Removal of dental amalgam restorations in patients with health complaints attributed to amalgam: A prospective cohort study

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Summary

Background: The Norwegian Ministry of Health and Care Services initiated a project including experimental treatment for patients with health complaints attributed to amalgam restorations.

Objective: The aim was to evaluate changes of general health complaints in patients who participated in the project and had all amalgam restorations removed.

Methods: The project was designed as a prospective cohort study and organised by the Dental Biomaterials Adverse Reaction Unit in Bergen, Norway. The dental treatment was provided by the patient’s local dentist. The main target group consisted of patients with medically unexplained physical symptoms, attributed to dental amalgam restorations (Amalgam cohort). The primary comparison group consisted of patients with medically unexplained physical symptoms without attribution to dental amalgam restorations (MUPS cohort). Primary outcome was self-reported general health complaints (GHC index) at follow-up 12-months after completed amalgam removal.

Results: In the Amalgam cohort, a significant reduction of GHC index from 43.3 (SD 17.8) at baseline to 30.5 (SD 14.4) at follow-up (mean reduction 12.8, SD 15.9; n = 32; P < .001) was observed. The change scores for GHC index indicated that the reduction of complaints was significantly higher (P = .004) in the Amalgam cohort compared with the MUPS cohort (mean reduction 1.2, SD 12.3, n = 28). After adjustment for age, gender, education and baseline GHC index, the mean adjusted difference was −8.0 (95% confidence interval from −15.4 to −0.5; P = .036).

Conclusion: In a group of patients with medically unexplained physical symptoms, which they attributed to dental amalgam restorations, removal of amalgam restorations was followed by a significant reduction of health complaints.

KEYWORDS
dental amalgam, dental care, dental materials, humans, prospective studies, subjective health complaint
Dental amalgam is a mixture of metallic mercury and an alloy mainly consisting of silver, tin, copper and zinc. The mixing ratio between mercury and the alloy is approximately 1:1 by weight. Mercury is continuously released from the amalgam restorations, absorbed and stored in the body, including the brain, and one of the drawbacks of dental amalgam is the potential risk for chronic mercury toxicity. Since almost any protein can be a potential target for mercury, in principle, all kinds of adverse effects from mercury exposure could be possible. The described variability in symptoms and signs from elemental mercury vapour exposure could possibly reflect various genetic polymorphisms.

Even though the use of dental amalgam has decreased in the last decades in favour to polymer-based restorative materials, a large number of people will have amalgam fillings in their teeth for decades ahead, since well-placed dental amalgam restorations usually hold for many years. In the general population, there is a significant concern about potential negative health effects of exposure to mercury released from dental amalgam restorations. In Norway, an estimated 8 per cent of the adult population has had their amalgam fillings removed for health reasons only. Thus, in 2006 the Norwegian Ministry of Health and Care Services initiated a project for patients with health complaints, which they attributed to amalgam or other dental materials. The project included removal of existing amalgam fillings as experimental treatment, and an evaluation of possible changes in health status related to the amalgam removal. A study protocol was developed by a task group appointed by the Norwegian Directorate of Health. The Dental Biomaterials Adverse Reaction Unit, organised at Uni Research AS in Bergen and funded by the Ministry of Health and Care Services, was appointed by the Norwegian Directorate of Health to implement the project.

Amalgam-attributed health complaints are heterogeneous and a variety of symptoms has been attributed to amalgam. Since the symptom pattern is unspecific, amalgam-attributed health complaints are difficult to validate and are, for the most part, quantified using symptom scales. Notably, amalgam-attributed health complaints are largely similar to complaints experienced by patients with so-called ‘medically unexplained physical symptoms’ (MUPS) or ‘medically unexplained symptoms’ (MUS). In order to operationalise and measure patients’ subjective health complaints, the MUPS concept was applied to patients who attributed their health problems to amalgam. This strategy allowed the comparison to patients suffering from MUPS, without symptom attribution to amalgam, in order to control for the natural history of health complaints and regression to the mean.

### Objective of the study

The aim of the present study was to evaluate changes of general health complaints after removal of dental amalgam fillings in patients with MUPS who attribute their health complaints to amalgam fillings.

### Methods

#### Study design

The project was designed as a prospective cohort study using a non-equivalent comparison-group design with pre- and post-test. Three groups were recruited separately: The main target group consisted of patients with MUPS, which they attributed to dental amalgam restorations (Amalgam cohort). Furthermore, these patients expressed their wish to have their amalgam fillings removed and had to fill in and sign an application to participate in the study. Two groups served as comparison groups: One primary comparison group of patients with MUPS recruited from general practice (MUPS cohort), and one secondary comparison group of participants, who identified themselves as healthy (Healthy cohort). The Healthy cohort was primarily recruited at dental practices. Participants in the comparison groups were recruited regardless of amalgam status. The study was not purely observational, but quasi-experimental, since patients in the Amalgam cohort had to actively apply and fulfil some criteria.

#### Setting

The Dental Biomaterials Adverse Reaction Unit in Bergen organised the study in collaboration with the Research Unit for General Practice in Bergen, both being located at Uni Research Health in Bergen, Norway. Several Regional Dental Centers of Competence were appointed for the clinical post-treatment examination of patients in the Amalgam cohort.

#### Participants

Inclusion criteria for all three groups were age between 20 and 70 years, permanent residence in Norway and ability to comply with the protocol. Specific eligibility criteria for each of the three cohorts are listed in Table 1, a flowchart and a summary of the recruitment procedures are given in Figures 1 and 2. Recruitment period was from March 2013 to December 2015. Further details regarding the recruitment procedures for the three cohorts are presented in the following sections.

##### Amalgam cohort

In November 2013, the Directorate of Health sent a letter with information about the project to all dentists and general physicians (GPs) in Norway. They were informed about the inclusion criteria and that the patients had to be examined according to the official guidelines for examination and treatment of patients with adverse reactions related to dental materials published by the Norwegian Directorate of Health prior to inclusion in the project. Information was also given via the internet pages of the
TABLE 1 Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amalgam</td>
<td>Age between 20 and 70 years</td>
<td>Patient’s dentist assesses that there are no major risks for complications following amalgam removal (eg need for root canal treatments or extractions)</td>
</tr>
<tr>
<td>MUPS</td>
<td>Permanent residents in Norway</td>
<td>Subjective symptoms without corresponding objective findings after medical examination(s), including symptoms not explained by patient’s diagnoses</td>
</tr>
<tr>
<td>Healthy</td>
<td>Able to comply with the protocol</td>
<td>Moderate or severe functional impairment (physician-assessed)</td>
</tr>
<tr>
<td></td>
<td>Health complaints attributed (by the patient) to dental amalgam restorations</td>
<td>Subjectively healthy (self-assessed)</td>
</tr>
<tr>
<td></td>
<td>No attribution to amalgam and no explicit wish to remove amalgam</td>
<td>No medication (intake of vitamins and minerals allowed)</td>
</tr>
<tr>
<td></td>
<td>≥ 3 months duration of the health complaints attributed (by the patient) to amalgam restorations</td>
<td>Exclusion criteria</td>
</tr>
<tr>
<td></td>
<td>Presence of at least one amalgam filling</td>
<td>Pregnancy (or planned pregnancy) and lactation</td>
</tr>
<tr>
<td></td>
<td>Wish to have all amalgam fillings removed</td>
<td>Life-threatening disease</td>
</tr>
<tr>
<td></td>
<td>Examination by patient’s physician and dentist according to guidelines from the Norwegian Directorate of Health</td>
<td>Patients with ongoing cancers, severe cardiopulmonary, neurological, or psychiatric diseases (assessed by the GP)</td>
</tr>
<tr>
<td></td>
<td>Diagnosed diseases adequately treated</td>
<td>Organic cause of all complaints (according to checklist, see text)</td>
</tr>
<tr>
<td></td>
<td>Patient’s general practitioner/family physician and dentist assess that the general and dental health of the patient most likely not will deteriorate due to participation in the project</td>
<td></td>
</tr>
</tbody>
</table>

Note: Abbreviation: n.a., not applicable.
FIGURE 1 Flowchart showing number of participants
Patients who had longstanding health complaints attributed to dental amalgam fillings, and who were interested to participate in the project were instructed to send an application together with declarations from the patient’s dentist and the patient’s general practitioner to the study office. The dentist had to declare whether the patient was fully examined and treated with regard to oral diseases and conditions, and whether medical conditions and diseases were adequately taken care of. The dentist was also asked whether the patient’s health complaints had lasted for 3 months or longer. In addition, we asked for the dentist’s assessment (clinical judgment), if the patient’s dental and medical conditions were likely to deteriorate due to participation in the project. The patients were informed about potential risks for adverse events associated with the removal of amalgam fillings and replacement with new restorative materials. The risk for complications (e.g., endodontic treatment and extractions) due to the dental treatment should be low and acceptable, as assessed by the dentist (clinical judgment). The dentist should also include a treatment plan, dental X-rays, and an estimation of the treatment costs to the application.

The declaration from the GP included the following questions: (a) Is the patient fully examined with regard to medical conditions and are the patient’s diseases adequately treated? (b) Have the patient’s health complaints lasted for 3 months or more? (c) Do you think the patient’s dental or medical conditions are likely to deteriorate due to participation in the project? Actual diagnoses and actual medication should be declared as well.

After application of the inclusion and exclusion criteria (Table 1) and after having returned the signed informed consent, the patient was included in the study (Figure 2). Questionnaire 1 (Q1; baseline) was mailed to the patient, and after having returned it to the study office the patient was sent a letter with instructions to make an appointment with his or her GP. The GP was asked to collect a blood sample and to complete a short questionnaire about the medical examination of the patient, diagnoses and prescribed medication the last 12 months. A question regarding the GP’s assessment of the functional impairment of the patient was also included in the questionnaire. When the GP’s assessment was received by the study office and the serum sample was stored in the biobank, the dentist was informed that the removal of amalgam fillings could start.

The dental treatment included removal of all visible amalgam fillings according to pre-defined procedures. Both the dentist and the patient completed a diary to document all treatment sessions in
detail (use of rubber dam during amalgam removal, restorative materials, local anaesthesia, complications etc).

After completed removal, the patients were examined by a dentist affiliated to a Regional Dental Center of Competence or appointed by the study office. The cost of the dental treatment (amalgam removal and replacement with other types of restorations) was paid by the project according to pre-defined rules and administered by the Regional Dental Centers of Competence.

One year after the last amalgam removal session, a follow-up questionnaire (Q2; follow-up) was sent by mail to the patient and the patient was asked to make an appointment with the GP for assessment and collection of a blood sample (Figure 2).

### 2.3.2 MUPS cohort

Patients in the MUPS cohort were recruited by their family physician/GP. GPs in two counties in Norway were invited to identify consecutive patients who fulfilled inclusion criteria (Table 1). After a regular consultation of the GP, patients who fulfilled criteria were given an envelope with written information about the study. Patients who were interested to participate in the study (labelled as “Changes of health complaints over time”) signed the written informed consent and sent it to the study office. Questionnaire 1 (Q1; baseline) was sent to all participants who had returned the signed consent form. After completion of Q1, the participants received a letter with instructions to make an appointment with the GP for collection of a blood sample and to ask the GP to complete a short questionnaire about the medical examination of the patient including an assessment of functional impairment, diagnoses and prescribed medication over the last 12 months.

Two years after completion of Q1, a new questionnaire (Q2; follow-up) was mailed and the patient was asked to make an appointment with the GP for a new assessment and collection of a blood sample.

### 2.3.3 Healthy cohort

Participants in the Healthy cohort were mainly recruited via dental clinics participating in the project and should have no chronic diseases or permanent medication (but intake of vitamins and minerals was allowed), they should not be pregnant (or having plans to become pregnant) or breastfeeding (Table 1).

After returning the signed written informed consent, Questionnaire 1 (Q1; baseline) was mailed to the participants. After returning Q1 to the study office, the participants were asked to make an appointment with the GP for collection of a blood sample. Two years after completion of Q1, a new questionnaire (Q2; follow-up) was mailed to the participants and they were asked to make an appointment with the GP for collection of a blood sample. After completion of each questionnaire and having returned it to the study office, the participants in the Healthy cohort were sent five lottery tickets (at a total worth of 125 NOK; approximately 13 €) as compensation for their time.

### 2.4 Timeline of the study

The timeline for the study is shown in Figure 1. The duration of amalgam removal varied between the participants, but it was anticipated that the treatment period, at an average, could last for one year. Thus, the follow-up questionnaire (Q2) of the MUPS cohort and the Healthy cohort was mailed two years after completion of the first questionnaire (Q1). The follow-up period was from June 2015 to September 2018.

### 2.5 Variables

Primary outcome was the General Health Complaints index (GHC index) at 12-month follow-up after completed amalgam removal. The GHC index is the sum score of 12 items scored by use of numeric rating scales (range 0 to 10) of the following items: Musculoskeletal complaints, gastrointestinal complaints, cardiovascular complaints, skin problems, complaints related to eyes/sight, complaints related to ears/hearing/nose/throat, tiredness, dizziness, headaches, memory problems, difficulty concentrating and anxiety/depression. Secondary outcomes were the SF-36 Physical and Mental Component Summary scores (SF-36v2 Health Survey; Medical Outcomes Trust and QualityMetric Incorporated).

Other secondary outcomes included the Giessen Subjective Complaints List (GBB-24, total score), a 50 items symptom list previously used in the German Amalgam Trial (GAT), the Hospital Anxiety and Depression Scale (HADS), inorganic mercury in serum, cytokine profile, health resource use, sick leave and costs. Results from these outcomes will be reported elsewhere.

Potential confounders to be considered were age, gender and education. Attribution of health complaints to dental amalgam fillings was considered as a potential effect modifier. In order to obtain a quantitative measure of attribution to amalgam, the item ‘Amalgam dental fillings’ included in the Modern Health Worries scale was used. The item was rated by the participants on a five-point scale, ranging from 1 (no concern) to 5 (extreme concern). Although being represented on an ordinal scale, this variable was included in the analysis as approximately interval scaled. In order to assess potential sources of bias, background variables (age, gender, education, civil status, smoking habits and GHC index at baseline) for the main target group were compared with the primary comparison group. In addition, age, gender, education and baseline value of the outcome were included in the adjusted analyses.

### 2.6 Data sources

Data were retrieved from questionnaire Q1 and Q2, and from the questionnaire completed by the patient’s GP after examination. Missing data for single items of the GHC index were replaced by the cohort mean value for the respective item. If data for more than 50% of the items were missing, the sum score was coded as ‘missing’. 
2.7 Sample size and power calculations

Using data from a previous study\(^{22}\) the following initial assumptions were made: (a) A mean difference in GHC-index score for general health complaints of 5.0 between the amalgam cohort and the MUPS cohort (corresponding to a mean difference before-after of 10.0 in the amalgam group versus a mean difference of 5.0 in the MUPS cohort). (b) A common within-group standard deviation of 10.0. Based on these assumptions and with criterion for significance \(P = 0.05\) with two-tailed tests, a sample size of 100 patients in the amalgam cohort and 50 patients in the MUPS cohort would give the study a power of 82\% to yield a statistically significant result. Based on a more realistic ratio of the group sizes of 1:1 for amalgam and MUPS cohorts, a secondary power analysis showed a similar power of 83\% for a total of 60 patients given a mean difference of 2.5 in the MUPS cohort (means a between-group difference of 7.5 in GHC change scores with all other assumptions identical).

2.8 Quantitative variables

Continuous variables were presented as mean values with standard deviation (SD) and in box-plots indicating median, percentiles, max and min values. In addition, 95\% confidence intervals for mean values were presented when appropriate. Categorical variables were presented as frequencies.

2.9 Statistical methods

The statistical model was built upon the pre-defined null-hypothesis that there were no differences between the Amalgam cohort and the MUPS cohort with respect to the change scores for the primary outcome variable. Statistical testing of potential differences between the groups was performed by analysis of variance complemented by an adjustment for covariates (baseline value of the primary change score, age, gender and education).\(^{25}\) In addition, predictors of change of the primary outcome measure at follow-up were subject to multivariate analysis including the potential effect modifier. The comparison between treatment group and comparison group included only patients who responded to the follow-up questionnaire (per-protocol analysis). When appropriate, \(P\)-values were adjusted for multiple comparisons using the Bonferroni correction. Analyses were performed using IBM-SPSS (IBM Corp. IBM SPSS Statistics for Windows, version 25, Armonk, NY, USA).

2.10 Ethical aspects

The study was approved by the local research ethics committee (REK2012/331) and registered at ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT01682278; NCT01682278). A stop group was appointed consisting of the Advisory Board of the Dental Biomaterials Adverse Reaction Unit. In addition, a Scientific Advisory Board was assigned to the study.

2.11 Patient involvement

In the planning phase of the study, the patient organisation Forbundet Tenner og Helse (FTH; http://ffo.no/Medlemsorganisasjon/Forbundet-Tenner-og-Helse/) participated at repeated meetings with the study protocol task group to discuss and give comments to the study protocol. In addition, representatives from FTH were invited to comment the presentation of data in the present manuscript.

3 RESULTS

3.1 Participants

A total of 129 subjects (\(n = 49, n = 52\) and \(n = 28\) in the Amalgam, MUPS and Healthy cohorts, respectively) were recruited and signed informed consent; \(n = 95\) subjects (\(n = 37, n = 33, n = 25\) fulfilled all eligibility criteria, adhered to all protocol specifications for enrolment and were included in the study; and \(n = 79\) (\(n = 32, n = 28, n = 19\) were available for follow-up analysis (Figure 1). Further details about each group are presented in the following sections.

3.1.1 Amalgam cohort

Between August 2013 and December 2015, 59 individuals sent an application for removal of all amalgam fillings as experimental treatment. Of these, 49 fulfilled inclusion criteria (Figure 1) and signed the written informed consent form. Questionnaire 1 (Q1) was sent and returned by all \(n = 49\) participants (Figure 1). The questionnaire completed by the GP regarding the general health of the participant was returned for 46 participants. MUPS criteria were fulfilled by 37 patients in the amalgam group (Table 2).

Removal of amalgam restorations was started for all 37 patients in the amalgam cohort. One patient terminated her participation due to health reasons and four patients had to be excluded for different reasons (Table S1). Thirty-two patients in the amalgam cohort finished the dental treatment and completed Questionnaire 2 (Q2) one year after the last treatment session (Figure 1).

3.1.2 MUPS cohort

In the period March 2013 to January 2015, 52 patients accepted to participate and signed the written informed consent form. Questionnaire 1 was sent by mail to all of these, and 44 patients completed the questionnaire, and sent it back to the study office (Figure 1). The questionnaire to the GP regarding the patient’s...
health was returned for 39 patients. After assessment by the patient’s GP, the MUPS criteria were applied. Thirty-three patients fulfilled the criteria and were included in the MUPS cohort. Two years later, Questionnaire 2 was mailed and returned by 28 patients in the MUPS cohort (Figure 1). In the baseline questionnaire, section ‘What do you think could be the reason for your health complaints?’, no patients in the MUPS cohort listed ‘amalgam fillings’ or ‘mercury from amalgam fillings’ as a possible cause of their health complaints.

### 3.1.3 Healthy cohort

Thirty-one potential participants were recruited between March 2014 and March 2016 and received a consent form. Of these, 28 returned the signed informed form and 25 responded to Questionnaire 1 (Figure 1). In the Healthy cohort, 19 participants completed Questionnaire 2 two years after completion of Questionnaire 1.

### 3.2 Baseline characteristics

The proportion of women was much higher in the MUPS cohort (88%) than in the amalgam cohort (60%) and the healthy cohort (68%). The distribution of age, civil status and smoking habits did not differ significantly, but gender and education were not equally distributed between the cohorts (Fishers exact test; \( P = .024 \) and \( P = .004 \), respectively) (Table 2).

At baseline, the GHC index was highest in the Amalgam cohort (mean 42; Table 2). In the MUPS cohort and in the Healthy cohort, the mean values were lower (mean values 35, and 10, respectively). The mean baseline value in the Amalgam cohort and in the MUPS

### Table 2 Demographics, baseline data

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Amalgam (n = 37)</th>
<th>MUPS (n = 33)</th>
<th>Healthy (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender, n (%)</td>
<td>22 (59)</td>
<td>29 (88)</td>
<td>17 (68)</td>
</tr>
<tr>
<td>Age (years); mean (SD)</td>
<td>51.0 (7.9)</td>
<td>48.6 (10.4)</td>
<td>46.7 (12.8)</td>
</tr>
<tr>
<td>Education a, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary and lower secondary school</td>
<td>3 (8.1)</td>
<td>4 (12.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Upper secondary school, vocational program</td>
<td>10 (27.0)</td>
<td>9 (27.3)</td>
<td>1 (4.0)</td>
</tr>
<tr>
<td>Upper secondary school, general program</td>
<td>4 (10.8)</td>
<td>9 (27.3)</td>
<td>6 (24.0)</td>
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<tr>
<td>Higher education (less than 4 years)</td>
<td>11 (29.7)</td>
<td>9 (27.3)</td>
<td>6 (24.0)</td>
</tr>
<tr>
<td>Higher education (4 years or more)</td>
<td>9 (24.3)</td>
<td>2 (6.1)</td>
<td>12 (48.0)</td>
</tr>
<tr>
<td>Civil status, n (%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>24 (64.9)</td>
<td>22 (66.7)</td>
<td>12 (48.0)</td>
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<td>Cohabitation</td>
<td>6 (16.2)</td>
<td>5 (15.2)</td>
<td>7 (28.0)</td>
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<tr>
<td>Single</td>
<td>3 (8.1)</td>
<td>5 (15.2)</td>
<td>4 (16.0)</td>
</tr>
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<td>Divorced</td>
<td>4 (10.8)</td>
<td>1 (3.0)</td>
<td>2 (8.0)</td>
</tr>
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<td>Household yearly income; median group</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1000 NOK</td>
<td>550-750</td>
<td>550-750</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Smoking habits, n (%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No, never ever</td>
<td>15 (40.5)</td>
<td>17 (51.5)</td>
<td>14 (56.0)</td>
</tr>
<tr>
<td>No, stopped less than one year ago</td>
<td>1 (2.7)</td>
<td>2 (6.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>No, stopped more than one year ago</td>
<td>16 (43.2)</td>
<td>6 (18.2)</td>
<td>6 (24.0)</td>
</tr>
<tr>
<td>Yes, but not daily</td>
<td>0 (0)</td>
<td>3 (9.1)</td>
<td>3 (12.0)</td>
</tr>
<tr>
<td>Yes, daily</td>
<td>5 (13.5)</td>
<td>3 (9.1)</td>
<td>2 (8.0)</td>
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<tr>
<td>Missing data</td>
<td>0 (0)</td>
<td>2 (6.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Sick leave/sickness benefits, n (%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>24 (64.9)</td>
<td>21 (63.6)</td>
<td>1 (4.0)</td>
<td></td>
</tr>
<tr>
<td>GHC; mean (SD)</td>
<td>42.4 (17.4)</td>
<td>35.4 (14.6)</td>
<td>10.5 (14.0)</td>
</tr>
<tr>
<td>SF-36 Physical Component Summary; mean (SD)</td>
<td>35.3 (9.3)</td>
<td>37.3 (8.0)</td>
<td>54.3 (4.8)</td>
</tr>
<tr>
<td>SF-36 Mental Component Summary; mean (SD)</td>
<td>45.7 (9.2)</td>
<td>47.8 (11.1)</td>
<td>53.9 (5.8)</td>
</tr>
<tr>
<td>Worry about risk for personal health—Dental amalgam fillings b; mean (SD)</td>
<td>3.6 (0.9)</td>
<td>2.2 (1.2)</td>
<td>1.5 (1.0)</td>
</tr>
</tbody>
</table>

aFor definitions, see Ref 36
bItem from Modern Health Worries 24 coded from 1 (no concern) to 5 (extreme concern).
The proportion of patients on sick leave or receiving other sickness benefits was similar in the Amalgam cohort and in the MUPS cohort (64.9% and 63.6%, respectively). Household income was also similar in the two groups (Table 2, Figure S2). There were no major differences between the groups regarding household type (Figure S3).

### 3.3 Main results

From baseline to follow-up, the GHC index was significantly reduced in the Amalgam cohort, \( P < .001 \), while no significant change was observed for the MUPS or Healthy cohorts (Table 3). The GHC-index change score (GHC index at Q1 minus GHC index at Q2) was significantly higher in the Amalgam cohort (mean 12.8, SD 15.9) compared with the MUPS cohort (mean 1.2, SD 12.3; \( P = .004 \), Table 3).
indicating more symptom reduction in the Amalgam cohort. In Figure 3, box-plots show data from Q1 and Q2 for participants with observations at both baseline and follow-up.

After adjustment for covariates (gender, age, education and baseline GHC index), the mean difference in GHC-index change score between the Amalgam cohort and the MUPS cohort was −8.0 (95% confidence interval from −15.4 to −0.5; \(P = .036\), Table S2).

### 3.4 Other analyses - Secondary outcomes

From baseline to follow-up, the SF 36 Physical and Mental Component Summary scores increased significantly in the Amalgam cohort (\(P = .001\) and \(P = .009\), respectively), indicating improved health status. In the MUPS cohort and the Healthy cohort, there were no significant changes from baseline to follow-up (Table 3, Figures S5 and S6).

The change score of SF 36 Physical Component Summary in the Amalgam cohort (mean −5.1, SD 7.9) was significantly larger compared with the MUPS cohort (mean 0.9, SD 7.1; \(P = .004\); Table 3) indicating more improvement in the Amalgam cohort. The SF-36 Mental Component change score was not significantly different between the Amalgam (mean −4.3, SD 8.7) and the MUPS cohorts (mean −1.5, SD 10.4; \(P = .682\), Table 3). The mean adjusted difference between amalgam cohort and MUPS cohort for SF 36 Physical Component Summary was 5.9 (95% confidence interval from 1.5 to 10.3, \(P = .009\), Table S2).

### 3.5 Supplementary analyses of the Amalgam cohort

For the Amalgam cohort, predictors of change of the GHC index at follow-up were analysed in models without (Model 1) and with (Model 3) the potential effect modifier (item ‘Amalgam fillings’ from the Modern Health Worries questionnaire), which also was analysed separately (Model 2). Significant effects were found for GHC index at baseline (\(P < .001\)) and for education (Model 1 and 3, Table S3; Figure S4). Participants with higher education had significantly more improvement as measured by the GHC index.

In corresponding analyses of potential predictors of change at follow-up for SF-36 Physical Component Summary and Mental Component Summary scores, none of the variables included in the model were significant predictors, except the SF-36 Mental Component Summary at baseline (Model 1 and 3, Table S3). The potential effect modifier ‘Amalgam dental fillings’ from the Modern Health Worries scale was not significant in any of the models (Table S3).

Exploratory post hoc analyses of the change of separate GHC items showed that the mean values of all items decreased after removal of amalgam restorations. The decrease was statistically significant for all but three items (symptoms from ear/nose/throat, headache and gastrointestinal symptoms). Reductions by more than one unit were observed for the items difficult to concentrate, anxiety/depression, pain from muscles and joints, fatigue, cardiovascular symptoms, memory problems and dizziness. Thus, the response was more general, and therefore best described by the GHC summary score.

### 3.6 Analysis of participants lost to follow-up

In the Amalgam cohort, four patients were excluded (Table S1) and one patient terminated participation due to health reasons. In the MUPS cohort and in the Healthy cohort, 11 participants did not respond to the follow-up questionnaire (Q2; Figure 1). The mean baseline GHC index for these was 36.9 (SD 15.9), 28.9 (SD 16.8) and 12.1 (SD 10.8) in the three cohorts (Amalgam, MUPS, and Healthy cohorts, respectively).

### 4 DISCUSSION

#### 4.1 Key results

The main finding of this study was that the intensity of general health complaints decreased after removal of dental amalgam fillings in patients with MUPS who attributed their health complaints to amalgam fillings. The comparison group showed similar health complaints (as measured with the GHC index), and no change was observed over time. In addition, the SF-36 Physical and Mental Summary scores increased significantly after removal of amalgam fillings, indicating better health after amalgam removal.
4.2 | Strengths and Limitations

To our knowledge, this is the first study of amalgam removal focusing on patients with MUPS with or without symptom attribution to dental amalgam fillings. Strengths of the study include an independent dental follow-up examination of patients after amalgam removal, a comprehensive outcome assessment including the most common symptoms in the patient group (GHC index, Munich Amalgam Checklist) as well as generic quality of life (SF-36), and a follow-up duration sufficient to mirror symptom changes after amalgam removal, as observed in previous studies. In addition, a long-term follow-up five-year after amalgam removal is planned.

The study was initiated by Norwegian health authorities as part of a treatment project for patients with health complaints attributed to dental materials (amalgam). Because of the specific framework of the treatment project, including ethical concerns, a randomised control design was not deemed feasible. In this context, the MUPS concept was used to operationalise the comparison between patients with health complaints attributed to amalgam and patients with similar health complaints but without attribution to amalgam, thus allowing for a prospective comparison matched for symptoms.

Blinding of the treatment was also not possible. Thus, expectations about the treatment effects could influence the results. However, the improvement of health after amalgam removal is reported to last for many years, which may reduce the probability of placebo as the only cause of the improvement. The possibility of a discontinuation of a hypothetical nocebo effect from amalgam fillings has been suggested as one potential explanation for a reduction of health complaints following amalgam removal. Another possibility is observation bias, since the symptom and quality of life outcomes are documented by self-report, and patients offered the desired treatment free of charge could possibly exaggerate their improvement. However, symptom reduction after amalgam removal has been reported to be associated with the reduction of concentration of inorganic mercury in serum as well as the concentration of mercury in urine at baseline before treatment. Such associations between symptoms and laboratory parameters cannot be observed by the patients, which makes observation bias an unlikely explanation for the improvements. Regression to the mean and natural recovery can also contribute to symptom reduction; however, the MUPS cohort with similar symptoms at baseline had no improvement. Admittedly, baseline GHC scores were higher in the Amalgam cohort (mean 43.3) than in the MUPS cohorts (36.6), thus leaving more room for improvement. However, the outcome difference in favour of the Amalgam cohort remained significant after adjustment for baseline scores as well as demographics, even though the pre-defined sample size of the study was not met.

4.3 | Interpretation

The study provides additional evidence of reduction of health complaints in patients with attribution of health complaints to amalgam after amalgam removal. Since neither blinding nor placebo control was used, the observed reduction of the intensity of general health complaints can be interpreted as an effect from both specific and non-specific treatment effects. A reduction of health complaints is in agreement with data from previous controlled studies and studies without comparison groups. In cross-sectional studies of large cohorts, people with many amalgam fillings did not have more symptoms or diagnosed diseases than people with few fillings. Thus, the findings that patients with health complaints attributed to amalgam and who have their amalgam fillings removed report lower intensity of health complaints after amalgam removal could seem contradictory. However, a relatively low prevalence of health complaints attributed to amalgam fillings in the general population and a relatively low correlation between number of amalgam fillings and health complaints in the patient group could be of importance and explain the seemingly conflicting results.

In the present study, we used both the GHC index, which is designed to monitor health complaints attributed to amalgam, and the generic SF-36 questionnaire. Both showed significant improvement of health. As a rule of thumb, a change score of a half standard deviation is considered a clinically meaningful difference. A mean increase of 5 points of the SF-36 Physical Component scale (SD = 10 points) in the Amalgam group indicates a marked improvement in physically oriented quality of life after removal of amalgam fillings.

4.4 | Generalisability

Since we used inclusion and exclusion criteria of the participants in this study, the external validity is limited to patients who have MUPS attributed to their amalgam fillings and fulfilling the criteria. All patients included in the Amalgam cohort were examined both by the patients’ GP and the patient’s dentist. Both assessed that there was no major risk for deterioration of the health of the patient if they participated in the project. Thus, this is an important limitation and must be considered in relation to the generalisability of the results from the study.

5 | CONCLUSION

This study supports the hypothesis that MUPS attributed to amalgam fillings, as present in our participants in the Amalgam group, are reduced after removal of amalgam fillings in patients fulfilling the criteria used in this study.

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CONFLICT OF INTEREST
The authors of this manuscript have declared no competing interests. LB is employed by the Norwegian Dental Biomaterials Adverse Reaction Unit, which is funded by the Norwegian Ministry of Health and Care Services; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

AUTHOR CONTRIBUTION
HH, FM, TA, LB, EW and WW involved in study conception and design. LB and EW involved in acquisition of data. LB, FM, TA, HH, EW and WW involved in analysis and interpretation of data. LB involved in drafting of manuscript. LB, FM, TA, HH, EW and WW involved in critical revision. All authors approved the final manuscript.

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