at an average, a larger reduction of the general health complaints score at follow-up than individuals with low scores at pre-treatment (Figure 3). Concentration of mercury in urine at pre-treatment and the difference between mercury concentration in urine at pre-treatment and at the follow-up after one year (calculated by subtracting the value at

Table 4. Mean values and standard deviations for index scores for intensity of intraoral, extra-oral and general health complaints at pre-treatment and follow-ups after three months, one, three and five years ($n = 17$).

	Pre-treatment		3 months		1 year		3 years		5 years		
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	p Value[a]
Intraoral index	6.5	(3.9)	6.6	(4.6)	4.5	(5.3)	5.1	(3.8)	6.7	(6.9)	.374
Extra-oral index	7.1	(7.1)	6.1	(6.4)	2.5	(3.2)	4.6	(4.4)	5.8	(7.4)	.055[b]
General index	44.6	(20.7)	40.6	(24.0)	33.5[c]	(18.9)	32.3[c]	(14.6)	32.8[c]	(18.2)	.001

[a]p Value from test of within subjects change over time.
[b]Adjusted for sphericity by Greenhouse–Geisser method.
[c]Significantly different from the value at pre-treatment (test of within-subjects contrasts).

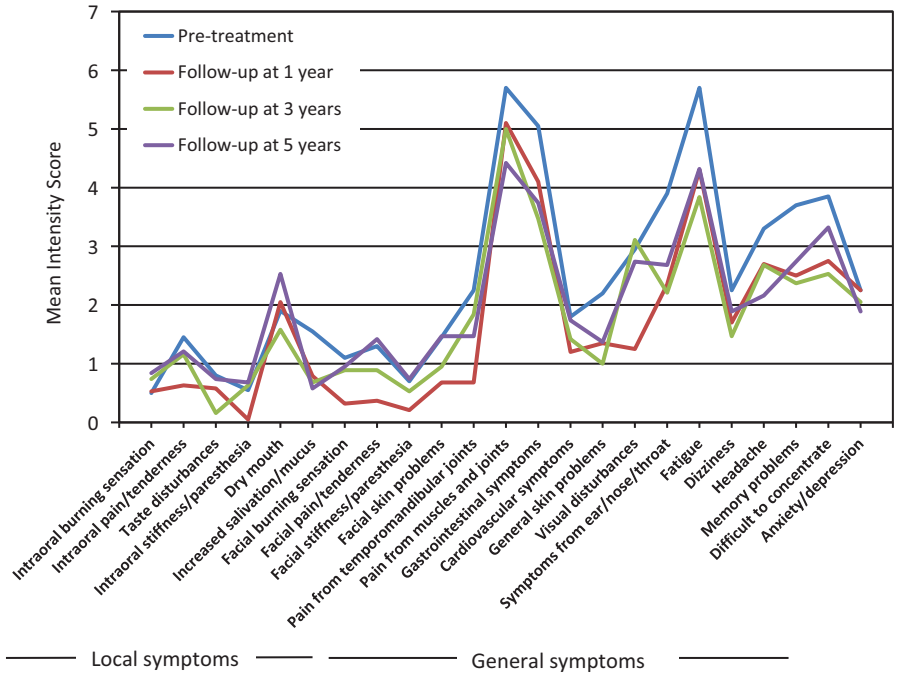

Figure 1. Mean intensity of local and general health complaints in the treatment group at pre-treatment ($n = 20$) and at follow-ups one ($n = 20$; for local symptoms $n = 19$), three ($n = 19$) and five years ($n = 19$) after amalgam removal.

Table 5. Mean intensity and standard deviations of health complaints at pre-treatment and at the five year follow-up. Mean change, 95% confidence intervals and p values are given ($n = 19$).

	Pre-treatment		Follow-up at 5 years				
	Mean	(SD)	Mean	(SD)	Mean change	95% C.I.	p Value
Intraoral burning sensation	0.5	(0.9)	0.8	(1.8)	0.3	−0.7 to 1.3	.522
Intraoral pain/tenderness	1.5	(1.9)	1.2	(2.0)	−0.3	−1.7 to 1.0	.625
Taste disturbances	0.7	(1.3)	0.7	(2.3)	0.1	−0.7 to 0.8	.891
Intraoral stiffness/paresthesia	0.6	(1.1)	0.7	(1.3)	0.1	−0.5 to 0.7	.734
Dry mouth	2.0	(2.7)	2.5	(2.5)	0.5	−0.5 to 1.6	.315
Increased salivation/mucus	1.4	(1.8)	0.6	(1.2)	−0.8	−1.6 to 0.0	**.048**
Facial burning sensation	1.2	(2.2)	1.0	(2.0)	−0.2	−1.5 to 1.1	.734
Facial pain/tenderness	1.4	(2.8)	1.4	(2.5)	0.1	−1.6 to 1.7	.946
Facial stiffness/paresthesia	0.7	(1.7)	0.7	(1.9)	0.0	−1.2 to 1.2	1.000
Facial skin problems	1.5	(2.2)	1.5	(2.4)	−0.1	−0.9 to 0.8	.899
Pain from temporomandibular joints	2.4	(2.9)	1.5	(2.0)	−0.9	−2.2 to 0.4	.179
Pain from muscles and joints	5.7	(2.9)	4.4	(2.6)	−1.3	−2.4 to −0.3	**.017**
Gastrointestinal symptoms	5.3	(2.4)	3.7	(2.7)	−1.6	−3.1 to −0.1	**.040**
Cardiovascular symptoms	1.9	(2.4)	1.7	(2.0)	−0.2	−0.8 to 0.5	.635
General skin problems	2.3	(2.5)	1.4	(2.0)	−0.9	−1.9 to 0.0	.058
Visual disturbances	3.0	(2.8)	2.7	(2.4)	−0.2	−1.3 to 0.9	.700
Symptoms from ear/nose/throat	3.8	(2.6)	2.7	(2.2)	−1.2	−2.4 to 0.1	.069
Fatigue	5.9	(2.8)	4.3	(2.6)	−1.6	−2.6 to −0.5	**.005**
Dizziness	2.4	(2.9)	1.9	(1.8)	−0.5	−1.6 to 0.7	.403
Headache	3.5	(3.7)	2.2	(2.3)	−1.3	−2.7 to 0.0	.058
Memory problems	3.9	(2.5)	2.7	(2.4)	−1.2	−2.0 to −0.3	**.011**
Difficult to concentrate	4.1	(2.5)	3.3	(2.2)	−0.7	−1.4 to 0.0	**.040**
Anxiety/depression	2.4	(2.6)	1.9	(2.2)	−0.5	−1.3 to 0.3	.226

pre-treatment from the value at follow-up) was significantly correlated with change scores at one and three years (Table 10, Figure 3). No other variables showed significant correlations with the change scores.

Eight of the 20 participants reported increased health complaints in conjunction with amalgam removal. Index scores for general health complaints for all follow-ups were available for seven of these participants and for 10 participants who did not report increased health complaints in conjunction with amalgam removal. Change over time of general health complaints by reaction status indicated slightly different patterns for the two groups (Figure 4). Analyses of variance for repeated measures indicated a statistically significant ($p<.001$) change over time, but the interaction (time × reaction status) was not statistically significant ($p=.126$). The MMPI-2 profile at pre-treatment of participants who reported increased symptoms in conjunction with amalgam removal was slightly different compared with the MMPI-2 profile in participants who did not report increased symptoms in conjunction with amalgam removal. The Depression ('Depressive Symptoms'; D), Hysteria ('Awareness of problems and vulnerabilities'; Hy) and Psychopathic Deviate ('Conflict, struggle, anger, respect for society's rules'; Pd) scales were significantly lower in participants who did not report symptoms in conjunction with amalgam removal ($p<.05$, Figure 5). The mean scores from the PSY-5 scales were not statistically different between participants who reported increased symptoms in conjunction with amalgam removal and participants who did not (data not shown).

Discussion

The main finding of this study was the long term reduction of general health complaints after removal of amalgam restorations in participants who attributed health complaints to their amalgam restorations. The decrease of health complaints was significantly correlated with mercury concentration in urine collected before the removal. Participants who had higher concentration of mercury in urine had, at an average, a greater reduction of general health complaints. Mercury concentration in urine is a suitable proxy for inorganic mercury exposure while mercury in plasma may reflect both inorganic and organic mercury exposure [63].

A decrease of health complaints after amalgam removal is consistent with other prospective studies [28,49,50,64]. The long term results from the follow-up five years after amalgam removal are in agreement with the findings in the treatment group at the three year follow-up [51] and with data from the study by Nerdrum et al. [50] seven years after amalgam removal. Intensity of pain from muscles and joints, gastrointestinal symptoms, and fatigue were significantly reduced both at the three year follow-up [65] and the five year follow-up. Memory problems and difficulties to concentrate were significantly reduced only at the five year follow-up, while taste disturbances and complaints from ear/nose/throat were significantly reduced only at the three year follow-up [65]. The SHC inventory showed no significant decrease of symptom load. Since the SHC inventory uses only four response categories (*none*, *some*, *much* and *severe*), it may not be sensitive enough to detect changes over time, even though the SRM of the change (0.79, 0.76 and 0.75) may be considered as a medium effect [66]. Even though the

Table 6. Correlations between index score for intensity of general complaints and total score from SHC at pre-treatment and at follow-up after three months, one, three and five years.

	Pre-treatment	3 months	1 year	3 years	5 years
Correlation coefficient (*r*)	0.762	0.814	0.763	0.672	0.808
p Value	<.001	<.001	<.001	.002	<.001
n	19	19	19	18	16

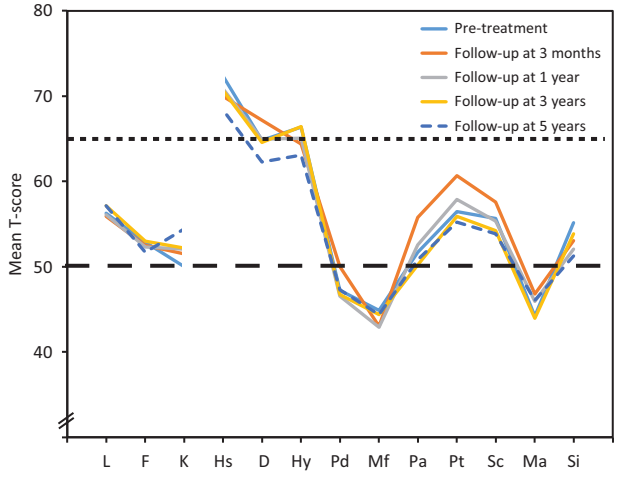

Figure 2. Results from MMPI-2 at pre-treatment and follow-up at three months, one, three and five years after amalgam removal. The lines are drawn between mean values ($n=17$) for the three validity scales and between mean values ($n=17$) for the 10 clinical scales. Abbreviations: L: Lie; F: Infrequency; K: Defensiveness; Hs: Hypochondriasis; D: Depression; Hy: Hysteria; Pd: Psychopathic Deviate; MF: Masculinity/Femininity; Pa: Paranoia; Pt: Psychasthenia; Sc: Schizophrenia; Ma: Hypomania; Si: Social Introversion.

Table 7. Results from the SHC (subjective health complaints inventory) at pre-treatment and follow-up after three months, one, three and five years. Mean values and standard deviations for total score and subscales are given.

	Pre-treatment		3 months		1 year		3 years		5 years		*p* Value[a]
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	
Total score ($n=14$)	22.7	(9.5)	22.7	(11.2)	20.4	(11.2)	20.1	(9.0)	20.6	(9.9)	.596
Musculoskeletal pain-severity ($n=14$)	7.9	(4.1)	7.6	(4.8)	7.8	(4.8)	7.2	(3.8)	8.6	(4.5)	.754
Pseudoneurology-severity ($n=14$)	5.6	(3.1)	5.4	(3.5)	4.6	(3.6)	5.1	(2.4)	5.7	(3.5)	.755
Gastrointestinal problems-severity ($n=14$)	5.3	(2.4)	5.3	(3.9)	4.6	(3.1)	4.8	(2.9)	4.0	(3.3)	.358[b]
Allergy-severity ($n=14$)	2.6	(2.9)	2.9	(3.1)	2.3	(2.2)	2.1	(2.1)	1.4	(1.6)	.187
Flu-severity ($n=15$)	1.5	(2.0)	1.6	(1.5)	0.9	(1.5)	0.8	(1.2)	0.9	(1.2)	.244

[a]*p* Value from test of within subjects change over time.
[b]Adjusted for sphericity by Greenhouse–Geisser method.

Table 8. Results from measures of life satisfaction estimated by cantril ladder of life scale at pre-treatment and follow-up after three months, one, three and five years. Mean values and standard deviations are given.

	Pre-treatment		3 months		1 year		3 years		5 years		
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	*p* Value[a]
Current ($n = 16$)	5.8	(1.8)	5.8	(2.2)	6.5	(2.0)	6.3	(1.7)	6.9	(1.7)	.166
12 months ago ($n = 14$)	5.4	(1.8)	5.7	(2.1)	6.0	(2.2)	5.3	(2.5)	5.6	(2.4)	.757
12 months ahead ($n = 13$)	7.1	(2.3)	7.8	(2.1)	7.7	(1.9)	7.8	(2.2)	7.9	(1.7)	.373

[a]*p* Value from test of within subjects change over time.

Table 9. Results from analyses of trace elements in serum (μg/L; $n = 18$) and urine (μg/g creatinine; $n = 11$). Mean and standard deviations are given.

	Pre-treatment		3 months		1 year		3 years		
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	*p* Value[a]
Serum									
Mercury	1.01	(0.46)	0.51[d]	(0.24)	0.52[d]	(0.32)	0.52[d]	(0.34)	<.001[b]
Silver	0.27	(0.24)	0.08[d]	(0.07)	0.09[d]	(0.07)	0.11[d]	(0.17)	.001[b]
Tin	2.48	(0.90)	2.45	(1.21)	3.14	(2.31)	0.25[d]	(0.31)	<.001[b]
Urine									
Mercury	4.07	(2.55)	n.a.		1.13[d]	(0.47)	n.a.		.004[c]

n.a.: not applicable.
[a]*p* Value from test of within subjects change over time.
[b]Adjusted for sphericity by Greenhouse–Geisser method.
[c]Paired *t*-test.
[d]Significantly different from value at pre-treatment (test of within-subjects contrasts).

Table 10. Correlation coefficients between change scores for general index and potential predictor variables.

	Change score at 1 year			Change score at 3 years			Change score at 5 years			Mean change score		
	Correlation	*p* Value	n	Correlation	*p* Value	n	Correlation	*p* Value	n	Correlation	*p* Value	n
Change score at 3 years	0.788	<.001	19	1.000	–	19	0.632	.005	18	0.927	<.001	18
Change score at 5 years	0.529	.020	19	0.632	.005	18	1.000	–	19	0.821	<.001	18
Mean change score	0.881	<.001	18	0.927	<.001	18	0.821	<.001	18	1.000	–	18
General index at pre-treatment	−0.464	.039	20	−0.733	<.001	19	−0.530	.020	19	−0.652	.003	18
Age	−0.234	.322	20	−0.152	.536	19	−0.071	.773	19	−0.232	.354	18
Amalgam surfaces	0.252	.285	20	0.199	.414	19	0.442	.058	19	0.326	.186	18
Concentration of mercury in serum at pre-treatment	0.103	.667	20	−0.125	.611	19	−0.084	.733	19	−0.053	.835	18
Concentration of silver in serum at pre-treatment	0.334	.150	20	0.141	.564	19	0.105	.668	19	0.240	.337	18
Concentration of tin in serum at pre-treatment	−0.047	.843	20	0.048	.845	19	0.148	.546	19	0.089	.727	18
Concentration of mercury in urine at pre-treatment [Hg(U)pre]	−0.586	.028	14	−0.613	.026	13	−0.339	.257	13	−0.573	.051	12
Concentration of mercury in urine at follow-up after one year [Hg(U)1yr]	0.098	.709	17	0.314	.237	16	0.130	.632	16	0.220	.430	15
Difference ([Hg(U)1yr] − [Hg(U)pre])	0.608	.047	11	0.665	.036	10	0.472	.169	10	0.616	.077	9
MMPI-scales[a]												
L	−0.391	.088	20	−0.299	.213	19	−0.385	.104	19	−0.413	.088	18
F	0.129	.589	20	0.079	.747	19	0.280	.246	19	0.209	.405	18
K	−0.192	.417	20	−0.116	.635	19	−0.126	.606	19	−0.167	.507	18
Hs	0.078	.742	20	−0.188	.441	19	0.219	.368	19	0.072	.776	18
D	0.075	.754	20	−0.087	.723	19	0.202	.407	19	0.109	.668	18
Hy	0.016	.947	20	−0.348	.144	19	−0.014	.953	19	−0.103	.683	18
Pd	0.099	.679	20	−0.133	.589	19	−0.002	.992	19	0.020	.937	18
Mf	0.068	.775	20	0.225	.354	19	0.201	.408	19	0.247	.324	18
Pa	−0.269	.252	20	−0.378	.110	19	−0.310	.197	19	−0.367	.134	18
Pt	0.025	.916	20	−0.138	.573	19	0.235	.333	19	0.088	.727	18
Sc	0.056	.814	20	−0.027	.911	19	0.256	.291	19	0.142	.575	18
Ma	−0.022	.926	20	−0.192	.432	19	0.145	.554	19	−0.008	.975	18
Si	0.012	.960	20	0.160	.512	19	0.207	.395	19	0.160	.527	18
Aggressiveness	0.053	.825	20	0.120	.624	19	−0.047	.849	19	0.041	.872	18
Psychoticism	0.396	.084	20	0.217	.373	19	0.291	.227	19	0.355	.148	18
Disconstraint	0.059	.806	20	0.156	.522	19	0.293	.224	19	0.204	.416	18
Negative emotionality/neuroticism	0.184	.438	20	−0.099	.686	19	0.119	.628	19	0.116	.646	18
Introversion/low positive emotionality	0.137	.564	20	0.086	.727	19	0.083	.736	19	0.125	.622	18

[a]Abbreviations are given in legend to Figure 2.

symptom load of general health complaints was significantly reduced after amalgam removal, the mean total symptom load measured by SHC was still considerably higher than the mean value of 10.58 reported for a sample aged 15–84 years from the general population in Norway [67]. However, despite the remaining high symptom load in the treatment group, participants described that the amalgam removal was associated with an experience of relief [68].

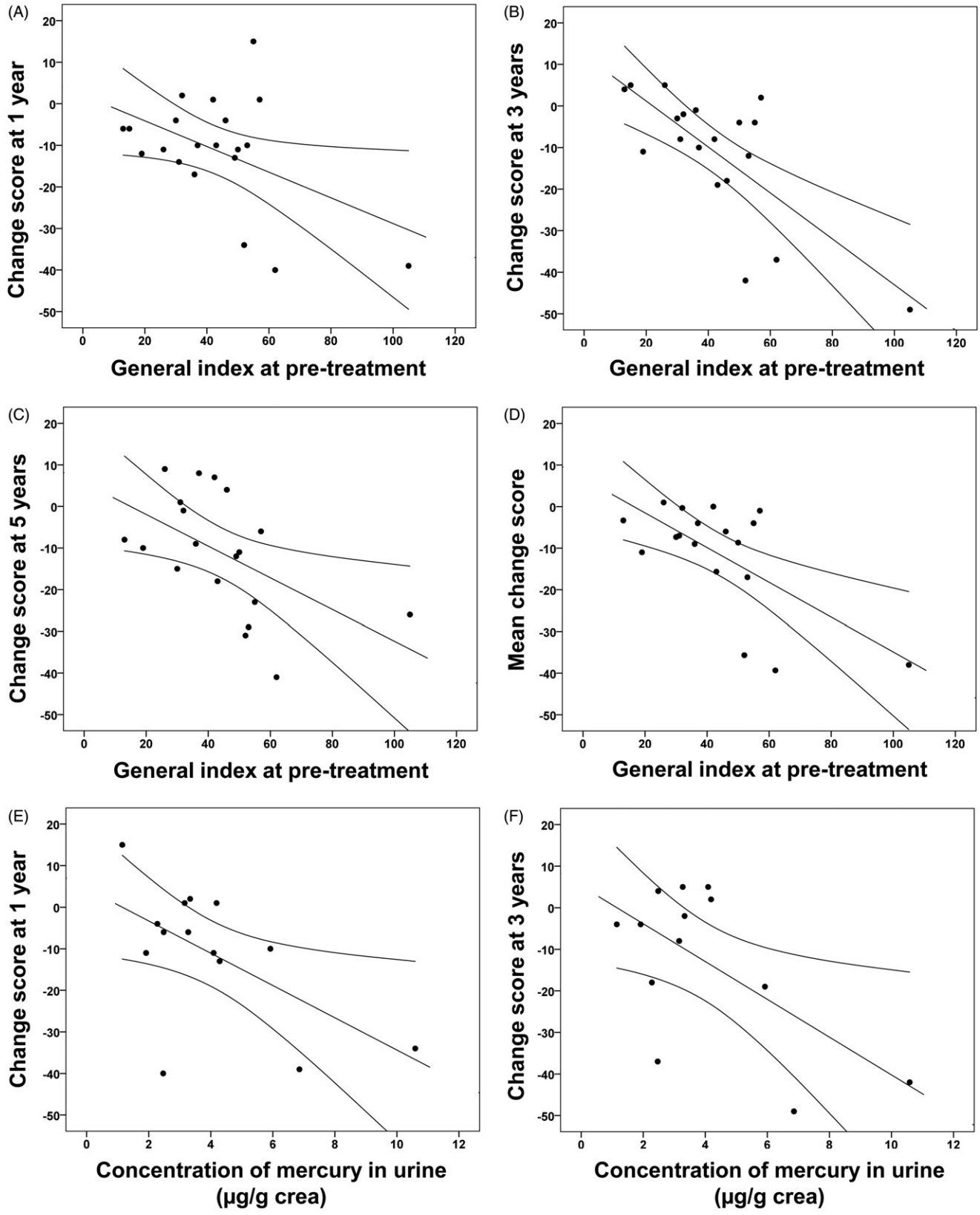

Figure 3. Scatter plots of the relationship between the general health complaints index score at pre-treatment and change scores at follow-up after one (A; $n = 20$), three (B; $n = 19$) and five years (C; $n = 19$), and the mean change score (D; $n = 18$). The relationships between concentration of mercury in urine at pre-treatment and change score at one year and three years are shown in panel E ($n = 14$) and F ($n = 13$). Regression lines with 95% confidence intervals are given.

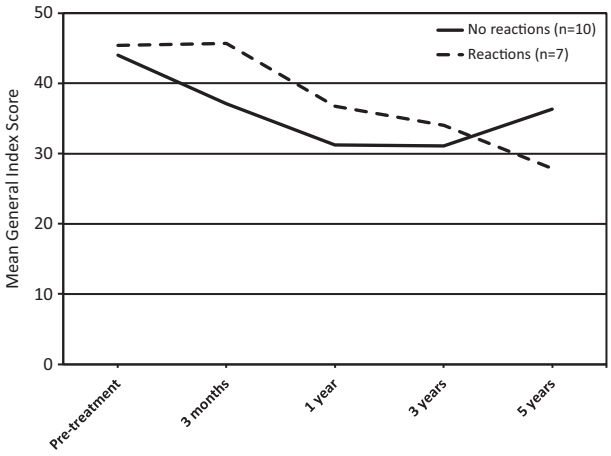

Figure 4. Intensity of general health complaints over time for participants who reported increased symptoms in conjunction with amalgam removal ($n = 7$) and for participants who did not report increased symptoms in conjunction with amalgam removal ($n = 10$).

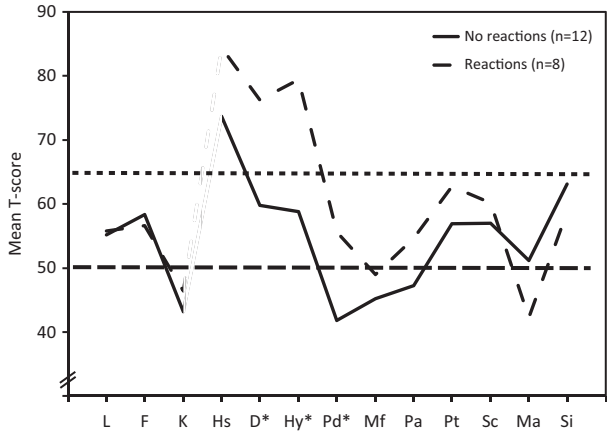

Figure 5. MMPI-2 profiles at pre-treatment for participants who reported increased symptoms in conjunction with amalgam removal and for participants who did not report increased symptoms in conjunction with amalgam removal. Abbreviations are given in legend to Figure 2.

As expected, mercury concentration in serum and urine was significantly reduced after amalgam removal, which is in agreement with other studies [23,69,70]. In addition, concentration of both silver and tin in serum was reduced.

Most of the knowledge about toxic effects from exposure to elemental mercury vapour is from studies on workers with occupational exposure. Smith et al. [32] reported effects of exposure to mercury vapour in workers in a chlor-alkali plant. Increased exposure was associated with increased prevalence of a number of medical findings (including loss of appetite, loss of weight, objective tremor, insomnia, shyness, diastolic blood pressure, frequent colds, nervousness and diarrhoea). Even though, dental personnel are exposed to considerably lower levels of mercury vapour, neurobehavioural effects and cognitive symptoms related to occupational exposure to mercury have been reported [71–73]. Thus, symptoms related to toxic effects from exposure to elemental mercury vapour can be categorized as unspecific, and studies have found similar complaints to be relatively common in the general population [67]. However, at a group level, people with a high number of amalgam restorations do not have more health complaints or more ill health than people with few amalgam restorations [42,74]. Thus, epidemiological studies on amalgam fillings and health complaints do not leave any support for a direct dose–response relationship on a population level. A central question is if the observed reduction of pain from muscles and joints, gastrointestinal symptoms, and fatigue could be caused by the reduced exposure to mercury (or other metals) released from the amalgam fillings. A statistically significant correlation between reduction of general health complaints and reduction of mercury concentration in urine has been reported earlier [29] and suggests a causal relationship. It has been hypothesized that there may be subgroups in the population with increased genetic sensibility to mercury [40]. In theory, this subgroup could be 'amalgam sensitive' and experience adverse reactions at lower exposure levels than the general population. Idiosyncratic sensitivity to mercury has been described [75], and has later been associated with genetic polymorphisms [76]. Several genetic polymorphisms may have relevance for mercury metabolism and neurotoxicity, but this far there is no clear evidence that genetic polymorphisms strongly modify susceptibility to mercury-induced neurotoxicity [77]. Animal experiments have shown that metal exposure from dental amalgam may contribute to immunological aberrations in genetically susceptible strains [78,79]. Possible effects on the immune system from exposure to low levels of mercury [80,81] or interactions between the immune system and exposure to corrosion products from amalgam restorations may be of importance and additional studies are warranted [82].

There may be several other possible explanations for the observed reduction of health complaints [51]. One of these is that the reduction may have been caused by expectations (placebo) or discontinued nocebo effect (given that amalgam fillings contain and release toxic corrosion products including mercury, patients may expect to get adverse health effects from their amalgam fillings). One of the hypotheses of the project was that changes in intensity of health complaints after removal of amalgam fillings would be associated with personality variables and the association between change scores of health complaints and neuroticism was of specific interest. The results from the correlational analyses did not leave any statistically significant support for this hypothesis. It has been reported that neuroticism was a negative predictor for the formation of placebo effects [53]. However, this finding was not confirmed by Darragh et al. [83], who reported that neuroticism was related to greater placebo responses. A recent study on nocebo pain could, however, not relate nocebo to neuroticism [84]. Nevertheless, it cannot be excluded that expectations, (negative or positive) may have impact on the results [52].

An important limitation of the present study is that the sample size of 20 individuals permits only detection of strong correlations. There was 80% power to detect a correlation of 0.58. Thus, there was not enough power to detect small (0.1–0.3) and medium (0.3–0.5) correlations. Nevertheless, if there were strong correlations between reduction of general health complaint intensity and the MMPI-2 scales, there was a reasonable chance to detect this in the present project.

Conclusions

In patients who attribute health complaints to their amalgam restorations, removal of amalgam restorations was followed by a reduction of the concentration of mercury and silver in serum and a long term reduction of self-reported general health complaints. The finding of a dose–response relationship should be interpreted in relation to similar studies and may contribute to the assessment of causality [85]. There were no statistically significant changes in measures of personality variables or life satisfaction. In addition to mercury exposure, several other factors may be of importance for the long term reduction of general health complaints. There was, however, no statistical evidence of any consistent impact from age, number of amalgam surfaces, concentration of mercury in serum, or personality variables.

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Disclosure statement

The authors have no conflicts of interest to declare.

Notes on contributors

LB conceived of the study, served as principal investigator, had the primary responsibility for statistical analysis and wrote the manuscript; TTS collaborated in collection, analysis and interpretation of the data and writing the manuscript; KD collaborated in study design, was responsible for the personality tests, participated in the clinical part of the study, collaborated in interpretation of the data and in preparation of the manuscript; GBL collaborated in study design, analysis and interpretation of the data and writing the manuscript; TLLB collaborated in the clinical study, interpretation of the data, and writing the manuscript; JS collaborated in the clinical study, interpretation of the data and in preparation of the manuscript; BFL collaborated in study design, participated in the clinical part of the study, and in preparation of the manuscript.

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