

Patients' experiences of changes in health after removal of dental amalgam

- quantitative and qualitative approaches

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Scientific environment

The work presented in this thesis is part of a larger study that was carried out at the Norwegian Dental Biomaterials Adverse Reaction Unit, Uni Research Health, with Lars Björkman (Ph.D.) as principal researcher. Björkman, who is also an Adjunct Professor at the Department of Clinical Dentistry, Faculty of Medicine and Dentistry, has been my main supervisor. Due to the cross-disciplinary quality of the study, I have also had the privilege of having three co-supervisors: Gunvor Bentung Lygre (Dr. Odont.), Professor Knut Dalen (Dr. Philos.) and Professor Per-Einar Binder (Dr. Psychol.). Björkman and Bentung Lygre (Dental Biomaterials Adverse Reaction Unit) both have backgrounds in dentistry, whereas Dalen (currently working at the private practice nevropsykolog.no) and Binder (Department of Clinical Psychology, Faculty of Psychology) are both specialists in clinical psychology. My own background is also in psychology (Cand. Psychol./certified psychologist).

The Faculty of Medicine and Dentistry granted me a three-year, full-time scholarship and one year of duty work. During these years, I was employed at the Department of Clinical Dentistry. As a Ph.D. candidate, I was enrolled in the doctoral programs at the Department of Clinical Dentistry, and at the Graduate School of Clinical and Developmental Psychology, Faculty of Psychology. The Biomaterials research group, Faculty of Medicine and Dentistry, and the (now dissolved) Group for Qualitative Research on Mental Health, Faculty of Psychology, have also been important for the conceptualization and realization of the present work.

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Therese Thornton Sjursen

May 2016

* Deceased March 2016

List of abbreviations

CFS: chronic fatigue syndrome

EEC: European Economic Community

FDA: U.S. Food and Drug Administration

Hg: mercury

IBS: irritable bowel syndrome

ICP-SFMS: inductively coupled plasma-sector field mass spectrometry

ITT: intention-to-treat

MUS: medically unexplained symptoms

NRS: numeric rating scale

OLCL: oral lichenoid contact lesion

PP: per-protocol

RCT: randomized controlled trial

SHC: subjective health complaints

SRM: standardized response mean

SCENIHR: Scientific Committee on Emerging and Newly-Identified Health Risks

TMJ: temporomandibular joint disorder

USPHS: U.S. Public Health Service

WHO: World Health Organization

Abstract

Patients with medically unexplained health complaints attributed to dental amalgam often wish to have their amalgam fillings replaced with other materials. The main purpose of this thesis was to explore how patients with health complaints attributed to dental amalgam experienced changes in health after removal of all amalgam fillings.

Forty patients with health complaints attributed to dental amalgam were included and assigned to a treatment group (n=20; amalgam removal) and a reference group (n=20; no treatment). An external reference group (n=441) from the general population was also used for comparisons with the treatment group. Follow-up in the treatment group included measurements of mercury in serum and urine and questionnaires with numeric rating scales for 6 intraoral, 5 extraoral, and 12 general health complaints. The same questionnaire was also used in the reference groups. After the final follow-up, twelve of participants in the treatment group were asked to participate in semi-structured qualitative interviews exploring their experiences of changes in health after amalgam removal. Patterns and themes in the participants' descriptions were identified through an explorative and thematic analysis of the transcribed interviews.

In the treatment group, mercury concentration in serum and index scores for intraoral and general health complaints declined significantly three years after amalgam removal. In the reference group there was as a slight, but not significant, increase of index scores in the same period. Comparisons with the external reference group showed that even after amalgam removal, participants in the treatment group reported a significantly higher level of complaints for 6 of the 23 complaints. In the interviews, participants described feeling better after amalgam removal, but were reluctant to point to the removal as the only cause for their improved health. Despite not being sure of the importance of amalgam removal, all participants expressed that it had been important for them to get rid of the amalgam fillings. The mechanisms behind the reduced levels of health complaints after amalgam removal are probably compounded and not limited to reduced exposure to mercury. This was also acknowledged and underscored by the participants in the interview study.

List of publications

- I. Sjursten, T.T., Lygre, G. B., Dalen, K., Helland, V., Lægreid, T., Svahn, J., Lundekvam, B. F., & Björkman, L. (2011). Changes in health complaints after removal of amalgam fillings. *Journal of Oral Rehabilitation*, 38, 835-848.
- II. Lygre, G. B., Sjursten, T. T., Svahn, J., Helland, V., Lundekvam, B. F., Dalen, K., & Björkman, L. (2013). Characterization of health complaints before and after removal of amalgam fillings – 3-year follow-up. *Acta Odontologica Scandinavica*, 71, 560-569.
- III. Sjursten, T. T., Binder, P.-E., Lygre, G. B., Helland, V., Dalen, K., & Björkman, L. (2014). How unexplained health complaints were attributed to dental amalgam. *Nordic Psychology*, 66, 216-229.
- IV. Sjursten, T. T., Binder, P.-E., Lygre, G. B., Helland, V., Dalen K., & Björkman, L. (2015). Patients' experiences of changes in health complaints before, during and after amalgam removal. *International Journal of Qualitative Studies on Health and Well-being*, 10, 28157.

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1. Introduction

Dental amalgam, which has been used as a restorative material for almost 200 years (Brownawell et al., 2005; Rasines Alcaraz et al., 2014), has been crucial for the proliferation of affordable and durable dental treatment to the general population (Rathore, Singh, & Pant, 2012; Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR), 2008). Dental amalgam consists of approximately 50 percent metallic mercury (Hg) by weight, mixed with an alloy powder that usually consists of silver, tin and copper (Powers & Sakaguchi, 2006; SCENIHR, 2008). Mercury is a known toxicant (Bernhoft, 2012; Clarkson & Magos, 2006), and the safety of dental amalgam has been questioned since it was first introduced into modern dentistry (Molin, 1992; Rathore et al., 2012; SCENIHR, 2008). Due to its long history and widespread use, dental amalgam is presumably the most thoroughly investigated dental material to date, and reports of adverse reactions are considered rare (Kallus & Mjör, 1991). Nevertheless, there has been a recurring worry in the population that dental amalgam may cause ill-health (Molin, 1992; Mortensen, 1991; Rathore et al., 2012).

In response to this concern, the government of Norway (Norwegian Board of Health, 1999; Norwegian Directorate of Health, 2008) and other national governments, e.g. Sweden (Swedish National Board of Health and Welfare, 1987, 1994), Canada (Health Canada, 1996) and the United States of America (U.S. Food and Drug Administration (FDA), 2009; U.S. Public Health Service (USPHS), 1993, 1997) have funded reports and guidelines describing the use of, and potential risks associated with, dental amalgam. The World Health Organization (WHO, 2010) and the European Union (SCENIHR, 2008, 2015b) have also commissioned reports. So far, with the exception of contact reactions in the oral mucosa (Issa, Brunton, Glenny, & Duxbury, 2004), research and accumulated clinical experience have failed to demonstrate any strong evidence that patients' health is compromised by their amalgam fillings. However, the need to consider potentially sensitive groups such as pregnant women and the developing fetuses has been addressed (Richardson et al., 2009), and there has been a

call for further research into the relationship between genetic polymorphism and sensitivity to mercury (Richardson et al., 2009; SCENIHR, 2015b).

Due to the increased quality of tooth colored fillings (mostly polymer-based composites), concerns over the environmental impact of mercury disposed of in the course of dental practice, and public concerns related to negative health effects from amalgam fillings, the use of dental amalgam has decreased (Mitchell, Koike, & Okabe, 2007; Rasines Alcaraz et al., 2014). In Norway, products containing mercury have been banned since 2008 (Norwegian Ministry of the Environment and International Development, 2007). Dental amalgam, however, is still used in many countries throughout the world (Rasines Alcaraz et al., 2014), and due to its durability, patients will continue to keep their amalgam fillings for quite some time, even in countries where the use of dental amalgam has significantly declined or been banned (Anusavice, Shen, & Rawls, 2013b). Thus, the relationship between dental amalgam and health will be of continued importance.

1.1 Adverse reactions to dental amalgam

Dental amalgam is a biomaterial used to restore lost tooth substance, usually due to caries. A biomaterial can be defined as “a substance that has been engineered to take a form which, alone or as a part of a complex system, is used to direct, by control of interactions with components of living systems, the course of any therapeutic or diagnostic procedure” (Biomaterials, 2016). By definition, a biomaterial is designed to interact with biological systems, and can as such potentially also cause adverse reactions. Adverse reactions to a dental material can be defined as “any unintended, unexpected, and harmful response of an individual to a dental treatment or a biomaterial” (Anusavice, Shen, & Rawls, 2013a, p. 111). Adverse reactions to dental treatment can occur as a consequence of mechanical or thermal affections due to the operative procedures, or as the result of either a toxic or allergic reaction to one or several of the components of the dental biomaterial (Anusavice et al., 2013a). Unfortunately, it is often difficult to identify the mechanisms behind the adverse reactions (Anusavice et al., 2013a; Kallus & Mjör, 1991). In a study from 1991 (Kallus

& Mjör), the incidence of adverse reactions to dental materials, both subjectively reported by patients and clinically identified by dentists, was at a level of 1 per 700 treatments. Lichenoid reactions to amalgam restorations were the most frequent long-term side effects (Kallus & Mjör, 1991).

Dental amalgam and other materials used for dental restorations are classified as medical devices in the European Union as well as in the United States, being regulated as medium risk devices (Class II) (European Economic Community (EEC), 1993; FDA, 2009).

1.1.1 Allergic reactions

It is generally accepted that dental amalgam fillings can lead to local contact reactions (Issa et al., 2004; McParland & Warnakulasuriya, 2012). Oral lichenoid contact lesions (OLCLs) are found in direct topographic relationship with the dental material thought to have caused the reaction (Al-Hashimi et al., 2007). In the majority of cases, the suspected material is dental amalgam. If the material is removed, most OLCLs will improve or heal within months (Al-Hashimi et al., 2007; Issa et al., 2004). For dental amalgam, the oral lichenoid contact reactions are associated with delayed type hypersensitivity (Holmstrup, 1991; McParland & Warnakulasuriya, 2012; Mårell, Tillberg, Widman, Bergdahl, & Berglund, 2014). Other factors may also play a role, such as local toxic reactions and plaque build-ups on the fillings (Holmstrup, 1991). Rare cases of assumed immediate generalized hypersensitivity reactions to dental amalgam have also been reported (see for instance Kal, Evcin, Dundar, Tezel, & Unal, 2008; McGivern, Pemberton, Theaker, Buchanan, & Thornhill, 2000).

The Norwegian guidelines for examination and treatment of patients with suspected adverse reactions to dental biomaterials (Norwegian Directorate of Health, 2008) recommend replacement of dental restorations in direct contact with lesions in the oral mucosa. Replacement of fillings is also recommended if other hypersensitivity reactions to the dental materials have been shown (Norwegian Directorate of Health, 2008).

1.1.2 Toxic reactions

The main concern regarding the safety of dental amalgam has been related to the material's high content of mercury. Mercury is a metal that can be found in its elemental form as metallic mercury or mercury vapor. It can also be found in inorganic compounds, such as mercurous and mercuric salts, and in organic compounds such as methylmercury and ethyl mercury (Berlin, Zalups, & Fowler, 2015; Bernhoft, 2012). Mercury is a known toxicant (Bernhoft, 2012; Clarkson & Magos, 2006), and all forms of mercury can be toxic to humans (Berlin et al., 2015). The toxicological effects depend on the form of mercury one has been exposed to (Berlin et al., 2015; Bernhoft, 2012; Brownawell et al., 2005; Clarkson & Magos, 2006) as well as dose, duration and route of exposure (Berlin et al., 2015; Bernhoft, 2012). In the general population, the main sources for mercury exposure are dental amalgam (elemental mercury/mercury vapor) and consumption of fish (methylmercury) (SCENIHR, 2015b; WHO, 1991). People can also be exposed to mercury through their work, for instance in the chloralkali industry (production of chlorine and caustic soda) or as dental workers (Brownawell et al., 2005; WHO, 1991).

It is a well-established fact that amalgam fillings release low levels of mercury vapor into the oral cavity (Brownawell et al., 2005). With the exception of the increased mercury exposure that can occur when amalgam fillings are placed, polished or removed (Haikel, Gasser, Salek, & Voegel, 1990), the exposure to mercury from amalgam fillings can be described as a chronic low level exposure (Brownawell et al., 2005). Numerous studies have found statistically significant correlations between the number of amalgam fillings and concentration of mercury in blood (Björkman et al., 2007), urine (Olstad, Holland, Wandel, & Pettersen, 1987), saliva (Lygre et al., 1999) and the brain (Björkman et al., 2007; Eggleston & Nylander, 1987). Thus, the question is not whether amalgam fillings release mercury, but rather the extent to which the released mercury can cause ill-health at these predominantly low levels.

Most of our knowledge about the toxicity of elemental mercury has been derived from studies of people occupationally exposed to mercury vapor (Richardson et al., 2011; SCENIHR, 2008). Patients with amalgam fillings have, generally speaking,

substantially lower levels of mercury in respiratory air, blood, and urine than people who are exposed to mercury vapor through their work (Clarkson & Magos, 2006; SCENIHR, 2015b). In a study from 1998 (Sandborgh-Englund et al.), the daily dose of mercury was estimated at 5-9 micrograms/day in patients with an ordinary number of amalgam fillings. A summary of reports published in the late 1990s on mercury released from amalgam fillings estimated that daily mercury exposure from amalgam fillings ranged from 1 to 10 micrograms/day (Ekstrand, Björkman, Edlund, & Sandborgh-Englund, 1998). In comparison, the Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR, 2015b, p. 27) referred to an occupational limit of 70 micrograms/day for exposure to elemental mercury vapor. However, there is considerable individual variation when it comes to release and uptake of mercury from amalgam fillings, and some patients can present with mercury levels in plasma and urine comparable to levels found in people with high exposure to mercury through their work (Barregård, Sällsten, & Järvholm, 1995; Clarkson & Magos, 2006; SCENIHR, 2015b; Sällsten, Thorén, Barregård, Schütz, & Skarping, 1996).

Exposure to mercury vapor can cause neurological signs (Berlin et al., 2015), and high levels of exposure can lead to tremors, behavioral changes, personality changes, increased excitability, loss of memory, and insomnia (Berlin et al., 2015). In addition, symptoms such as gingivitis, stomatitis, excessive salivation, and, in some cases, kidney damage have also been seen in people with high occupational exposure to mercury vapor (Clarkson & Magos, 2006). These symptoms, however, are associated with exposure to mercury at much higher levels than levels normally associated with exposure to mercury from amalgam fillings. The possibility of adverse effects at lower exposure levels has been debated (Clarkson & Magos, 2006). At lower levels, the effects of mercury, if present, are likely to manifest as nonspecific symptoms which make it difficult to detect and diagnose possible chronic low level mercury poisoning (Clarkson & Magos, 2006; Homme et al., 2014).

1.1.3 Uncertainty related to the safety of dental amalgam

At the request of the European Union, the Scientific Committee on Emerging and Newly Identified Risks has prepared and adopted two scientific opinions on the safety of dental amalgam and alternative dental restoration materials for patients and users (SCENIHR, 2008, 2015b). In the opinions, scientific studies addressing adverse effects related to amalgam fillings are described, and the scientific evidence for the reported associations is evaluated. In the most recent opinion (SCENIHR, 2015b) it is stated that:

It is recognised that mercury, which is the major metallic element used in dental amalgam, does constitute a toxicological risk, with reasonably well-defined characteristics for the major forms of exposure. The reduction in use of mercury in human activity would be beneficial, both for the general decrease in human exposure and from environmental considerations. (p. 42)

Even though dental amalgam is comprised of several metals, the potential adverse effects of mercury have been given the most attention. In the most recent opinion (SCENIHR, 2015b), the risks associated with other elements than mercury was summarized as follows: “There is no scientific evidence that any of those elements currently used in dental amalgam restorations constitute a risk of adverse health effects in individuals apart from allergic reactions to the individual elements”(p. 26). In the opinion (SCENIHR, 2015b), the scientific committee acknowledged that local adverse effects in the oral cavity can occur when amalgam fillings are used. These reactions, however, were described as rare and easy to manage. In regard to possible systemic effects of mercury exposure from amalgam fillings, the committee categorized the scientific evidence as weak and concluded that “no increased risks on adverse systemic effects have been documented in the general population” (SCENIHR, 2015b, p. 43). However, the committee (SCENIHR, 2015b) also described studies (see for instance Basu, Goodrich, & Head, 2014) indicating that relatively common genetic variations can be associated with increased susceptibility to mercury exposure, and the committee stressed the need for further research into the possible significance this can have for exposure to mercury from amalgam fillings. Despite acknowledging that

reduced use of mercury would be beneficial and that further research is needed to better understand the effects of genetic polymorphism on individual susceptibility to mercury, the committee concluded that “dental amalgam is an effective restorative material for the general population, with low risk of adverse health effect” (p. 71). This is in line with conclusions from previous official reports on the safety of dental amalgam (see for instance Norwegian Board of Health, 1999; FDA, 2009; USPHS, 1997). For the majority of patients with amalgam fillings, the absorbed daily dose of mercury from the fillings seems to be quite low (Mackert & Berglund, 1997) and the estimated levels of exposure are well below levels permitted for occupational exposure (Clarkson & Magos, 2006; SCENIHR, 2015b). However, as described both in the scientific opinion (SCENIHR, 2015b) and elsewhere (see for instance Homme et al., 2014; Richardson et al., 2009; Richardson et al., 2011), there are uncertainties connected with the potentially adverse effects for sensitive individuals, and it has been argued that the current regulatory safety standards lack safety margins (Homme et al., 2014; Richardson et al., 2011). In addition, some of the assumptions made by the scientific committee (SCENIHR, 2008) regarding the toxicology of mercury have been criticized (Mutter, 2011).

1.2 Patients with health complaints attributed to dental amalgam

Patients with health complaints attributed to dental amalgam constitute a heterogeneous patient group (Langworth, Björkman, Elinder, Järup, & Savlin, 2002; Lindh, Hudecek, Danersund, Eriksson, & Lindvall, 2002). Common to all patients is the phenomenon that they suffer from unexplained, or partially explained health complaints that they or their dentist or physician believe are caused or aggravated by their amalgam fillings. A wide range of complaints related to multiple organ systems has been associated with amalgam fillings (Furhoff et al., 1998; Langworth et al., 2002; Malt et al., 1997). Tiredness, headaches, pain in muscles and joints, and problems with memory and concentration are among the most frequently reported complaints (Langworth et al., 2002; Lygre, Gjerdet, & Björkman, 2005; Vamnes,

Lygre, Grønningsæter, & Gjerdet, 2004). With the exception of local contact reactions (Al-Hashimi et al., 2007; Issa et al., 2004) and rare generalized hypersensitivity reactions (Kal et al., 2008; McGivern et al., 2000), the reported complaints mainly fall into the category of subjectively reported complaints. This means that the complaints, such as pain from muscles and joints, tiredness, headaches and so on, are based on patients' descriptions and cannot be identified through visual inspection, laboratory tests, radiographs et cetera. It is important to underline that this does not imply that the complaints are not real or not debilitating. It does, however, make the diagnostic process more difficult as there can be both competing and multiple explanations for the complaints.

Due to the wide range of reported complaints, as well as the mostly subjective nature of the complaints, there are no stringent criteria for identifying and describing patients with health complaints attributed to dental amalgam, or "amalgam patients" as they are sometimes also referred to. In the research literature, slightly different criteria for inclusion and exclusion have been applied. In a study from Norway (Malt et al., 1997), physicians and dentists who believed in the existence of an amalgam syndrome were asked to provide criteria for identifying patients with such a condition. The included practitioners deemed the following central in describing the patient group: "Multiple physical and psychological complaints developed over time starting with a few symptoms and gradually escalating to multiple symptomatology. Fluctuation in the clinical symptomatology may occur." (Malt et al., 1997, p. 33). The practitioners also provided an extensive list of complaints likely to be reported by amalgam patients (Malt et al., 1997). When investigating health complaints attributed to dental amalgam, some studies have relied on, and expanded on, questionnaires regarding common health complaints, such as the Giessener Symptom Complaints Checklist (Malt et al., 1997; Nerdrum et al., 2004), whereas other studies have used self-constructed questionnaires with health complaints that the researchers, based on the existing research literature and their own clinical experience, believe are core symptoms reported by patients with health complaints attributed to dental amalgam (Lygre et al., 2005; Melchart et al., 2008; Zwicker, Dutton, & Emery, 2014).

1.2.1 Psychological distress

The majority of studies investigating the relationship between subjectively reported health complaints and dental amalgam have been cross-sectional, and among their main findings is a high prevalence of psychological distress reported by patients with health complaints attributed to dental amalgam (see for instance Bailer et al., 2001; Bågedahl-Strindlund et al., 1997; Langworth et al., 2002; Malt et al., 1997). In several of the studies (Bailer et al., 2001; Bågedahl-Strindlund et al., 1997; Gottwald, Kupfer, Traenckner, Ganss, & Gieler, 2002; Malt et al., 1997) the high comorbidities between amalgam-related complaints and somatization, anxiety and depression were stressed, and based on the lack of findings linking the health complaints to mercury concentration in blood and urine, the researchers concluded that patients' complaints were more likely to have psychological than toxicological causes. The cross-sectional design of these studies does however make it difficult to say how the psychological distress and the reported physical health complaints are related.

In addition, inventories for anxiety and depression usually contain items addressing somatic aspects such as poor sleep, lack of appetite, et cetera, and can as such be influenced by the patients' experience of poor health. This could potentially have inflated the numbers characterized as suffering from anxiety and depression. However, it should also be noted that the somatic manifestations of both depression and anxiety can be interpreted by the patients themselves as signs of illness/disease not related to the psychological condition itself. This brings us closer to the understanding of somatization applied in some of these articles (see for instance Bågedahl-Strindlund et al., 1997; Gottwald et al., 2002; Langworth et al., 2002; Malt et al., 1997), i.e. as "a tendency to experience and communicate psychological distress in the form of physical symptoms, and to seek medical help for them" (Lipowski, 1987, p. 161). However, it has been amply described that patients living with health complaints which cannot be fully explained may experience psychological distress as a result of not being believed, being unable to establish an explanation for the complaints, and having to "fight" the medical profession and the social services to get sick leave, disability pension et cetera (Aamland, Werner, & Malterud, 2013; Kornelsen, Atkins,

Brownell, & Woollard, 2015; Nettleton, 2006). In view of all this, it is perhaps better to use the following definition of somatization: “the existence of physical bodily symptoms in the absence of a known medical condition” (Merriam-Webster Medical Dictionary, 2016). This does not mean that it can be dismissed that psychological distress can play a part in causing, upholding and exacerbating the experienced health complaints; it does mean, however, that one needs to proceed with caution when speculating about possible causal relationships between comorbid conditions.

1.2.2 Negative life events

In a study from 2002 (Langworth et al.), findings from semi-structured clinical interviews showed that a large number of patients had experienced negative life events earlier in life or shortly preceding the start of their amalgam-related symptoms, and many of the patients also reported having a stressful social situation and a poor social network. This led the authors to suggest that the tendency to somaticize that they also had identified in their sample could, in some cases, “be seen as a way of coping” (Langworth et al., 2002, p. 711). In a study from 2011 (Sundström, Bergdahl, Nyberg, Bergdahl, & Nilsson), cross-sectional analysis revealed that patients with health complaints related to dental amalgam reported having experienced significantly more negative life events than matched controls. In both groups the most frequently reported negative life event was somatic illness or surgical operation which was reported by 41% of the amalgam patients and 27% of the controls. The amalgam group reported more often than the controls that the life event was unexpected and that it was difficult to adjust to the event. The amalgam patients also reported having had lower control over the event than the control group.

1.2.3 Worry

We define amalgam patients as people who believe their medically unexplained, or partially explained, health complaints are caused or aggravated by their amalgam fillings. Consequently, worry related to potentially negative health effects from amalgam fillings can be considered a defining characteristic of this patient group. This has also been described in other studies: “A common finding was profound anxiety

about a connection between their symptoms and dental amalgam” (Langworth et al., 2002, p. 711). For anxiety patients, a cognitive processing priority for information related to their specific fears has been thoroughly demonstrated, and it has been argued that a similar mechanism could be important for the development and maintenance of medically unexplained complaints (Brosschot, 2002). People with a very strong concern or worry about somatic disease are likely to develop a cognitive bias for information related to somatic disease, and as such, bodily sensations and other information related to their worries could be experienced and interpreted as indicating ill-health. Increased monitoring of bodily sensations in combination with an increased risk of misattributing and/or over-reporting ambiguous stimuli, could potentially lead to increased reporting of health complaints (Brosschot, 2002). In a similar manner it has been suggested that the popular media’s preoccupation with possible links between illness and toxic and environmental causes can influence the way people experience and interpret nonspecific and common symptoms (Petrie et al., 2001). In a study from New Zealand (Petrie et al., 2001), a significant, albeit moderate, correlation was found between modern health worries and total number of self-reported health complaints. In a prospective study of the influence of modern health worries on symptom reporting, it was found that higher levels of modern health worries were associated with a higher number of complaints being attributed to pesticide after a planned pesticide spraying of participants’ residential area (Petrie et al., 2005). The authors (Petrie et al., 2005) suggested that modern health worries can influence people’s symptom expectations in such a way that, when activated by an actual situation, their bodily sensations and health complaints are monitored and interpreted within a confirmatory framework associated with the worry/worries in question.

1.2.4 Effects of amalgam replacement on subjective health complaints

There is a scarcity of prospective studies investigating the effects of amalgam replacement on subjective health complaints. In Table 1, examples of prospective studies with comparison groups are listed. Only one (Melchart et al., 2008) of the studies can be defined as a randomized controlled study. The other studies can be

<i>First author, year, country</i>	<i>Design^a</i>	<i>Study Groups^b</i>	<i>Main Measures</i>	<i>Follow-up</i>	<i>Findings</i>
Lygre, 2005, Norway ^c	Prospective cohort study	Removal group (n= 30) No removal (n=44) Reference group from the general population (n=441)	Self-report questionnaires including list of 23 symptoms ^d	1.5 years to 2.5 years after initial examination	Statistically significant reductions of intraoral complaints in the removal group (amalgam fillings and other dental materials). Patients who only had amalgam fillings replaced (n=22) had a small, but not statistically significant, reduction of intraoral, orofacial and general symptoms. Symptom profiles in the patient groups were similar to the profile in the reference group, but the intensity of the complaints was higher in the patient groups both at baseline and at follow-up.
Nerdrum, 2004, Norway	Prospective cohort study	Removal group (n=76) Patients with amalgam fillings (n=44) Patients with chronic disorders – ordinary family practice (n=51) Patients with chronic disorders – alternative family practice (n=51)	Self-report questionnaires including list of 131 items	2 and 7 years after removal	Reduced levels of physical and psychological complaints in amalgam removal group 2 years after amalgam removal. No further reduction of complaints from 2 to 7 years after removal of amalgam. At the 7 year follow-up, levels of physical complaints in the amalgam removal group were no longer significantly different from the levels in the alternative family practice group. Significant differences from the two other comparisons groups were still present.
Melchart, 2008, Germany	Randomized controlled trial	Removal group (n=25) Removal-plus group* (n=21) No-removal group** (n=21) *Amalgam removal and biological detoxification ** Health promotion program	Self-report questionnaires including list of 50 symptoms Mercury in erythrocytes, plasma and urine.	12 months and 18 months after baseline	Clinically relevant improvements in health (main complaints sum score) in all three groups between baseline and 12 months. Differences between groups were not significant. Improvements still present at 18 months follow-up. All measures of mercury except total mercury in erythrocytes were significantly reduced after removal of amalgam as compared with mercury levels in the no-removal group.

Stenman, 1997, Finland	Prospective cohort study	Psychiatric cases (n=57) Somatic cases (n=186) Oral cases (n=42) Cured patients* (n=26) Referents (n=37)** *Free of symptoms after removal of amalgam fillings ** Healthy volunteers with or without amalgam fillings	Self-report questionnaire including list of 144 symptoms Mercury in urine	1.5 to 3 years after initial examination	Study groups were classified according to whether the most predominant symptoms at baseline were still present at follow up. Of the included patients 26 were considered cured after amalgam removal. None of the patients who still had their amalgam fillings described themselves as cured at follow-up. Follow-up mercury to creatinine ratios were tested for 30 patients. No change for the 22 patients who did not replace their amalgam fillings. For patients that had their fillings removed the ratio decreased significantly.
Tillberg, 2005, Sweden ^c	Prospective cohort study	Total replacement (n=107) Partial replacement (n=96) No replacement (n=65) Reference group from the general population (n=2154)	Self-report questionnaire including questions about present health	From 0 to more than 9 years from initial examination	Patients in the no replacement or partial replacement groups had significantly higher risk of having unchanged or almost unchanged complaints than patients in the total replacement group. Higher prevalence of health complaints in total study group at follow-up than in the reference group from the general population.
Zwicker, 2014, Canada ^e	Prospective cohort study	Treatment (n=250), Positive amalgam (n=167) Never amalgam (n=538)	Self-report questionnaire including 14 questions about present health Measures of mercury in urine	At least 1 year after amalgam removal At least 6 months after amalgam removal	Greater odds for improvement for all symptoms in the treatment group than in the positive amalgam group. Odds ratios for two of the symptoms were significant. Removal of fillings reduced the odds for worsening of symptoms for all symptoms. Odds ratios for five of the symptoms were significant. Baseline urinary mercury levels in the amalgam groups were double the levels in the never amalgam group. All participants received bio- detoxification supplements, resulting in reduction in urinary mercury for both amalgam groups with a greater, but not significantly different, reduction in the treatment group.

Table 1: Prospective studies investigating the effects of amalgam removal in groups of patients with health complaints attributed to dental amalgam^f

^a Classification of design is based on Grimes and Schulz (2002)

^b n is given as per protocol numbers/numbers analyzed

^c Patients were referred for health complaints attributed to dental materials (mostly dental amalgam)

^d This is the same self-report measurement of health complaints that were used in the first two articles included in this thesis (see Appendix)

^e All participants with dental amalgam was offered amalgam removal. Reasons for accepting/declining were not described.

^f See Appendix for description of search terms

categorized as prospective cohort studies (Grimes & Schulz, 2002) if, in this context, we conceptualize the cohort as patients who were examined at a clinical unit because of health complaints attributed to dental amalgam. In the studies, patients were asked to participate in follow-ups sometime after the initial examinations. Comparisons could then be made between patients who had their amalgam fillings removed in the time since the initial examination and patients who chose not to remove their amalgam fillings. This is a simplified description of the design of the studies. For details and exemptions, see Table 1.

In all of the studies, some kind of improvement of health was reported by the patients who had all their amalgam fillings removed (Table 1). Different explanations, including patients' expectations (Melchart et al., 2008; Nerdrum et al., 2004; Tillberg et al., 2005), psychosocial treatment effects (Nerdrum et al., 2004), elimination of worry (Nerdrum et al., 2004), spontaneous recovery (Tillberg et al., 2005), and the natural course of the complaints (Melchart et al., 2008), were suggested for the reported improvements in health. However, not all of the reported reductions were statistically significant, and the complaints that were statistically reduced varied from study to study (not described in Table 1, see for instance Lygre et al., 2005; Zwicker et al., 2014). In the randomized controlled trial (Melchart et al., 2008), clinically relevant reductions of health complaints were found for all interventions, including the one without amalgam removal. In the studies with reference groups from the general population, health complaints after amalgam replacement were still higher, or more frequent, than health complaints found in the general population (Lygre et al., 2005; Nerdrum et al., 2004; Tillberg, Mårell, Berglund, & Eriksson, 2008).

In the studies that included measures of mercury, significant reductions of mercury were found after amalgam removal (Melchart et al., 2008; Stenman & Grans, 1997; Zwicker et al., 2014). In one of the studies (Zwicker et al., 2014), a significant reduction of mercury was also found in the non-removal group. The authors suggested this could have been due to all participants being offered detoxification supplements.

1.2.5 Disease, illness and sickness

Patients with health complaints attributed to dental amalgam have, as a group, encountered medical and dental services that have not been able to fully explain and cure their health complaints. It is our understanding that some of the difficulties patients and health professionals experience when faced with unexplained health complaints are rooted in the biomedical understanding of disease.

Within the biomedical model, it is assumed that disease can “be fully accounted for by deviations from the norm of measurable biological (somatic) variables” (p. 130, Engel, 1977). To separate the objective, measurable aspects of disease from the subjective experiences of the patient and the way these experiences influence the patients’ interactions with society, a distinction is often made between disease, illness and sickness (Engel, 1977; Hofmann, 2002). Disease is used to describe measurable physiological malfunctions that could result in actual or potential diminished physical capacity/life expectancy (Hofmann, 2002). Disease is often, but not always, accompanied by illness experiences, i.e. the patient’s subjective experience of having an undesirable state of health (Hofmann, 2002). Sickness refers to a social identity (sick role) that comes into play when the illness experience interferes with the patient’s ability to participate in his or her everyday life (Hofmann, 2002).

In the paper “The Need for a New Medical Model: A Challenge for Biomedicine”, Engel (1977) gave examples from both psychiatry and somatic medicine that could not be adequately addressed with a biomedical approach to disease, and he suggested that the biomedical model should be broadened to also encompass psychological, social and cultural determinants of health. Even though it can be argued that there has been a shift towards a biopsychosocial understanding of health, the application of this understanding in research and clinical settings is probably still hindered by factors such as the convenience of tradition and lack of time and resources to fully consider and address the psychosocial determinants of the patients’ health (Alonso, 2004). Given that the biomedical model was also embraced as a folk model in Western societies (Engel, 1977), the imprint of this model still influences the way patients and their family, friends and colleagues understand health and disease.

For patients with unexplained health complaints, the main hurdle posed by the biomedical model is being diagnosed with a disease in the first place. When a non-contested disease label is lacking, both patients and society may find it difficult to make sense of the patients' illness complaints, and the patients may also find it difficult to find acceptance for their illness in their everyday encounters and when asking for sick leave or applying for disability pension.

In our articles and in this summary, we use terms such as subjectively reported health complaints and unexplained health complaints. These terms are informed by the terminologies of subjective health complaints (SHC) (Eriksen & Ihlebæk, 2002; Ihlebæk, Eriksen, & Ursin, 2002; Ursin, 1997) and medically unexplained symptoms (MUS) (Brown, 2007). The term SHC was suggested by Ursin (1997) to provide a neutral, descriptive term for health complaints/diagnostic groups mainly depending on subjective statements from the patients themselves. MUS is another term used to describe such complaints and can be defined as "a heterogeneous group of conditions characterized by persistent physical symptoms that cannot be explained by medical illness or injury" (Brown, 2007, p. 769).

1.2.6 The importance of patients' experiences

The work presented in this thesis has been guided by the belief that to fully engage with and hopefully also in some ways alleviate patients' suffering, health personnel and researchers need to listen to the patients themselves. Patients' experience their health complaints in their everyday lives, and the meaning and the perceived consequences of the health complaints are contingent on patients' previous experiences, reactions from significant others, as well as the perceived present and longtime impact on their ability to carry out their duties, care for themselves and others, and of course, on their perceived chances of survival. Patients carry all this with them, both consciously and subconsciously, when they try to manage and make sense of their health complaints.

1.3 Thesis focus

As already described, the scientific community has been unable to state unequivocally whether dental amalgam is safe or not. The current understanding seems to be that “the question of ‘amalgam sensitivity’ should concentrate more on individual vulnerability, either in the form of biological (e.g. genetic) or psychosocial (e.g. personality, experiences, health beliefs and concerns) predisposition” (SCENIHR, 2015a, p. 9-10). This is an important step towards acknowledging that although there is an abundance of support for dental amalgam being a safe treatment alternative at group level, there are some uncertainties related to the safety of dental amalgam for potentially sensitive subgroups. The question is not limited to “is dental amalgam safe or not”, but has been broadened to include issues regarding sensitive subgroups, possible interactions et cetera. Despite this broadening of perspective pertaining to the relationship between dental amalgam and health, patients with subjective health complaints attributed to dental amalgam will probably find that the association between their health complaints and their amalgam fillings is still best characterized as ranging from “not likely” to “uncertain”. As such, their illness experiences are still associated with unclear disease status and a lack of indicated treatment strategies. Regardless of these uncertainties, patients with health complaints attributed to dental amalgam often wish to have their amalgam fillings removed.

Against this backdrop, we wanted to investigate what effects, if any, can be reasonably anticipated when patients decide to have their amalgam fillings removed. In continuation of this, we also wanted to gain knowledge about how patients with health complaints attributed to dental amalgam experience, describe and assign meaning to changes in health complaints before and after amalgam removal.

2. Aims

The overall hypothesis for the quantitative studies was that removal of all amalgam fillings in a group of patients with health complaints attributed to dental amalgam would be associated with long-lasting reductions of the complaints.

The general aim of the qualitative studies was to explore how patients who attributed health complaints to dental amalgam experienced changes in health complaints before and after amalgam removal.

The specific aims were:

- To investigate whether amalgam removal was associated with long-lasting reductions of composite scores for intraoral, extraoral and general health complaints (Paper I).
- To investigate whether amalgam removal was associated with reductions of mercury concentration in serum and urine (Paper I).
- To investigate and describe changes of each of the individual health complaints included in the composite scores (Paper II).
- To explore how patients came to associate their health complaints with dental amalgam (Paper III).
- To explore how patients gave meaning to changes in health complaints before, during and after amalgam removal (Paper IV).

3. Material and methods

The work presented in this thesis originates from the Bergen Amalgam Trial which consists of a clinical trial and an interview study. Paper I and Paper II draw upon data from the clinical trial (Figures 1 and 2). Paper III and IV present findings from the interview study (Figure 1). Readers are referred to the individual papers for details.

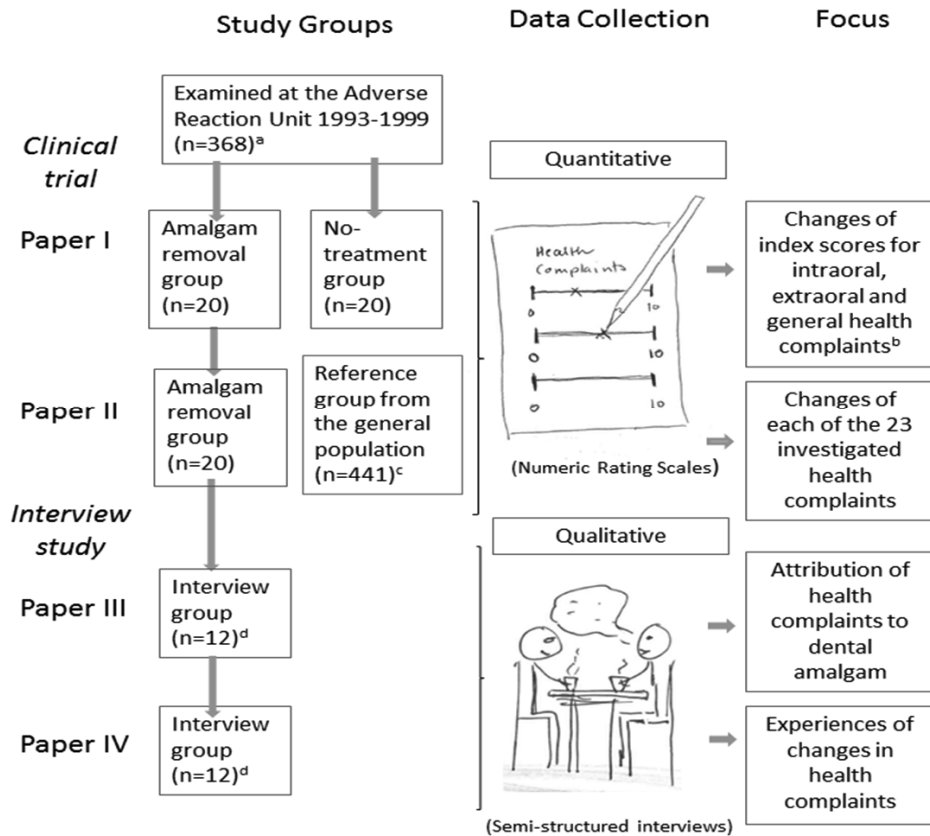


Figure 1: Study groups, methods for data collection and focus for analyses for Papers I–IV. ^a Full name of the Unit: the Dental Biomaterials Adverse Reaction Unit. ^b Changes in mercury concentration in serum and urine in the amalgam removal group were investigated. ^c Reference group sampled in relation to a previous study (Lygre et al., 2005). ^d Participants were recruited from the amalgam removal group.

3.1 Clinical trial

3.1.1 Design

The clinical trial was designed as an interventional before-and-after study with a no-treatment comparison group. In this text and in the papers, the terms reference group and internal reference group are frequently used to refer to the comparison group. The study population consisted of patients with unexplained health complaints attributed to dental amalgam. Included participants were assigned to a treatment group (amalgam removal) or a reference group (no treatment). For some analyses, results from the treatment group were compared with results from an external reference group from the general population.

3.1.2 Participants and procedure

Participants: Participants were recruited from patients referred to the Dental Biomaterials Adverse Reaction Unit during the years 1993 to 1999. In this period, 368 patients were examined at the unit. In 2000–2001 all patients with known contact information (n=358) received a questionnaire in the mail. The questionnaire was returned by 207 of the patients, yielding a response rate of 58 percent. The questionnaire contained questions about current health situation, medical and dental treatment since the examination at the unit, and demographic variables. Based on available data from the initial examination and information given in the questionnaires, 50 patients were found qualified under the following inclusion criteria:

- (i) Initially referred to the unit for examination of health complaints attributed to amalgam fillings
- (ii) Amalgam fillings still present
- (iii) Not diagnosed with contact allergy to substances in resin-based dental materials
- (iv) Health complaints from at least three different organ systems
- (v) Available data on mercury in blood and urine from initial examination
- (vi) Age 25-55 at initial examination
- (vii) Accepted to be contacted in a follow-up study

The 50 included patients were randomized to a treatment group (n=20 + 10 reserves) and a reference group (n=20). Based on clinical documentation, telephone interviews and dental and medical examinations (pre-treatment examination), six of the twenty participants assigned to the treatment group were excluded according to the following criteria:

- (i) Severe medical disorders (e.g. multiple sclerosis, ALS, severe rheumatoid arthritis)
- (ii) Severe food allergies
- (iii) Psychological difficulties or psychiatric disorders that could influence the dental treatment
- (iv) Need for complicated dental therapy (severe periodontitis, high caries activity, and/or need for complicated dental rehabilitation – e.g. bridges)
- (v) Inclusion criteria no longer fulfilled

The main reason for using these exclusion criteria was to ensure that the amalgam removal process could be carried out with as little risk and inconvenience as possible for the participants. The same exclusion criteria were applied in the group of reserves, leaving six participants eligible to replace the excluded participants. This left us with a treatment group of 20 participants (14 female, 6 male) and a reference group of 20 participants (16 female, 4 male). See Figure 2 for participant flow through the study.

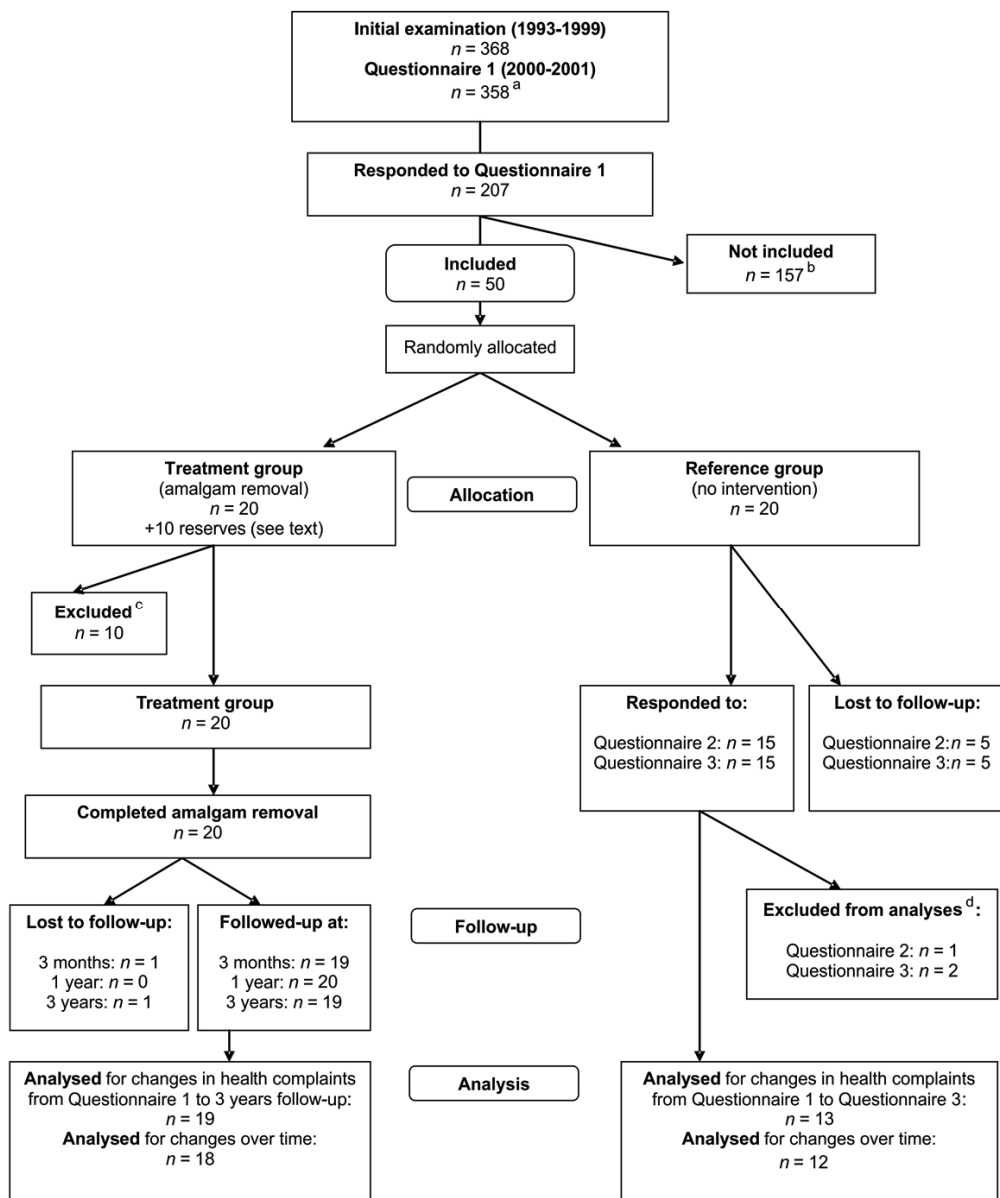


Figure 2: Flow diagram showing participant flow in the study. ^a Current addresses were missing for ten patients. ^b Did not fulfill inclusion criteria. ^c Excluded according to exclusion criteria. ^d Had removed all amalgam fillings. This figure was also used in Paper I (Sjursen et al., 2011).

Intervention: Participants in the treatment group had all amalgam fillings removed and replaced with other dental restorative materials (e.g. composites, ceramic restorations and metaloceramic crowns) by their own dentists. The cost was covered by project funds, and the dentists were asked to follow clinical guidelines from the adverse reaction unit aimed at limiting the exposure from mercury during removal sessions (Norwegian Dental Biomaterials Adverse Reaction Unit, 2002). The amalgam removal was performed by 18 dentists. One dentist treated three of the participants; 17 dentists treated one participant each. The main aim for the clinical trial was to compare replacement of amalgam fillings with the standard dental treatment (i.e. no removal of amalgam fillings) for patients with subjective health complaints attributed to dental amalgam. Consequently, no intervention was assigned to the reference group.

Clinical examinations: Data from the initial examination at the unit during the period 1993 to 1999, including data on mercury in blood and urine, was available for all participants. In addition, participants in the treatment group underwent a medical and dental examination at a pre-treatment examination in 2002. Dental examinations were also carried out at all follow-ups. Serum samples were collected at the pre-treatment examination and at all follow-ups; urine samples were collected at the pre-treatment examination and at the one year follow-up.

Questionnaires: Questionnaire 1 (Q1), which was used for inclusion in the study, was also used as a baseline measurement of self-reported health complaints for comparisons between the treatment group and the reference group. The scheduling of the subsequent measurements of health complaints differed between the treatment group and the reference group (see Figure 3 for a timeline of the study). In the treatment group, questionnaire data were collected at the pre-treatment examination in 2002 and at follow-ups three months and one, three and five years after completed removal of dental amalgam. In the reference group, questionnaires were administered by regular mail. Participants were sent Questionnaire 2 (Q2) in 2004 and Questionnaire 3 (Q3) in 2007.

External reference group: For some analyses, we compared the treatment group from this trial and an external reference group used in a previous study (Lygre et al., 2005). The external reference group was sampled based on similarity to patients referred to the Adverse Reaction Unit regarding age, gender and education. Questionnaires were sent to 800 individuals during the spring of 2004 and returned by 441 of them, resulting in a response rate of 55 percent.

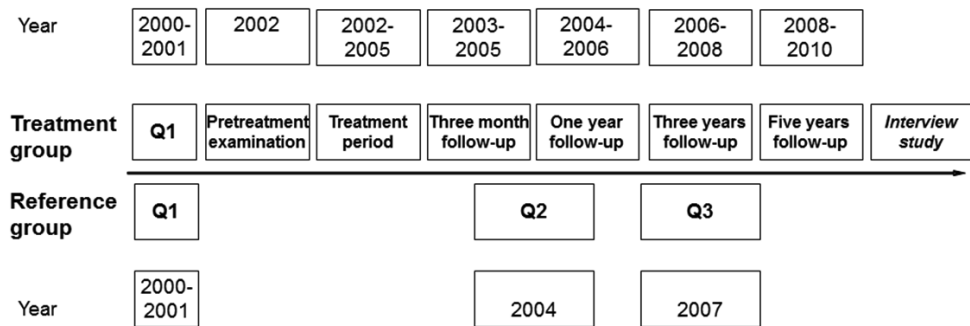


Figure 3: Timeline for the trial for the treatment group and the reference group. Q1, Q2 and Q3 indicate Questionnaire 1, Questionnaire 2 and Questionnaire 3. Timeframes for the data collection are given at the top for the treatment group and at the bottom for the reference group.

3.1.3 Measures

Self-reported health complaints: The presence and perceived intensity of self-reported health complaints were measured by numeric rating scales (NRS) for 23 health complaints often reported by patients with health complaints attributed to dental amalgam (Appendix). The scales were constructed at the adverse reaction unit and have been used in a previous study of a similar patient population (Lygre et al., 2005). Of the 23 items, 12 were related to general health complaints and 11 were related to orofacial complaints (complaints relating to the mouth and face). The orofacial health complaints were further categorized as intraoral (6 items) or extraoral health complaints (5 items). Participants were asked to indicate the intensity of their

complaints on horizontal scales marked with numbers ranging from 0 to 10. The scales were also verbally anchored with “No complaints” at the left side and “Worst possible complaints” on the right side. Index scores for intraoral, extraoral and general health complaints were constructed by adding the scores for all items within each category. The internal consistency, as measured by Cronbach’s alpha using the entire randomized sample (n=50), was found to be 0.66, 0.72 and 0.80 respectively for the intraoral, extraoral and general health complaints indices.

Mercury concentration in serum and urine: Concentration of mercury in blood serum was analyzed by inductively coupled plasma-sector field mass spectrometry (ICP-SFMS) (Rodushkin, Engström, Stenberg, & Baxter, 2004). Concentration of mercury in urine was analyzed by cold vapor atom absorption spectrometry (Vamnes, Eide, Isrenn, Höl, & Gjerdet, 2000).

3.1.4 Statistical analyses

Statistical analyses were conducted using the SPSS software, version 15 (SPSS Inc.). All significance tests were two-tailed. *P*-values < 0.05 were considered significant.

Power calculation: After application of the inclusion criteria, only 50 participants were eligible for participation in the clinical trial. After application of the exclusion criteria in the treatment group and the group of reserves, only 40 participants were left (20 participants in the treatment group and 20 participants in the reference group). Power calculations were made in order to determine if this sample would be sufficient to test the null hypothesis that changes in index scores for general health complaints were the same in the two groups. Assuming a mean difference in index scores of 10.0 between the two groups (that is, a mean difference of 10.0 in the treatment group from before amalgam removal to after amalgam removal versus a mean difference of 0.0 in the reference group between the score from Questionnaire 1 to the score from a later administered questionnaire), and a within-group standard deviation of 10, a sample size of 20 participants in each group will give the study a power of 87 percent to yield a statistically significant result.

Paper I: Independent samples *t*-tests were used for baseline comparisons between groups. The *P*-values from these analyses were not included in the manuscript. Within-group changes in health complaints over time were examined using mean values with 95-percent confidence intervals and repeated measures analysis of variance. These analyses were carried out as both intention-to-treat (ITT) and per-protocol (PP) analyses in both groups. Last observation carried forward was used to replace missing values for ITT analyses. Paired sample *t*-tests were used to investigate changes in mean mercury concentration in serum and urine from pre-treatment examination to follow-ups. Mean values (i.e. mean changes in the treatment group minus mean changes in the reference group) with 95-percent confidence intervals and independent samples *t*-tests were used for unadjusted comparisons of both per-protocol and intention-to-treat differences of changes in the treatment group and the reference group. Analysis of covariance was used to adjust for age, gender and complaint intensity at Q1 when comparing the changes in health complaints in the two groups.

Paper II: Paired sample *t*-tests were used to investigate changes in health complaints from the pre-treatment examination to the three-year follow-up in the treatment group. Effect sizes were calculated as standardized response means (SRM) with values of ≥ 0.20 , ≥ 0.50 and ≥ 0.80 representing small, moderate and large responsiveness. Mann-Whitney U-test and independent samples *t*-test were used to test differences in health complaints scores between the treatment group and the external reference group. Correlations between variables were investigated with Spearman's correlation.

3.2 Interview study

3.2.1 Design

To supplement the findings from the quantitative analyses of the self-report questionnaires, we wanted to carry out qualitative research interviews with some of the participants from the treatment group after they had completed all follow-ups after the amalgam removal. The motivation behind this was twofold:

-
- (i) We wanted to explore the participants' experiences on their own terms to gain insight into how they have lived with, interpreted and given meaning to their experiences of changes in health complaints before, during and after amalgam removal.
 - (ii) We also wanted to use the interviews as means to generate new hypotheses for further research and to open up for inclusion of additional relevant questions to questionnaires used in this patient group.

Prompted by the emphasis on exploration in both aims, we chose to carry out an explorative and reflexive thematic analysis of semi-structured interviews. Collection and analysis of data were strongly influenced by the step-by-step guides provided by Braun and Clarke (2006) and Binder, Holgersen, and Moltu (2012). Braun and Clarke (2006) described thematic analysis as “a method for identifying, analysing and reporting patterns (themes) within data” (p. 79), and they emphasized that thematic analysis can be applied by researchers informed by a range of theoretical approaches. In contrast to more pure phenomenological (i.e. descriptive/essentialist) or hermeneutic (i.e. interpretative) approaches, the explorative and reflexive approach to thematic analysis described by Binder et al. (2012) encourages the researchers to pursue *both* the descriptive (explorative) and the interpretative (reflexive) aspects of their material. This, however, is contingent on transparent descriptions of the steps undertaken by the researchers in order to arrive at the presented set of findings. In particular, researchers have to be aware of, and willing to scrutinize the tension between staying true to the participants' idiosyncratic or personal descriptions of their experiences, while at the same time being able to use the patterns of shared and divergent experiences to give meaningful interpretative descriptions of the participants' experiences. In order to address this tension as unreservedly as possible, the researchers are also expected to engage in self-reflection on how their social, cultural, professional and personal backgrounds and their relationship to the participants influence the research process and the way the findings can be interpreted (Binder et al., 2012).

3.2.2 Participants

We used a purposive sampling procedure. Participants were recruited from the treatment group in the amalgam trial, thus ensuring that they all had been through a complete removal of dental amalgam. Participants completed their amalgam removal at different times; consequently their follow-ups also took place at different times. The first six participants who finished the five-year follow-up were asked to participate in a qualitative research interview. The next six participants we asked were selected to ensure that both sexes and a diverse age range were represented. When we had completed the twelve interviews, we were able to identify both divergent and convergent experiences in the interview material and we had the impression that no new themes were brought to light during the last interviews. Seven women and five men participated in the interviews. Participants' age range was 45-65 years (mean age 54.4 years) at the time of the interviews.

3.2.3 Procedure

With the aim of facilitating an open dialogue with the participants suitable for the exploration of how they had experienced changes in health complaints before, during and after amalgam removal, we chose to carry out semi-structured, exploratory in-depth interviews with one participant at the time. All interviews took place at the neuropsychological outpatient clinic at the University of Bergen. Separate cameras were used to make video recordings of the participants and of the interviewer (me). Co-supervisor Knut Dalen was present at the outpatient clinic during all interviews. Neither of us had been present at the follow-ups at the Adverse Reaction Unit. The interview guide was initially developed by all coauthors of Paper III and Paper IV. After each interview, Knut Dalen and I discussed our first impressions of the interview. If needed, we also adjusted the interview guide. Mean duration of the interviews was 60 minutes (range 32 min. – 2 h 9 min.)

3.2.4 Analyses

We performed an explorative and reflexive thematic analysis (Binder et al., 2012; Braun & Clarke, 2006). Through comparing participants' individual accounts we wanted to identify patterns of similarities and differences in their experiences of changes in health complaints before, during and after amalgam removal. The steps in the analyses were the same for Paper III and Paper IV, but the focus was guided by the research question for each paper. The steps in the analyses can be summarized as follows:

- (i) Therese T. Sjursen (TTS/me) transcribed all video recordings verbatim.
- (ii) All authors read through the transcripts individually so they could get a basic sense of patterns in the participants' experiences.
- (iii) Each author discussed their first impressions of the written material with a special emphasis on patterns they thought constituted meaningful themes with TTS.
- (iv) TTS organized the text material into nodes in accordance with the tentative themes from step (iii). This systematic organization was carried out with the technical assistance of the NVivo9 software (QSR International Pty Ltd., 2010).
- (v) Based on TTS' written descriptions of the themes, the themes were further refined and condensed in cooperation with the coauthors. This was done as a combination of verbal discussions and written feedback to the drafts of the findings sections for Papers III and IV.
- (vi) To strengthen the transparency of our analyses, quotes and examples were included in the papers to illustrate patients' experiences.

3.3 Ethical approval

The project protocol for the Bergen Amalgam Trial was approved by the Regional Committee for Medical and Health Research Ethics in Western Norway (REK III

nr.24.01), and by the Norwegian Social Science Data Services. The trial was registered at ClinicalTrials.gov (NCT00346944). The protocol for the interview study was also approved by the Regional Committee for Medical and Health Research Ethics in Western Norway and by the Norwegian Social Science Data Services. Written consent was obtained from all participants at the start of the amalgam trial, and, for participants in the interview study, before agreeing on a date for the interview. Findings are presented without details that can identify individuals.

4. Summary of results

4.1 Paper I

“Changes in health complaints after removal of amalgam fillings”

The aim of this study was to investigate whether removal of all amalgam fillings in a group of patients with health complaints attributed to dental amalgam was associated with long-term changes in health complaints and mercury concentration in serum and urine. Changes in health complaints in the treatment group from Questionnaire 1 to the three-year follow-up were compared with changes in health complaints from Questionnaire 1 to Questionnaire 3 in a comparable reference group.

Between group comparisons: Per-protocol comparisons of changes in health complaints showed that changes in mean index scores for intraoral (7.9; 95% CI: 1.1 to 14.7; $P = 0.024$) and general (18.4; 95% CI: 6.8 to 30.0; $P = 0.003$) health complaints were significantly different in the two groups, whereas changes in extraoral index scores (3.2; 95% CI: -3.7 to 10.2; $P = 0.036$) were not significantly different in the two groups.

Within-group changes: In the treatment group we found statistically significant reductions in mean index scores for intraoral (3.7; 95% CI: 0.5 to 6.9) and general health complaints (9.7; 95% CI: 4.4 to 15.0) from Questionnaire 1 to the three-year follow-up. The reduction in extraoral health complaints in the same period (1.5; 95% CI: -2.8 to 5.8) was not statistically significant. In the reference group, all index scores increased from Questionnaire 1 to Questionnaire 3. The changes in the reference group were however not statistically significant.

Mercury concentration: In the treatment group, mercury concentration in serum and urine was significantly reduced after amalgam removal.

4.2 Paper II

“Characterization of health complaints before and after removal of amalgam fillings – 3-year follow-up”

The aim of this study was to describe changes in the 23 health complaints that were used to construct the index scores presented in Paper I. The levels of the complaints were also compared with levels of complaints in an external reference group.

Within-group changes: There was a general decrease of mean intensity of health complaints from the pre-treatment examination to the three-year follow-up with the exception of small increases in intraoral burning sensation and visual disturbances, and no changes in intraoral stiffness/paresthesia and dry mouth. The variation between participants was high. Statistically significant reductions were found for taste disturbances, pain from muscles and joints, gastrointestinal symptoms, symptoms from ear, nose and throat, and fatigue. No significant correlations were found between the change scores for these five items and reduction of mercury in serum. Reductions of one or more general health complaints were seen for all patients (n=19) in the treatment group; reductions of one or more orofacial complaints were seen for 17 patients.

Within-group correlations at pre-treatment: At pre-treatment, several significant positive correlations were found between complaints. Gastrointestinal problems, for instance, were positively correlated with facial skin problems, visual disturbances, fatigue, dizziness, memory problems and difficulty concentrating.

Between group comparisons: At the pre-treatment examination, mean intensities of all complaints were higher in the treatment group than in the external reference group. At the three-year follow-up, the mean intensities of facial pain and tenderness, pain from temporomandibular joints, pain in muscles and joints, gastrointestinal symptoms, memory problems and difficulty concentrating were still significantly higher in the treatment group than in the external reference group.

4.3 Paper III

“How unexplained health complaints were attributed to dental amalgam”

In this article, we explored how the participants remembered and described the experiences that led them to attribute their health complaints to dental amalgam. We found the following five themes to be of central importance for forming such an attribution:

- i. *Feeling puzzled*: All participants described suffering from health complaints that they could not fully understand.
- ii. *Picking up anecdotal evidence*: All participants described having heard about possible adverse reactions to dental amalgam before, but such anecdotal evidence did not seem to lead to an attribution of health complaints to dental amalgam unless encountered at a time when the patient was particularly open for such a connection.
- iii. *Temporal relationship between dental treatment and episodes of ill-health*: Some of the participants first started suspecting dental amalgam after having experienced episodes of ill-health and/or onset of long-lasting complaints in relation to dental treatment involving dental amalgam.
- iv. *A trusted person suggested dental amalgam as an explanation for my complaints*: Almost half of the participants said that either their physician or their dentists were the first to suggest a link between their health complaints and dental amalgam.
- v. *Feeling a resonance with descriptions of amalgam poisoning*: When the association between dental amalgam and health complaints had been brought to the participants' attention through one or several of the ways described in the previous themes, descriptions of amalgam poisoning in the media or obtained from patient organizations seemed to be of importance for examining the personal relevance of the attribution. For most of the participants, this resulted in a feeling of recognition and confirmation of the attribution.

4.4 Paper IV

“Patients’ experiences of changes in health complaints before, during and after amalgam removal”

In this article we explored how the participants experienced and gave meaning to changes in health complaints before, during and after amalgam removal. Through our analysis of the participants’ experiences we found the following themes to be of importance:

- i. *Something is not working: betrayed by the body:* All participants described the experience of something not working inside their bodies. Some seemed confused, and even betrayed, by their overly sensitive bodies.
- ii. *You are out there on your own:* Most of the participants had actively searched for explanations for their health complaints. Several expressed disappointment in how difficult it had been to get help from the medical profession, and some of the participants had also turned to chiropractors, physiotherapists and practitioners of alternative medicine for help.
- iii. *Not being sure of the importance of amalgam removal:* Most of the participants reported feeling better after amalgam removal, but due to difficulties in untangling effects of other changes in their lives from the effects of amalgam removal, participants found it difficult to claim with certainty that the changes were caused by the removal.
- iv. *The relief experienced after amalgam removal:* Despite not being able to point to dental amalgam as the sole explanation for feeling better, the majority of participants reported that they were in a much better place in their lives than before the amalgam removal and that they believed that the removal was partially responsible for this. In addition, all participants expressed relief that they no longer had to worry about their amalgam fillings.
- v. *To accept, to give up, or to continue the search:* For many of the participants, the amalgam removal seemed to have led to reduced urgency in their search for

answers, and some participants seemed to have moved towards accepting their health complaints.

5. Discussion

5.1 Methodological considerations

In this thesis, both quantitative and qualitative approaches have been used to investigate changes in health complaints before and after amalgam removal.

Regardless of whether the approach is quantitative or qualitative, scientific inquiry is characterized by the application of systematic methods for collection, organization and interpretation of data material (Kazdin, 2003; Malterud, 2001).

In quantitative research, the collected data is expressed as numbers, and investigation and analyses are usually carried out according to pre-determined and strictly defined research questions. The quantitative method is the method of choice if we want to estimate the prevalence or incidence of a condition in a given population, or if we want to establish causality, for instance when investigating the effects of an exposure or a treatment. However, despite its obvious importance for medical progress, quantitative research with its focus on “phenomena that can be controlled, measured and counted” (Malterud, 2001, p. 397), is not necessarily the best approach to answer questions about *how* patients’ experience their conditions, their treatment regimens and their interactions with health personnel, friends, family et cetera.

For research aims related to patients’ experiences, qualitative research that aims “to investigate the meaning of social phenomena as experienced by the people themselves” (Malterud, 2001, p. 398) is a better choice. In qualitative research, the collected data is expressed as words and data collection is often carried out through interviews. However, blog posts, patients’ diaries and even patients’ artwork can also constitute sources for analysis. Analysis, however, is usually carried out on textual material, for instance interview transcripts. The research questions are usually open-ended and continuously evolve both during data collection and analysis of data. In qualitative research, the aim of being able to identify themes and patterns in the data material should always be balanced with appreciation and preservation of participants’ idiosyncratic experiences.

In the individual papers included in this thesis, we chose not to apply a mixed-methods design. This choice was grounded in the acknowledgement of the different levels of analysis and different knowledge claims associated with quantitative and qualitative research methods. Nevertheless, as findings from both the quantitative and the qualitative studies are discussed in this thesis summary, the thesis in itself can be described as having a design close to an *explanatory sequential mixed-methods design* (Creswell, 2014, p. 224). Our design is a two-phase design where we first carried out a quantitative study followed by a qualitative study. However, even though the qualitative study was designed with the intent of using the findings from the interviews to supplement and nuance the findings from the clinical trial, we did not systematically use the quantitative results to plan the second qualitative phase.

The thrust of the research, however, has been carried out within either a quantitative or a qualitative framework, and therefore, the following discussion of methodological considerations will be described separately for the clinical trial and the interview study.

5.1.1 Clinical trial

In the clinical trial we wanted to investigate the effects of amalgam removal on changes in subjective health complaints. The inferences we can draw from our findings are contingent on both the design and the execution of our study. See Figure 4 for a short description of the questions associated with the internal, external and construct validity of an experimental study.

Internal validity: In treatment research, internal validity refers to the degree to which it can be surmised that the observed outcome is caused by the treatment and not by extraneous factors (Kazdin, 2003; Slack & Draugalis, 2001). Ideally, when investigating the effects of a treatment, the only difference between the groups should be the treatment(s) under investigation. In experimental studies, researchers can exert more control over extraneous variables than in observational studies. Randomized controlled trials (RCTs) are experimental studies in which participants are randomized to the different treatment conditions. This is done with the aim of reducing selection

bias and to disperse potential confounding participant characteristics across all groups in the trial. In evidence based medicine, RCTs are frequently placed high in hierarchies of evidence (Grimes & Schulz, 2002; Hannan, 2008), and to further reduce bias such as observer bias and responder bias, blinded or double blinded administration of treatment is preferential. Due to necessary modifications of randomization and follow-up, however, the design of our study does not qualify as an RCT. Instead it can be categorized as a quasi-experimental study or as a non-randomized clinical trial, or, when more detail is needed, as an interventional before-and-after study with a no-treatment comparison group. Several threats to the internal validity of experimental studies have been described (Kazdin, 2003; Slack & Draugalis, 2001). Some of these will be discussed below.



Internal validity: The extent to which the intervention, and not extraneous factors, can be considered to account for the results.

External validity: The extent to which the results can be generalized or extended to other people, settings, measures etc.

Construct validity: Assuming that the intervention was the cause of the changes, what is the conceptual basis/explanation for the changes?

Figure 4: Questions addressed by internal, external and construct validity. Descriptions adapted from Table 2.1, page 23, in Kazdin (2003).

History and *maturation* refer to possible influences of events because of the passage of time (Kazdin, 2003; Slack & Draugalis, 2001). History refers to events other than the intervention that could influence the outcome of the experiment. To be considered a threat to internal validity, the historical events (which could be events in the news, at work, at home etc.) should affect all or the majority of the subjects and the hypothesized effects on the results have to be plausible. In our study, the most likely

influences of history are changes in caretaking responsibilities in relation to children growing up, parents growing older and parents dying. Maturation refers to psychological and physiological processes within the participants that may change with the passage of time, such as growing wiser, growing older, reaching menopause et cetera. However, due to the demographic similarities between the treatment group and the reference group, similar effects of history and maturation are likely to occur in both groups.

Regression to the mean refers to the phenomenon that people with very high or very low scores are likely to have less extreme scores the next time they are measured (Kazdin, 2003; Slack & Draugalis, 2001). However, given the fact that participants in the reference group had higher levels of health complaints at baseline and that they did not report reductions of health complaints, regression to the mean does not seem to be a plausible explanation for the differences in changes between the two groups.

Selection bias refers to the presence of systematic differences between groups that were present before administration of treatment or that were somehow introduced during the course of the study (Kazdin, 2003; Slack & Draugalis, 2001). If these differences influence the outcome of the study (i.e. act as confounds) the inferences we draw based on our findings can be biased either towards accentuation or attenuation of the effect of the treatment. Selection bias can be eliminated or substantially reduced by randomizing participants to the different treatment conditions. In our study, participants were randomized to a treatment group, a group of reserves and a reference group. After randomization, exclusion criteria were applied in the treatment group in order to ensure that the amalgam removal would not be too burdensome for the participants. This could have introduced a selection bias connected to known (more severe conditions in the reference group than the treatment group) and unknown variables. This could pose a threat to the internal validity if, for instance, participants in the reference group suffered from progressive conditions to a greater extent than participants in the treatment group. Reduced health complaints in the treatment group could thus be hypothesized as associated with the natural variation of less severe complaints, whereas lack of changes, or increased health complaints, in the reference

group could be associated with participants' health condition either remaining unchanged or deteriorating due to other conditions. Baseline comparisons showed that even though the two groups were similar in regard to demographic variables, the reference group did in fact report higher levels of health complaints than the treatment group. The differences between the groups, however, were not statistically significant, and the reported changes of intraoral and general health complaints three years after amalgam removal remained statistically significant when adjusted for gender, age and complaint intensity at baseline (Paper I). Post-hoc application of exclusion criteria in the reference group resulted in exclusion of only two of the initial twenty participants (Paper I). Comparisons of per-protocol changes in the treatment group and the reference group with the two participants excluded yielded similar result as comparisons of per-protocol changes between the treatment group and the full reference group. As a side note, application of exclusion criteria was motivated by ethical and practical considerations and should not be interpreted as a dismissal of an association between dental amalgam and the excluded conditions.

Attrition and diffusion of treatment can also threaten the internal validity (Kazdin, 2003; Slack & Draugalis, 2001). Attrition, or experimental mortality, refers to participants lost to follow-up, and diffusion of treatment refers to situations where treatment is inadvertently administered to the control group. Attrition can introduce selection bias to the study if the loss to follow-up is different in the treatment group and the reference group, either through more participants dropping out from one of the conditions or through participants dropping out for different reasons from the two groups. Given that the participants in the reference group were not offered any treatment, it was expected that the loss to follow-up would be greater in the reference group than in the treatment group. In addition, it was expected that some of the participants in the reference group would choose to initiate amalgam removal on their own accord during the follow-up period. For ethical and practical reasons, participants in the reference group were only followed-up by questionnaires sent by regular mail. If asked to participate in clinical examinations and follow-ups, participants would be reminded to a greater extent of a possible association between their health complaints and their amalgam fillings. Given that the participants in the reference group would

not be offered treatment, it seemed unethical to ask them to go through with such an extensive follow-up regime. It was also speculated that extensive follow-up would increase participants' wish to have their amalgam fillings removed, which might result in withdrawal from the study due to participants' disappointment in not being offered such treatment, and diffusion of treatment through participants initiating amalgam removal on their own accord. Consequently, the follow-up in the two groups differed substantially. Despite the limited follow-up in the reference group, the loss to follow-up in this group was greater than in the treatment group (Figure 2). Participants from the reference group who confirmed that they had removed all amalgam fillings were excluded from analyses (Figure 2).

To summarize, there are apparent threats to the internal validity of the study. However, some of the threats, such as maturation and history, are probably evened out across groups, and some of the other threats have been controlled for in statistical analyses that render them less plausible as rival explanations for the effect of the intervention. However, even if we consider the different changes in the two groups as a result of the intervention (amalgam removal), we still have to consider threats to external validity and construct validity.

External validity: In treatment research, external validity refers to the degree to which the effect of the treatment can be generalized to other people and other settings than the ones investigated in the experiment (Kazdin, 2003; Slack & Draugalis, 2001). The generalizability of the results is therefore highly dependent on the representativeness of the sample studied as well as the transferability of the treatment conditions from the experimental setting to the relevant natural settings. In experimental studies, the internal validity is often high. However, due to often strictly defined inclusion and exclusion criteria, the external validity of experimental studies has been criticized. In our study *sample characteristics, stimulus characteristics and settings* and *research participation effects* are the most important threats to the external validity (Kazdin, 2003; McCambridge, Witton, & Elbourne, 2014).

Sample characteristics such as age, gender and socioeconomic status have to be considered when discussing the generalizability of the results. The participants

included in our sample were recruited from patients referred to the Adverse Reaction Unit for health complaints attributed to dental amalgam. Therefore, it is not certain that patients with subjective health complaints who do not attribute their health complaints to their amalgam fillings would achieve similar reductions of health complaints after amalgam removal. The generalizability of the results to all patients with subjective health complaints attributed to dental amalgam can also be questioned. At the initial examination at the Unit, no recommendation was made to the participants that they have their amalgam fillings removed, and in the period between the examination and inclusion into the study, they had not had all amalgam fillings removed on their own initiative. The reasons for this could be related to participants trusting the advice given at the Unit and/or not having the financial means necessary to have amalgam removed. This means that the results are not necessarily generalizable to participants with a stronger conviction and/or an economic status enabling them to carry out amalgam removal. However, follow-up studies of participants having had their amalgam fillings removed on their own initiative have also found reduced health complaints after amalgam removal (Lygre et al., 2005; Nerdrum et al., 2004; Tillberg et al., 2005).

Stimulus characteristics and settings refer to the possibility that the treatment effects obtained in the experimental condition could be contingent on, or influenced by, features of the study that are not necessarily transferable to other treatment settings (Kazdin, 2003). *Research participation effects* refers to the potential effects on participants' behavior from the knowledge that one is being studied, and conversely, these are not likely to occur in a setting where patients are not participating in a study (McCambridge, Kypri, & Elbourne, 2014; McCambridge, Witton, et al., 2014). Both of these threats to external validity can also affect construct validity and will therefore be discussed in more detail in the next section.

Construct validity: The construct validity of an experimental study has to do with how the causal relation found in the study is interpreted (Kazdin, 2003). In our study, even though there are obvious threats to the internal validity, it does seem that the intervention in the treatment group caused changes in the treatment group that were

not found in the reference group. Whether these changes are caused by the amalgam removal or other components associated with the amalgam removal should be considered, however. In the next sections, non-specific factors related to the treatment context will be discussed. These factors can influence both the generalizability (external validity) and the construct validity of the study.

Placebo: People who are skeptical of a link between dental amalgam and health complaints are quick to interpret reported changes in health complaints after amalgam removal as a placebo effect. Strictly speaking, placebos are “drugs, devices or other treatments that are physically and pharmacologically inert” (Wager & Atlas, 2015, p.403). Consequently, placebo interventions will not have any direct treatment effects (Wager & Atlas, 2015). Therefore, the placebo effect, which is a true psychobiological response (Price, Finniss, & Benedetti, 2008), must be interpreted as elicited by the context in which the treatment was administered (Wager & Atlas, 2015). Even though originally used to describe the effect of inert treatment, the placebo effect, along with its counterpart the nocebo effect, is now increasingly used to also denote the non-specific treatment effects (i.e. effects not caused by the intervention itself) of any medical treatment (Hauser, Hansen, & Enck, 2012). Wager and Atlas (2015, p. 403) described placebo effects as “brain-body responses to context information that promote health and well-being”, and they advocated that a large part of the therapeutic response to medicaments, surgery, psychotherapy et cetera is likely to have been caused by the treatment context rather than the specific interventions. Consequently, some of the reported changes in health complaints after amalgam removal can have been caused by non-specific treatment responses. For instance, it can be speculated that the experienced changes have been accentuated by both internal and external context information (Wager & Atlas, 2015), such as the patients’ expectations that amalgam removal would lead to reduced health complaints as well as a presumably positive treatment atmosphere while undergoing the necessary dental treatment at their own dentists. However, this does not preclude that some of the experienced changes are due to specific treatment effects of the amalgam removal.

Nocebo: In addition, albeit undoubtedly difficult to untangle from the placebo effect, the nocebo effect, or rather discontinuation of the nocebo effect, may also have influenced the experienced reductions in health complaints. In the same way as placebo effects originally referred to beneficial effects of inert or sham interventions, nocebo effects originally referred to adverse effects or worsening of symptoms in response to an inert/sham treatment (Hauser et al., 2012). However, nocebo response can also be used to refer to adverse effects or exacerbated symptoms caused by internal and external context information, such as negative expectations or negative communication, both verbal and non-verbal, in the treatment setting (Hauser et al., 2012). It cannot be excluded that for patients with health complaints attributed to dental amalgam, some of the experienced health complaints could be thought of as nocebo effects elicited by the fear that the amalgam fillings may cause ill-health. This information, however, is more likely to have come from stories in the media or from acquaintances, for instance, than from the dentists who originally treated the patients. Moreover, once this worry had been elicited, the black amalgam fillings might have served as a constant visible reminder of the potentially detrimental health effects related to the fillings. When the amalgam fillings were removed, it is reasonable to assume that potential nocebo responses as well as the worry associated with the fillings were eliminated.

Research participation effects: The mere act of participating in a study can lead to changed behavior and biased reporting. This can make it difficult to study the targeted phenomenon without influencing the outcome through observing and interacting with the participants. This has often been referred to previously as the Hawthorne effect (McCambridge, Kypri, et al., 2014; McCambridge, Witton, et al., 2014). Recently the term “research participation effects” has been suggested to highlight the effects that knowing one is being studied can have on participants’ behavior (McCambridge, Kypri, et al., 2014; McCambridge, Witton, et al., 2014). In prospective studies, repeated data collection brings attention to aspects of the participants’ lives that they, perhaps, would not have given as much thought to if they were not participating in the study. This can result in participants looking at and interpreting the measured variables

in new ways, as well as in changes in behavior, which obviously can also influence the results. In addition, there is also a risk that, to come across as good subjects, participants may consciously or unknowingly modify or weigh their responses to match what they perceive as the researchers' goals (McCambridge, Kypri, et al., 2014). Even though it is unlikely that the participants remembered in detail how they rated their health complaints at the pre-treatment examination and at the different follow-ups, we have to consider that the wish to convey gratitude and to show that amalgam removal can be considered an efficient treatment alternative can have influenced the way in which the participants interpreted and reported their health complaints at each measurement point.

Stimulus characteristics and settings: In addition to the treatment effects either directly or indirectly caused by the amalgam removal itself, and possible research participation effects, it is also possible that the participants in this study can have had treatment effects related to the follow-up given both by their dentists and by the personnel at the Adverse Reaction Unit. It is well known that patient-centered communication can have health promoting effects (Stewart, 1995; Van Dulmen & Bensing, 2002), and many of the interviewed participants highlighted that they had felt well taken care of both at the Adverse Reaction Unit and by their own dentists (Paper IV). Health personnel with a genuine interest in the patients and sufficient time to listen to their experiences conducted the pre-treatment examination and all follow-ups at the Adverse Reaction Unit. It is not unlikely that these encounters can have had positive effects on patients' health through their experiences of being seen and heard, but also through being given the opportunity to reflect upon possible connections between their health complaints and other areas of their lives. This aspect was perhaps most strongly voiced by one participant who emphasized that the questions asked by the project's physician at the pre-treatment examination had initiated a change towards making more room for herself in her life (Paper IV).

In summary, we find it reasonable to believe that all these factors can have influenced the results. Based on findings from the interviews, we believe that patient-centered communication, both in the dentist's office and at the Adverse Reaction Unit, was of

particular importance. In addition, participants' descriptions of relief related to having had their amalgam fillings removed indicate that discontinuation of nocebo effect and elimination of worry were also important for the reported reductions of health complaints. This has important implications for the generalizability of our findings and for the construct validity of our study as it can be speculated that our results are contingent on not only the amalgam removal but also on the patient-centered communication at the dentists and at the Adverse Reaction Unit. In addition, the potential effects of the amalgam removal in itself are not necessarily derived only from reduced mercury exposure given that discontinued nocebo effect/elimination of worry also could have influenced the results.

5.1.2 Interview study

Reflexivity: The preconceptions, personal values and previous experiences we as researchers, clinicians and individuals bring into the research process influence the questions we ask, the interactions we partake in, the inferences we draw and the findings we choose to present. In quantitative research, the aim is to limit the influences of anything other than the independent variables of interest, and some of the available methods/procedures for this were discussed under methodological considerations for the clinical trial. In qualitative research, the researchers' role in co-constructing the findings is acknowledged, and it is understood that research carried out by other researchers in a different context would result in different findings (Finlay, 2002). Nevertheless, we still have to actively investigate how the subjective aspects, such as our preconceptions, and intersubjective aspects, such as how we engage in creating meaning together with the research participants, influence our research and our findings. Reflexivity, which can be defined as "thoughtful, conscious self-awareness" (Finlay, 2002, p. 532) can be used systematically to carry out a continual, reflexive analysis of the way the subjective and intersubjective elements interact with and influence the research process.

In our study, we as researchers, and I as the interviewer, actively shaped the research process through the questions we decided to include in the interview guide, through

the themes I chose to explore, or not to explore, during the interviews, and through the subsequent analysis and interpretation of the transcribed interviews. Throughout the research process, we sought to actively analyze and reflect upon how our preconceptions and our experiences of the unfolding research process influenced the way we engaged with the participants and the data material. Analyses and reflections were carried out both individually and collectively.

The risk of interpreting participants' descriptions through a clinical lens was among the topics we discussed collectively. Each co-author for Papers III and IV has a clinical background. Therefore, it was important that we were able to take a step back from a purely anamnestic interpretation of participants' descriptions so that we could better tune in on participants' experiences of living with these health complaints. This aim was something that we had to remind ourselves of at different times during the research process. Of course, as health personnel, we are also obligated to use our clinical knowledge to identify the need for treatment and act upon it; procedures for this were in place for the interviews. Throughout the research process, we also had ongoing discussions about how patients with subjective health complaints are often described as strongly dismissive of psychological and social explanations for their health complaints. Despite the fact that we consider such categorizations both inaccurate and unhelpful, there is nevertheless a risk that a societal preconception such as this could influence our interactions with the participants and the way we interpret our findings. However, since one of our findings is that all the participants pointed to several explanations for their health complaints, including social and psychological explanations, this notion has been thoroughly disconfirmed for the participants in our sample. On the other hand, the desire to avoid just such a "preconception trap" may have prompted us to highlight participants' attempts to explain their complaints within a multifactorial framework. Given my own understanding of health as determined by many factors, there is a risk that I, through subtle cues, might have encouraged the interview participants to describe their experiences within such a framework. Knut Dalen, who listened in on the interviews, did however have the impression that all explanations were met with equal encouragement. Nevertheless, this could have been experienced differently by the participants themselves.

Scope and limitations: The sample characteristics discussed in the section for external validity for the clinical trial, such as strength of the amalgam attribution and lack of financial means necessary for amalgam removal, are also relevant for the scope of the findings from the interviews. The experiences described by our participants are likely to be different from the experiences of patients with a stronger conviction that their health complaints are caused by their amalgam fillings, and also from the experiences of patients who can finance amalgam removal on their own. We also have to consider the effects participation in the clinical trial may have had on participants' experiences of changes in health. The systematic collection of data through questionnaires and dental examinations, as well as the obvious amalgam focus of the follow-ups, may have influenced participants' experiences of changes in health and how they perceive the association between dental amalgam and health.

Even though the interviews took place in a different setting than the follow-ups, it was evident that participants thought of the interviews as a continuation of the clinical trial. Limitations related to the interview context, such as prompting explanations suitable for medical encounters, the context-related accentuation on the importance of amalgam removal and the wish to present a coherent picture of experienced changes in health complaints, are discussed in more detail in the Reflexivity, scope and limitations-sections of Papers III and IV. Some of these limitations could perhaps have been reduced if we had chosen to carry out focus group interviews instead of individual interviews. For instance, it is reasonable to assume that the wish to present a coherent picture could have become less salient in a focus group interview where participants would have been exposed to a variety of experiences, some similar to their own and some diverging from their own. Through participants listening to descriptions of each other's' experiences, it is also likely that they could have been triggered to remember and think of a greater range of experiences than in the individual interviews. However, there are also advantages related to carrying individual interviews. It can, for instance, be easier to address more personal and private aspects of participants' experiences in individual interviews.

In summary, we have to acknowledge that we have only gained insight into parts of the participants' experiences, and because of the interview context and our research questions, the importance of the amalgam attribution and the amalgam removal can have been inflated.

5.2 Ethical considerations

5.2.1 Clinical trial

For participants in both the treatment group and the reference group in the amalgam trial, there was a risk that participation in the study would lead to an increased focus on amalgam fillings and health complaints, which in turn could potentially result in increased health complaints and discomfort. Participants in the treatment group were informed about possible side effects from new fillings and possible complications connected with the dental procedures. To minimize the risk of complications, the dentists followed written guidelines on how to remove the dental amalgam (Norwegian Dental Biomaterials Adverse Reaction Unit, 2002). The participants in the reference group were not asked to go through a clinical examination at the beginning of the study, and they did not receive any treatment. This was done to reduce the possibility of participants in the reference group choosing to remove their dental amalgam on their own because of the re-examination. Due to lack of proven interventions for amalgam-related health complaints without objective findings, the lack of treatment in the reference group is deemed acceptable by ethical standards (World Medical Association, 2013, Paragraph 33).

5.2.2 Interview study

Participants were asked to participate in the interview study at the final follow-up five years after amalgam removal. Extra care was taken to communicate that participants were under no obligation to participate in the interview study; nevertheless, given the context, there is a risk that participants might have felt obligated to comply with the request. However, our impression was that they were eager to participate, and some

said they were happy to get a chance to elaborate on the answers they had given in the questionnaires. The focus for the interviews was on attribution of health complaints to dental amalgam and experienced changes in health complaints before, during and after amalgam removal. We did make it clear, however, that we were interested in other aspects of their lives that might have influenced their health and quality of life. As with participation in the amalgam removal trial, there was a risk that asking participants to focus on dental amalgam and health complaints might result in perceived increased health complaints and discomfort. There was also a risk that participation in the interview could trigger other emotional issues. All interviews were carried out by Therese T. Sjørusen (me), who is a psychologist, and under the supervision of Knut Dalen, who is a specialist in clinical neuropsychology. The interviews were scheduled at times when Dalen could be present if something should arise. Dalen watched video recordings of each interview, and Dalen and Sjørusen discussed the content of the interviews during the same workday when they were carried out. All participants were instructed that they should contact the Adverse Reaction Unit if they had any thoughts or questions regarding the amalgam trial or the interviews.

5.3 Findings

Overall, the results from the quantitative studies support the hypothesis that removal of all amalgam fillings in a group of patients with health complaints attributed to dental amalgam is associated with long-lasting reductions of the complaints. These results were supported, but also further nuanced, by the findings from the qualitative studies. In addition, the qualitative findings have given us increased insight into the active role of patients when it comes to experiencing, acting upon and giving meaning to health complaints without corresponding objective medical findings.

5.3.1 Reduced health complaints after amalgam removal

The participants in the treatment group reported that they felt better after amalgam removal. In the quantitative part of the study, we found significant reductions of index scores for intraoral and general health complaints three years after amalgam removal (Paper I), and we found that 19 of the 23 investigated health complaints were lower at the three-year follow-up than before amalgam removal (Paper II). Reductions of health complaints after amalgam removal have also been reported in previous amalgam removal studies (Table 1).

In Paper I, changes in health complaints in the group that had amalgam replaced were compared with changes in health complaints in a no-treatment reference group. Changes in index scores for intraoral and general health complaints were found to be significantly different in the two groups. In the reference group, there was a slight increase of index scores from Questionnaire 1 to Questionnaire 3. In Paper II, we compared the levels of the 23 investigated health complaints in the treatment group with the levels found in an external reference group from the general population. At the pre-treatment examination, patients in the treatment group reported a higher level of all health complaints than the participants from the external reference group. The difference between the treatment group and the external reference group was statistically significant for 11 of the 23 complaints. At the three-year follow-up, only 6 of the 23 health complaints were still significantly higher in the amalgam removal group than in the reference group from the general population. Even though the reported health complaints were reduced in the amalgam removal group, participants in this group still reported higher levels of complaint than the background levels in the general populations. Similar findings have been reported in previous studies (Lygre et al., 2005; Nerdrum et al., 2004; Tillberg et al., 2005).

Patients with health complaints attributed to dental amalgam have consistently been described as a heterogeneous group (see for instance Langworth et al., 2002; Lindh et al., 2002). Even though application of exclusion criteria is likely to have reduced the heterogeneity to some degree, our sample can still be described as heterogeneous. There was a considerable pre-treatment variation between the participants regarding

the number of reported complaints and perceived intensities of complaints, and the reported changes in health complaints after amalgam removal also varied greatly between participants (Paper II). Unfortunately, the sample was not large enough to perform post hoc analyses comparing responders and non-responders to the amalgam removal intervention.

Even though the majority of amalgam removal studies (Table 1) report some kind of reductions of health complaints at group level, the understanding of the specific effects of amalgam removal remains complex and somewhat elusive. When it comes to changes in specific health complaints, normally only some of the reported changes are statistically significant, and the health complaints that are significantly reduced may vary from study to study. For instance, in our study, mean values for 19 of the 23 surveyed health complaints were lower at the three years follow-up than at the pre-treatment examination (Paper II) with statistically significant reductions found for “taste disturbances”, “pain from muscles and joints”, “gastrointestinal symptoms”, “symptoms from ear, nose and throat”, and “fatigue”. The same questionnaire was used in a previous study (Lygre et al., 2005) that investigated changes in health complaints after removal of dental restorations (mostly dental amalgam). This study found a small reduction of all health complaints except gastrointestinal symptoms. However, the reductions were only statistically significant for “taste disturbances”, “dry mouth” and “intraoral stiffness/paresthesia”. Comparisons between these studies show that “taste disturbances” were significantly reduced in both, whereas “gastrointestinal symptoms”, which were significantly reduced in our study, increased in the study by Lygre et al. (2005). Some of this elusiveness can of course be connected to the predominantly small samples in these studies which increase the risk of a Type II-error (i.e. failing to reject the null hypothesis when it is false). However, the lack of consistent findings when it comes to changes of the specific symptoms is also likely to reflect the heterogeneous character of the complaints, and thus, the effect of amalgam removal is likely to be different from patient to patient, and perhaps, due to application of different inclusion criteria, the way the studies are carried out, and how the health complaints are measured, also from study to study. In the qualitative part of the study, we found that most of the participants reported feeling better after

amalgam removal (Paper IV) although none of the participants reported a full recovery. In an interview study from New Zealand (Jones, 2004) two-thirds of the participants who had completed amalgam removal and a detoxification process described having obtained a full recovery, and several of the participants referred to dental amalgam as a dripping tap that, through amalgam removal, had been turned off.

5.3.2 Factors influencing the reported reductions of health complaints

As discussed under Methodological considerations, even though we have a quasi-experimental design, the design of our study does not allow us to make strong causal inferences. The described limitations of both the quantitative and qualitative parts of our study must be kept in mind when interpreting the results. Consequently, the following suggestions of factors that can have influenced the reported reductions of health complaints have to be considered as hypotheses.

Reduced exposure to mercury: Participants' in the treatment group had significantly lower levels of mercury in serum and urine after removal of dental amalgam (Paper I). The mercury levels in the treatment group, however, were low even before the amalgam removal, and exploratory analyses of correlations between reduction of mercury in serum and reductions in health complaints resulted in only small, and not statistically significant, positive correlations. As described in the Introduction, there is a lack of scientific support for adverse effects from low-level exposure to mercury. It has been claimed, however, that people with typical amalgam exposure could be on the threshold to what is considered tolerable daily exposure (Homme et al., 2014), and it has been pointed out that there is a need for more research into the effects of genetic polymorphism on individual susceptibility to mercury (SCENIHR, 2015b). Consequently, reduced exposure to mercury can have contributed to the reduction of reported health complaints. However, given the lack of strong support for adverse effects of low-level exposure to mercury and the heterogeneity of reported complaints and changes in complaints, we also have to consider that the reported reductions of health complaints can have been influenced by other elements of the intervention and by other changes in the participants' lives.

Improved intraoral conditions after amalgam removal: In paper I, we found that index scores for intraoral and general health complaints were significantly reduced after replacement of amalgam fillings. Even though participants were excluded if they needed a complicated dental rehabilitation, the reported reductions of intraoral index scores may have been associated with improved oral conditions after the amalgam removal. In Paper I, we concluded that given that the removed amalgam fillings were described as sound and well-functioning, it seemed unlikely that an effect of improved dental health should be prominent three years after completed amalgam removal. However, in the interviews, which were carried out five years after amalgam removal (Paper IV), several of the participants described that they felt their oral condition had improved after the amalgam removal, indicating that these changes were perceived as significant and long-lasting. It was also evident that participants found it easier to connect experienced changes in intraoral health complaints with the amalgam removal than changes in general health complaints (Paper IV).

Non-specific factors related to the treatment context: As discussed under the heading Construct validity it is likely that non-specific factors related to the treatment context have influenced the results. Some of these factors, such as elimination of worry, are likely to be transferred to other settings, whereas the patient-centered communication and the general care associated with the follow-ups are not likely to be associated with amalgam removal in the general context. Even though the dentists may be as friendly and skilled as the dentists in our study, it is not likely that amalgam removal would be associated with an extensive follow-up in addition to the dental treatment.

5.3.3 Comparisons with other patient groups

Some of the complaints that amalgam patients report are similar to health complaints associated with chronic low-level exposure to mercury (Melchart et al., 2008). The reported complaints, however, are also similar to complaints found in groups of patients with diagnoses such as fibromyalgia (Clauw, 2009), chronic fatigue syndrome (Yancey & Thomas, 2012) and multiple chemical sensitivity (Winder, 2002), as well as to complaints found, albeit at lower levels, in the general population (Ihlebak et al., 2002). Due to the subjective nature of the complaints and the number of organ systems

involved, this is hardly surprising. It does, however, highlight the difficulties related to the demarcation of this patient group, and it points us towards situating patients with health complaints attributed to dental amalgam within the field of subjective health complaints or medically unexplained health complaints.

Patients with health complaints attributed to dental amalgam are sometimes described, particularly by the patients themselves and patient organizations, as suffering from amalgam illness, amalgam disease, or amalgam syndrome. Syndrome can be defined as: “A group of symptoms which consistently occur together, or a condition characterized by a set of associated symptoms” (Oxford Dictionaries, 2016). The defining feature of amalgam syndrome is the hypothesized cause of the complaints, and amalgam syndrome can as such be compared with other exposure-based syndromes, or sensitivity-related illnesses, like multiple chemical sensitivity, sensitivity to electromagnetic fields, and food intolerance, which are all characterized by patients reporting adverse health effects in relation to low-dose environmental triggers (Genuis, 2010). Within the field of subjective health complaints there are also a number of symptom-focused syndromes, or central sensitivity syndromes, for example chronic fatigue syndrome (CFS), irritable bowel syndrome (IBS) and temporomandibular joint disorder (TMJ)(Chinn, Caldwell, & Gritsenko, 2016). Both the exposure-based and symptom-focused syndromes are sometimes referred to as contested illnesses to delineate that the diagnoses are based on self-reported health complaints and that the etiology and demarcation of the syndromes are still unresolved (Dumit, 2006; Wainwright, Calnan, O'Neil, Winterbottom, & Watkins, 2006). However, recent advances, for instance in conjunction with dietary restrictions for patients with IBS (Ahmad & Akbar, 2015; Chey, 2016) and trials with the drug Rituximab for patients with CFS (Fluge et al., 2011; Mensah et al., 2015) have pointed to possible biological mechanisms associated with some of the experienced complaints in these conditions.

Within the field of subjective health complaints, there are many theories, terminologies and labels. However, for both patients and researchers/health personnel these can be experienced as lacking authoritative meaning if they are not validated by

biomedical findings and/or associated with clear prognoses or suggested treatments. When they are unable to obtain a diagnosis, or are diagnosed with a contested illness, patients can find it difficult to give meaning to their illness experiences, and for many patients the search for an answer can become important in itself. The complexities and uncertainties we as researchers face when trying to understand what lies behind the reported changes in health complaints can steer us towards appreciating how daunting the search for an answer can be for the patients themselves.

5.3.4 Life is complicated-let's fix it!

Through participants' descriptions of trying to live with and make sense of changes in health complaints, we identified a tension between acknowledging that health is determined by many factors and difficulties related to utilizing such an understanding when trying to deal with health complaints in everyday life.

Patients with health complaints attributed to an exposure such as dental amalgam run the risk of being perceived as only accepting and pursuing this one explanation for their health complaints, and patients with subjective health complaints are often described as dismissive of psychological and social explanations for their complaints (Risør, 2009). The findings from our interviews do not support such interpretations for our study group, and other studies have also identified complex illness explanations held by groups of patients with medically unexplained health complaints and contested diagnoses (Risør, 2009; Soderlund & Malterud, 2005)

The opening phrase of the interviews went something like: "The focus for this interview is possible changes in health complaints and quality of life after amalgam removal. However, we do know that things in life are connected, so we are interested in the big picture." This wording is of course likely to have set the tone for a conversation in which participants were prompted to think of and describe health as determined by many factors. The degree to which such aspects were interwoven in the participants' descriptions of both the attribution process and the way they experienced changes in health complaints, however, indicates that this is close to how they think of their health complaints in their everyday lives.

Even though the biopsychosocial model for disease was never specifically mentioned by the interviewer or the participants, all participants described having carried out a broad exploration of how the different factors in their lives, such as work conditions, family obligations, food, stress, worry et cetera could have influenced their health complaints both before and after removal of dental amalgam (Paper III and IV). Based on participants' descriptions, a pattern of behavior emerged involving a search for an answer, testing of a solution, and evaluation of the effect (Figure 5). In the interviews, the participants described this problem-solving sequence in detail in the pursuit of dental amalgam as a possible cause of their health complaints. However, participants also described having searched for other possible explanations before, in parallel with, and after pursuing the amalgam angle, and they also described at length how they had made a lot of different changes in their lives such as taking vitamin-supplements, changing their work conditions, experimenting with diets et cetera (Paper IV). An active search for answers has also been described in other studies of patients with medically unexplained health complaints, and the importance of naming (i.e. obtaining a diagnosis) is often stressed (Glenton, 2003; Kornelsen et al., 2015; Whitehead, 2006). In the study by Kornelsen et al. (2015) the search was described as “an “emotional rollercoaster” of hope that a diagnosis—and subsequent treatment—would be forthcoming” (p. 4).

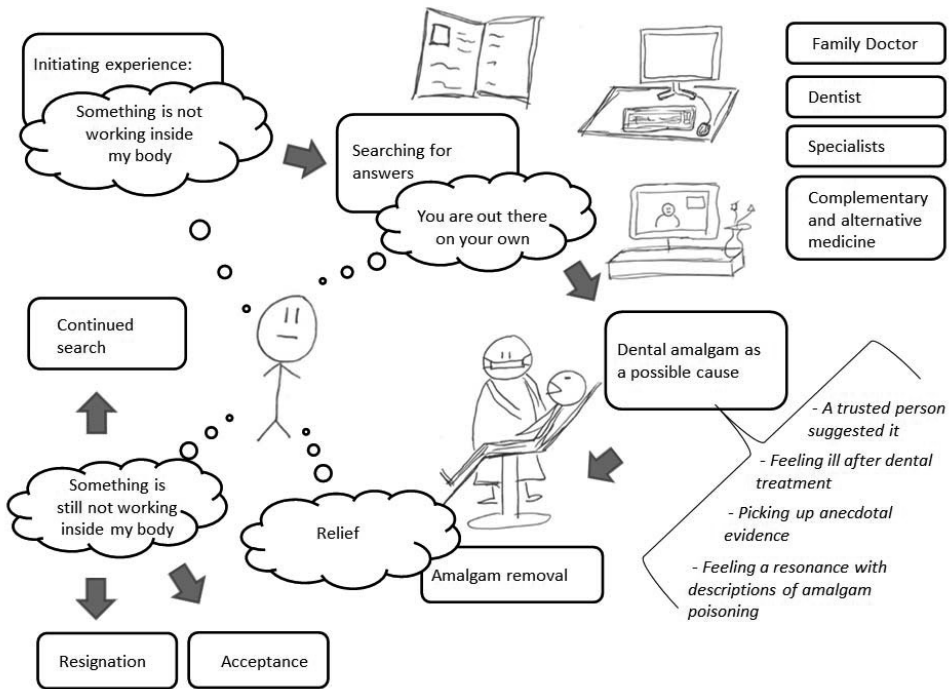


Figure 5: The pattern of searching for an answer, trying out a solution and evaluating the effect illustrated with dental amalgam as the explanation being tried out.

Most attribution theories (see for instance Försterling, 1988; Sensky, 1997) assume that people are motivated to seek causal explanations for their complaints and that they do this through methods similar to the ways scientists determine causality. This seems to be a good description for the participants in our sample. In their search for an explanation for their health complaints, they considered multiple possibilities, and when the search, due to one or more eliciting experiences, pointed in the direction of their amalgam fillings, they set out to evaluate whether this seemed to be a reasonable explanation for their health complaints. In Paper III, we identified five themes in participants' descriptions of the attribution process. In the first theme "Feeling puzzled" participants described that both characteristics of their health complaints, such as feeling that their whole body was influenced by something from the outside, and the lack of other explanations for their complaints, opened up for thinking that the complaints could be connected to their amalgam fillings. In the next three themes,

“Picking up anecdotal evidence”, “Temporal relationship between dental treatment and episodes of ill-health”, and “A trusted person suggested dental amalgam as an explanation for my complaints”, participants described different, but not mutually exclusive, routes to how they first started thinking of a possible link between their health complaints and their amalgam fillings. Other studies have also identified experiences of ill-health in relation to dental treatment (Lindh et al., 2002; Norheim & Ramstad, 2006; Tillberg et al., 2005), picking up anecdotal evidence (Jones, 2004) and suggestions from friends (Jones, 2004) as eliciting factors for forming an amalgam attribution. In the fifth theme in Paper III, “Feeling a resonance with descriptions of amalgam poisoning”, the initial suspicion was further processed through participants’ search for more knowledge and subsequent evaluation of whether this could apply to them. The majority of participants described feeling a strong sense of recognition at this point, and some described a feeling of relief associated with arriving at an amalgam attribution for their health complaints. For some of the participants, thinking of their health complaint as being caused by their amalgam fillings gave them hope that there might be a cure for their complaints. Consequently they could, for a while, stop searching for other explanations.

Even though some of the participants described letting go of the pursuit of other explanations for a while, it can be argued that inflexibility connected to pursuit of explanations is a more fitting description of the medical profession’s reactions to patients with subjective health complaints. In the interviews, participants described how living with and making sense of health complaints that are neither fully accepted nor satisfactorily understood by the medical profession took its toll both practically and emotionally (Paper IV). The process of trying to identify, or at least hypothesize, how interactions between biological, psychological and social variables influence the reported complaints, is cognitively taxing. As researchers and health personnel, we can easily end up in a far from satisfactory situation by arriving at either all-encompassing and useless explanations like “everything connects to everything else” or dismissive and equally useless explanations like “if the complaints cannot be objectively identified, there is no (somatic) pathology”. Common to both is the lack of a reasonable next step. In contrast to these non-actionable explanations, it is not hard to

understand that interactions or possible causes that in some way stand out can prompt patients to arrive at actionable, but limited, attributions. It is not difficult to understand the appeal of an explanation where one factor, such as the presence of amalgam fillings, could potentially explain the majority—or all—of the complaints for which the health profession has failed to find explanations. In addition to its simplicity, it also points towards a very concrete and implementable, albeit expensive, solution, namely amalgam removal.

As previously mentioned, both folk models and the models used by the medical and dental profession, easily revert to a biomedical understanding of disease where the way forward is dependent on objective findings pointing us towards a diagnosis. However, for people with subjective health complaints, a diagnosis is not always within reach, or if diagnosed with a contested illness, the patient might associate the diagnosis with almost as many unknowns as he/she had to face before being diagnosed (Kornelsen et al., 2015). Perhaps some of the emotional tug of the biomedical model is connected to the simplicity of thinking of disease as something concrete that can be controlled and attacked? In the words of Engel (1960):

To be able to think of disease as an entity, separate from man and caused by an identifiable substance, apparently has great appeal to human mind. Patients prefer to blame their illness on something they “caught” or ate, or that happened to them, and to think of disease as something apart. Physicians also find such ways of thinking attractive, particularly if they can see the “cause” of the disease as something which they can attack and destroy. (p. 48)

For patients with subjective health complaints such a conceptualization, however, is far from their everyday experiences. Given the lack of answers associated with subjective health complaints, it can be difficult for patients to know where to direct their energy. Is their energy best spent searching for an explanation and thereby hopefully also a cure? On the other hand, is it better to spend energy on trying to adapt to and live with the health complaints? Juxtaposed with the sheer number of interactions one potentially has to consider within a biopsychosocial framework, the

allure of more simple and actionable conceptualizations, such as an amalgam attribution or a non-contested diagnosis, is not difficult to understand.

5.3.5 Finding meaning

However, to look at subjective health complaints merely as problems that can be fully solved or fully understood if only one spends enough time, money and brain power on it, either at macro level (e.g. research efforts) or at micro level (i.e. each individual's quest for a solution), could lead us to miss important parts of the puzzle. When faced with health complaints, both explained and unexplained, patients often experience the need to find meaning in their complaints. For patients with unexplained health complaints, this process can be hindered, and sometimes even “railroaded”, by the search for a diagnosis.

In paper IV, we used Cassel's (1982) definition of suffering: “suffering occurs when an impending destruction of the person is perceived; it continues until the threat of the integration has passed or until the integrity of the person can be restored in some other manner” (p. 640). In this lies an important distinction between pain/health complaints and the suffering associated with them. Health complaints that are interpreted as signifying “impending destruction”, for instance through threatening participants' life span, relationships and/or perception of self, are associated with more suffering than health complaints that are interpreted as transient or controllable. Health complaints with unknown prognoses are likely to cause more suffering than equally severe health complaints where one is expected to make a full recovery within a reasonable time frame. Consequently, it is not difficult to understand that the lack of answers associated with subjective health complaints can lead to increased suffering. When so much is unknown, it is hard to evaluate the severity and the probability of “the impending destruction”, and the necessary steps either to fend off the destruction or to find some other way to “restore the integrity of the person” may not be readily seen. This puts an extra pressure on both patients and health personnel. However, as also discussed in Paper IV, in the context of medical encounters, patients and health personnel mostly focus on the pain or the health complaint in question and not on the suffering associated with it (Loeser, 2000).

When a resolution of the complaints cannot be obtained through standard diagnostic procedures, both patients and health personnel may react with frustration and the quality of communication can deteriorate. In Paper IV, participants' described feeling left to their own devices when physicians were unable to explain their health complaints. The importance of having someone with whom they could discuss their health complaints was pointed to by several of the participants. Some of them described having a close relationship with practitioners of alternative medicine, and most of the participants described that they had really appreciated the follow-up they had received from the personnel at the Adverse Reaction Unit during the trial. Some of the perceived benefits are probably related to patients being seen and heard. However, it is also likely that to have someone with whom to discuss perceived health complaints and potential consequences of the health complaints, can result in assuaged worries and increased confidence in being able to manage one's health complaints.

In our material, participants' suffering was perhaps most strongly communicated when they described their feelings of not being able to perform as well as others because of their health complaints. From an outsider's perspective, the participants' descriptions of what they managed to do despite their health complaints were impressive. The participants themselves, however, did not seem to share this view. Instead they pointed to a number of activities and obligations they were not able to participate in or carry out as they wanted. Several expressed sadness at not being able to perform as effortlessly as people without health restraints. With the exception of wanting to be a better parent, spouse et cetera, many of the activities they said they were unable to carry out (such as participating in social activities at work, meeting friends and acquaintances, etc.) could easily have been deprioritized by people without similar health complaints. Nevertheless, not being able to carry out these activities seemed to have almost symbolical value for some of the participants. This is probably related to participants' feeling that they did not have a choice when they had to drop participation in these activities. However, the discord between facing challenges and obligations with energy and drive, as we also touched upon in Paper IV, and having to say no to participating in activities may also partly explain the participants' sadness and frustration. When describing these situations, and the differences between

themselves and people without similar health complaints, a threat to the person's integrity could be felt, and the uncertainties related to prognosis seemed to accentuate their suffering.

Participants also seemed to grapple with where they should direct their energy: Should they continue their search for other explanations or should they consider their health complaints as something to be expected and as a part of their everyday life? Some of the participants expressed relief, but also resignation, in terms of relaxing their efforts to find an answer. Several of the participants acknowledged that the search for an explanation and/or effective treatment strategies had been time consuming and exhausting, and they saw clear benefits in easing up on their efforts and instead focusing on enjoying the best life possible despite their health complaints. For several of the participants, however, it seemed important that they had pursued many different potential explanations, and thereby had truly made an attempt to get better. For several of the participants, the amalgam removal was described as a necessary step towards accepting their health complaints. Without the removal, they suspected that they would always have had a lingering suspicion that their health complaints were associated with their amalgam fillings.

We believe that it is important to find a way of routinely addressing the effects that patients' health complaints have on their everyday lives and their hopes and fears for the future. Through staying close to patients' experiences of their health complaints, the suffering related to the health complaints and the way the health complaints influence their everyday life, we believe health personnel can gain important insight into patients' experiences, and hopefully, patients will be enabled to find an arena for creating meaning of their illness experiences. For patients with subjective health complaints, the importance of having a good patient-physician relationship with room for exploration of patients' experiences has been repeatedly described (see for instance Kornelsen et al., 2015; Peters et al., 2009). When relevant medical examinations have been carried out, it is important that both health personnel and patients acknowledge that even though it is not always possible to find the answers, or even to agree on the probable cause of the complaints, many patients will nevertheless still need help to

find ways of living with their health complaints. In a biopsychosocial perspective, there should be many ways to address this and hopefully also to ease the burden for patients. However, if the patients believe that a likely effective treatment, such as amalgam removal, is within reach, it is likely that other approaches seem deficient and perhaps even insensitive.

6. Conclusion

The participants reported reduced levels of health complaints after amalgam removal. Analyses of mercury concentration showed that mercury levels in serum and urine were significantly reduced after amalgam removal. The mechanisms behind the reported reductions in health complaints are probably compounded, however, and not limited to the reduced exposure to mercury. This was also acknowledged and underscored by the participants in the interview study, and their experiences of changes in health complaints after amalgam removal can be summarized by the statement “It was certainly important to get rid of the amalgam, but it is uncertain how important the removal was for the experienced changes in health complaints.”

Different explanations for the reported changes in health complaints were suggested, including non-specific treatment effects associated with the interventions. This is important to keep in mind when estimating the effects of amalgam removal on health complaints in a regular treatment context or if designing future amalgam removal studies. The effects of the amalgam removal, particularly related to participants feeling better, which was evident both in the quantitative and qualitative part of our study, should not be dismissed, however. Similar findings have also been reported in previous studies (Table 1). In the interviews, several participants emphasized the importance of amalgam removal for moving towards an acceptance of health complaints as part of life, and regardless of perceived health effects of the amalgam removal all participants expressed relief in having had all their amalgam fillings removed.

7. Future perspectives

When maneuvering a field with a lack of definite answers and diagnoses, it is important to make room for addressing the suffering associated with pain, health complaints and illness experiences in medical encounters. If we, as researchers and health personnel, take the time to listen to patients' explanations for their health complaints and their fears associated with them, we can better understand and hopefully also help. We may also find that patients' explanations are far more complex than what we normally catch on to within the short and, often tightly scripted, medical and dental encounters that normally take place. In addition to making sure that the patients receive appropriate and exhaustive medical and dental examinations, we should, together with the patients, explore the different ways social and psychological factors interact with the experienced health complaints.

In our encounters, we should also take in that reassurances such as “dental amalgam is considered a safe treatment alternative at group level” could have limited value for patients who suspect that this does not hold true for them. We should also take in that our study and other studies such as the studies described in Table 1, find that patients report improved health after replacement of amalgam fillings. Even though the mechanisms behind this are most likely compounded and not limited to the reduced exposure to mercury, the fact that we do not fully understand the reasons for the reported reductions of health complaints is perhaps of greater concern for researchers and health personnel than for the patients themselves. Patients who still fear their health complaints are caused by their amalgam fillings after having had the chance to discuss their concern with health personnel who possess updated knowledge and have the time and motivation to listen to the patients, should be given the opportunity to have their amalgam fillings removed at a cost they can afford. However, other causes for the health complaints must be properly investigated and excluded before initiating amalgam removal and the risk associated with removing sound fillings must be explained in advance (Norwegian Directorate of Health, 2008).

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Papers I-IV

Changes in health complaints after removal of amalgam fillings

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SUMMARY The aim of the present study was to investigate whether removal of all amalgam fillings was associated with long-term changes in health complaints in a group of patients who attributed subjective health complaints to amalgam fillings. Patients previously examined at the Norwegian Dental Biomaterials Adverse Reaction Unit were included in the study and assigned to a treatment group ($n = 20$) and a reference group ($n = 20$). Participants in the treatment group had all amalgam fillings replaced with other restorative materials. Follow-ups took place 3 months, 1 and 3 years after removal of all amalgam fillings. There was no intervention in the reference group. Subjective health complaints were measured by numeric rating scales in both groups. Analysis of covariance was used to compare changes in health complaints over time in the two groups. In the treatment group,

there were significant reductions in intra-oral and general health complaints from inclusion into study to the 3-year follow-up. In the reference group, changes in the same period were not significant. Comparisons between the groups showed that reductions in intra-oral and general health complaints in the treatment group were significantly different from the changes in the reference group. The mechanisms behind this remain to be identified. Reduced exposure to dental amalgam, patient-centred treatment and follow-ups, and elimination of worry are factors that may have influenced the results.

KEYWORDS: health complaints, amalgam, before-and-after study, dental, restoration

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Introduction

For decades, dental amalgam has been extensively used in the treatment of caries lesions. Dental amalgam consists of approximately 50% metallic mercury mixed with an alloy mainly consisting of silver, tin and copper (1). The safety of dental amalgam has been questioned, and it has been discussed to what extent mercury released from amalgam fillings may lead to adverse health effects (2–8). Generally, no deleterious effects from amalgam are detected in

studies on samples of the general population (5, 9–11), and no adverse reactions could be detected in two randomised controlled studies on school children treated with dental amalgam (3, 4). Dental amalgam fillings release elemental mercury vapour in the mouth, resulting in elevated concentrations of mercury in blood, plasma and urine, and concentration of inorganic mercury in the brain (12–19). The possibility that a small fraction of the population may have predispositions to rare adverse reactions to dental amalgam cannot be ruled out; thus, research on adverse effects associated with exposure to dental amalgam should focus on the possibility of rare outcomes (20). People with health complaints

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attributed to dental amalgam believe their health complaints are caused, or aggravated, by mercury released from their amalgam fillings. It has been established that dental amalgam fillings may lead to local adverse reactions, including oral lichenoid reactions (21), and removal of amalgam fillings in contact with the lesions is generally recommended. However, for a number of patients, no objective signs of adverse reactions to amalgam fillings, or other diseases explaining their complaints, can be observed (22). Patients who attribute subjective health complaints to dental amalgam describe a number of health complaints including tiredness, headaches, pain from muscles and joints, and problems with memory and concentration (18, 22). There is a lack of treatment options for patients without objective signs of adverse reactions to amalgam fillings, and removal of sound amalgam fillings is generally not recommended. Some patients nevertheless decide to remove all amalgam fillings at their own initiative (23), and studies have reported significant improvements in subjective health complaints after the removal of amalgam fillings (24, 25).

The aim of the present study was to investigate whether removal of all amalgam fillings in a group of patients who attributed subjective health complaints to dental amalgam (treatment group) was associated with long-lasting changes in subjective health complaints. The underlying null hypothesis was that there would be no significant differences in long-term changes in health complaints between the treatment group and a comparable reference group. In addition, secondary analyses of changes in health complaints in the treatment group and the reference group were investigated independently, testing the null hypotheses of no changes in health complaints within each group. Within-group changes in mercury concentration in serum and urine in the treatment group were also investigated.

Materials and methods

Design

The study was designed as a before-and-after study with a comparison group (reference group) comparing changes in health complaints in a treatment group, which had all amalgam fillings replaced with other restorative materials, with changes in health complaints in a comparable reference group, which did not receive any intervention.

Participants

Participants were recruited from patients ($n = 368$) examined at the Norwegian Dental Biomaterials Adverse Reaction Unit in the period 1993–1999 (initial examination; Fig. 1). The majority of the patients had been referred to the unit because of health complaints attributed to amalgam fillings (22). Generally, either the patient or the referring physician/dentist had raised the question that dental materials could be a causal or contributing factor related to the patient's health problems. In 2000–2001, patients with known addresses ($n = 358$) were sent a questionnaire (Questionnaire 1) regarding current health complaints and medical and dental treatment since the initial examination. The questionnaire was returned by 207 patients (Fig. 1). Based on the responses to the questionnaire, 157 patients did not fulfil one or more of the inclusion criteria listed in Table 1, leaving 50 patients who were randomly allocated into a treatment group ($n = 20$), a reference group ($n = 20$) and a group of reserves ($n = 10$; Fig. 1). The function random number in Microsoft Excel 97 was used for the allocation. The exclusion criteria listed in Table 1 were applied to the treatment group in order to increase the probability of participants in this group being able to complete the replacement process. Six participants were excluded from the treatment group according to these criteria. The same exclusion criteria were used in the group of reserves for sequential inclusion into the treatment group, resulting in four participants not being eligible for participation in the treatment group. The remaining six participants from the group of reserves were used to replace the excluded participants from the treatment group. The criteria were applied based on clinical documentation, telephone interviews and a clinical examination (pre-treatment examination). The exclusion criteria were initially not applied to the reference group as no intervention was planned for this group.

Initial examination (1993–1999)

At the initial examination at the unit (22), patients underwent a medical and dental examination. Blood and urine samples were collected and analysed for mercury in addition to routine analyses (17). Patients were also asked to complete questionnaires regarding suspected adverse reactions to dental materials, current and previous health complaints and demographic

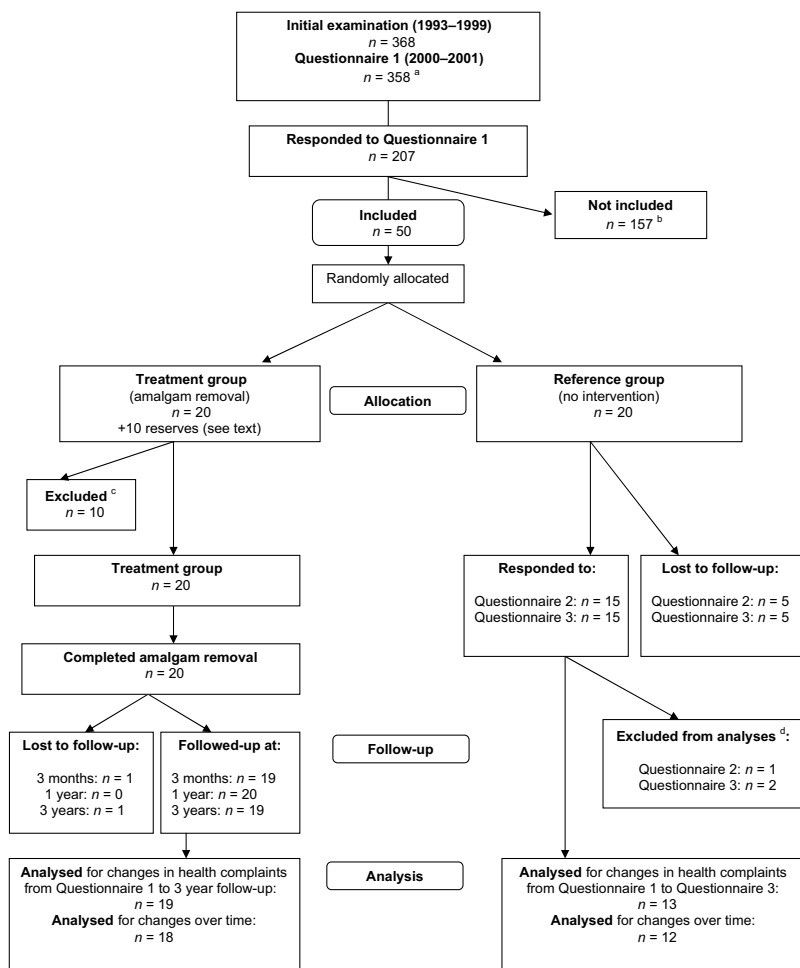


Fig. 1. Participant flow. Flow diagram showing participant flow in the study. The study is a before-and-after study with a comparison group (reference group). ^aCurrent addresses were missing for 10 patients; ^bdid not fulfil inclusion criteria listed in Table 1; ^cexcluded according to exclusion criteria listed in Table 1; ^dremoved all amalgam fillings.

variables. Participants included in the present study had at the initial examination neither signs of contact allergic reactions to dental materials nor a known history of such reactions and consequently were not recommended removal of amalgam fillings.

Questionnaire 1 (2000–2001)

Questionnaire 1 included questions regarding current health complaints, treatment since the initial examina-

tion and demographic variables. Health complaints were measured by numeric rating scales using numbers from 0 to 10. No information on a planned intervention study was given in the questionnaire. Responses to Questionnaire 1 were used for identifying patients eligible for participation and as baseline values for comparisons of changes in health complaints in the treatment group and the reference group. Questions from Questionnaire 1 were included in all subsequent questionnaires.

Table 1. Eligibility criteria and number of patients not included. Inclusion criteria were applied based on information from initial examination and Questionnaire 1. Exclusion criteria were applied in the treatment group and reserves, and were applied in relation to the pre-treatment examination in September 2000

Inclusion criteria	Numbers not fulfilling criterion [†]
Referred to the Norwegian Dental Biomaterials Adverse Reaction Unit for examination of health complaints attributed to amalgam fillings	33
Amalgam fillings still present	79
No diagnosed contact allergy to substances in resin-based dental materials	54
Health complaints from at least three different organ systems	25
Data on mercury in blood and urine from initial examination	59
Age 25–55 at initial examination	10
Accepted to be contacted in a follow-up study	11
Exclusion criteria (treatment group and reserves)	Numbers excluded
Severe medical disorders (e.g. multiple sclerosis, ALS, severe rheumatoid arthritis)	1
Severe food allergies	1
Psychological difficulties or psychiatric disorders that could influence the dental treatment	3
Complicated therapy (severe periodontitis, high caries activity and/or need for complicated dental rehabilitation – e.g. bridges)	4
Inclusion criteria no longer fulfilled	1 [‡]

[†]One hundred and fifty-seven patients did not fulfil one or more of the inclusion criteria.

[‡]Completed removal of amalgam fillings since responding to Questionnaire 1.

Pre-treatment examination

In September 2002, participants in the treatment group underwent a pre-treatment examination consisting of medical and dental examinations and collection of samples of blood serum and urine. Blood serum was analysed for mercury concentration by sector field inductively coupled plasma–mass spectrometry (26, 27), while urine was analysed for mercury concentra-

tion by cold vapour atomic absorption spectrometry (28). Participants also responded to a questionnaire similar to Questionnaire 1. The pre-treatment examination and all subsequent follow-ups took place at the Dental Biomaterials Adverse Reaction Unit. Participants in the reference group were not assigned any treatment and were not asked to go through a pre-treatment examination.

Intervention

The assigned intervention in the treatment group was removal of all amalgam fillings. The amalgam fillings were replaced with other dental restorative materials (e.g. composites, ceramic restorations and metallo-ceramic crowns). All treatment costs were covered by project funds. Replacement of amalgam fillings is not possible to mask, and thus, no blinding was used. The replacement was carried out by the participants' own dentists according to clinical guidelines aiming at minimal exposure to mercury during removal sessions (29). The dentists were instructed to use rubber dam, high-volume suction, water cooling and to remove fillings in chunks using a sharp dental bur. Eighteen dentists from 18 different dental practices were involved in the study. One dentist treated three patients; the other dentists treated one patient each. Participants were given written instructions to contact the Dental Biomaterials Adverse Reaction Unit if they experienced increased health complaints like chills, fever, pain and rashes in relation to the amalgam replacement process. These instructions included advice to the patient's physician regarding blood tests to be taken (leucocytes, CRP, IgE and mercury concentration in blood) in case of increased health complaints after dental treatment.

To compare replacement of amalgam fillings with the standard treatment (i.e. no amalgam replacement), no intervention was assigned to the reference group.

Follow-up

Treatment group. Routines for the follow-ups were similar to the pre-treatment examination. Follow-ups took place 3 months, 1 and 3 years after completed replacement of amalgam fillings (Fig. 2). The follow-ups included control of the new dental restorations by a dentist, questions about experienced side effects like post-operative dental pain and other complications, and collection of serum samples. Urine samples were

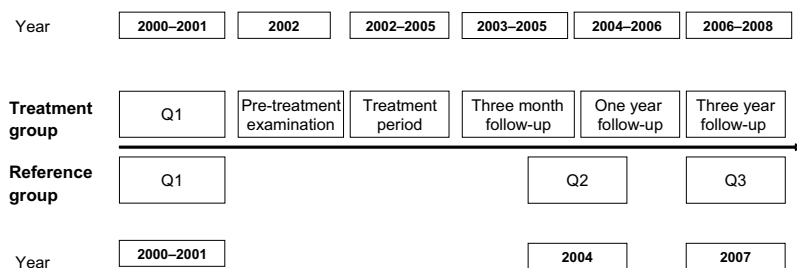


Fig. 2. Timeline for the study. Timeline for the trial for the treatment group and the reference group. Q1, Q2 and Q3 indicate Questionnaire 1, Questionnaire 2 and Questionnaire 3, respectively. Time frames for the activities are indicated for the treatment group (top) and the reference group (bottom).

collected at follow-up after 1 year. No general medical interview or health guidance was included.

Reference group. Follow-ups in this group were limited to questionnaires sent by post. Participants were sent Questionnaire 2 in 2004 and Questionnaire 3 in 2007. Questionnaire 2 was given at approximately the same time as the majority of participants in the treatment group went through their 1-year follow-up. Questionnaire 3 was given in parallel with the 3-year follow-up in the treatment group (Fig. 2). Based on available information from the initial examination and Questionnaire 1, the exclusion criteria used in the treatment group were applied *post hoc* to the reference group, resulting in two of the initial 20 participants being excluded. Reasons for exclusion were severe food allergy and complicated dental treatment (one patient) and diagnosed contact allergy to substances in resin-based dental materials (one patient). Results from comparisons of changes in health complaints in the treatment group and the reference group were calculated using both the initial reference group and the reference group with the two participants excluded from analyses.

Outcome variables

Primary outcome measures were changes in local oro-facial complaints and general health complaints from Questionnaire 1 (inclusion into study) to the 3-year follow-up in the treatment group and to Questionnaire 3 in the reference group. Current health complaints in both groups were measured by numeric rating scales (30) included in the questionnaires. The questionnaires

were given at all measure points. The same scales have previously been used in a similar patient population (8) and include 23 items addressing a diverse range of oro-facial and general health complaints frequently reported by patients with subjective health complaints attributed to amalgam fillings. Oro-facial complaints were categorised as either intra-oral (six items: intra-oral burning sensation, intra-oral pain/tenderness, taste disturbances, intra-oral stiffness/paresthesia, dry mouth and increased salivation/mucus) or extra-oral (five items: extra-oral burning sensation, extra-oral pain/tenderness, extra-oral stiffness/paresthesia, extra-oral skin problems and pain from temporomandibular joints). The sum scores for each category were used as index scores (8). Index scores for general health complaints (12 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) were constructed in the same way (8). Highest possible index score was 60 for intra-oral index, 50 for extra-oral index and 120 for the general health complaints index. Internal consistency for the indices was estimated by Cronbach's alpha using the entire group of patients randomised ($n = 50$; Fig. 1) and found to be 0.66, 0.72 and 0.80, respectively.

Power calculation

Number of participants included in this study was limited by available patients. One of the main objectives of the study was to test the null hypothesis that changes in index scores for health complaints were equal in the

treatment group and in the reference group. Assuming a mean difference in index score for general health complaints of 10·0 between the groups (corresponding to a mean difference before–after of 10·0 in the treatment group versus a mean difference of 0·0 in the reference group) and a common within-group standard deviation of 10·0, a sample size of 20 patients in each group will give the study a power of 87% to yield a statistically significant result. The criterion for significance (α) was 0·05, and the test was two-tailed.

Statistical methods

Mean values with 95% confidence intervals and analysis of variance were used for comparisons between groups. Paired-sample *t*-tests and analysis of variance for repeated measures were used to investigate within-group changes over time. Variables for changes in health complaints, from Questionnaire 1 to the 3-year follow-up in the treatment group and from Questionnaire 1 to Questionnaire 3 in the reference group, were constructed by subtracting the most recent scores from the scores from Questionnaire 1. A positive value indicated a reduction in complaints, whereas a negative value indicated increased complaints. The primary hypothesis of changes in reported health complaints in the treatment group compared with the reference group was tested by between-group comparisons of unadjusted pre–post per-protocol changes in the two groups using independent-sample *t*-tests. Adjustments for age, gender, and complaint intensity reported in Questionnaire 1 were made by analysis of covariance. We used last value carried forward to replace missing values for intention-to-treat analysis (ITT). SamplePower 2.0* was used for power calculations, and SPSS 15.0* was used for all other statistical analyses. *P*-values <0·05 were considered statistically significant for all analyses.

Ethical approval and registration

The project protocol was approved by the Regional Committee for Medical Research Ethics in Western Norway (REK III, 24.01) and registered at ClinicalTrials.gov (NCT00346944). Participants in the treatment group received information on possible side effects from

new fillings and possible post-operative complications following replacement of amalgam fillings. Written consent was obtained from all participants in both groups.

Results

Participant flow and numbers analysed

Treatment group. All 20 participants in the treatment group received the assigned intervention (replacement of all amalgam fillings). One participant could not attend the 3-month follow-up, and another participant could not attend the 3-year follow-up. For analysis of changes in health complaints from Questionnaire 1 to the 3-year follow-up, data from 19 participants were analysed (Fig. 1). For repeated measures analysis, data from 18 participants were analysed (Fig. 1).

Reference group. Questionnaire 2, which was sent to all 20 participants in the reference group in 2004, was returned by 15 participants. One participant reported having removed all amalgam fillings between Questionnaire 1 and Questionnaire 2. Questionnaire 3 was sent to all 20 participants in the reference group. The questionnaire was returned by 15 participants (Fig. 1). For analyses of changes in health complaints from Questionnaire 1 to Questionnaire 3, data from 13 participants were analysed. For repeated measures analysis, data from 12 participants were analysed. Changes in health complaints in the treatment group were also compared with changes in the reference group after *post hoc* application of exclusion criteria based on data from 12 participants in the reference group.

Initial examination and Questionnaire 1

Data from the initial examination and Questionnaire 1 were used as baseline values in the study. Number of amalgam surfaces and concentration of mercury in blood and urine were not significantly different between the groups at the initial examination (Table 2). Results from Questionnaire 1 showed that the final treatment group ($n = 20$) was similar to the reference group ($n = 20$) with regard to age, gender distribution, education level and medication. Levels of reported intra-oral, extra-oral and general health complaints were slightly lower in the treatment group, but

*SPSS Inc., Chicago, IL, USA.

Table 2. Descriptive background data. Background data for the treatment group, the reference group and for patients excluded from the treatment group. Data obtained at the initial examination and from Questionnaire 1 (Q1)

	Treatment group (<i>n</i> = 20)	Reference group (<i>n</i> = 20)	Excluded from treatment group (<i>n</i> = 10)	Data from
Women, <i>n</i> (%)	14 (70)	16 (80)	8 (80)	
Age (years) in September 2000, mean (s.d.)	46.9 (6.7)	44.7 (6.5)	52.6 (7.0)	
Education (years), mean (s.d.)	11.5 (3.6)	11.3 (2.8)	10.3 (2.6)	Initial ex.
Reported smoking at initial examination, <i>n</i> (%)	4 (20)	7 (35)	3 (30)	Initial ex.
On sick leave or disability pension, <i>n</i> (%)	9 (45)	7 (35)	9 (90)	Q1
Regular dental care, <i>n</i> /valid <i>n</i> [†] (%)	17/18 (94)	20/20 (100)	6/7 (86)	Q1
Used medication last 12 months, <i>n</i> (%)				
Analgesics	13 (65)	13 (65)	7 (70)	Q1
Antidepressants	6 (30)	3 (15)	2 (20)	
Vitamins/dietary supplements	13 (65)	13 (65)	8 (80)	
Participants' assessments of risks associated with dental amalgam, <i>n</i> (%)				
Very high	17 (85)	15 (75)	10 (100)	Q1
Medium	3 (15)	4 (20)	–	
Low	–	–	–	
Very low	–	–	–	
Missing	–	1 (5)	–	
Number of amalgam surfaces, mean (s.d.)	36.8 (11.1)	38.0 (11.3)	27.2 (16.3)	Initial ex.
Concentration of mercury, mean (s.d.)				
Blood (nmol L ⁻¹)	23.5 (10.4)	27.5 (12.5)	33.0 (22.1)	Initial ex.
Urine (nmol L ⁻¹)	24.0 (17.6)	22.0 (16.4)	21.0 (19.7)	
Urine (nmol per mmol creatinine)	2.7 (1.9)	2.6 (2.7)	2.4 (2.3)	
Self-reported health complaints, mean (s.d.)				
Intra-oral index	8.4 (6.6)	13.0 (12.0)	11.2 (7.2)	Q1
Extra-oral index	6.9 (8.4)	11.0 (9.3)	9.2 (8.0)	
General index	41.5 (16.0)	47.3 (21.2)	42.3 (15.0)	

[†]Five patients did not answer the question but had started removal of amalgam restorations.

the differences between the groups were not statistically significant. The proportion of individuals currently on sick leave or receiving disability pension was considerably higher in the group of individuals who were excluded from the treatment group compared to the treatment group and the reference group. Participants' assessments of risks associated with dental amalgam were similar across groups (Table 2).

Comparisons of changes in health complaints in the treatment group and the reference group

Per-protocol comparisons of changes in health complaints, from Questionnaire 1 to the 3-year follow-up in the treatment group and Questionnaire 3 in the reference group, showed that changes in mean index scores for intra-oral and general health complaints were significantly different in the two groups, whereas changes in extra-oral health complaints were not

significantly different (Table 3). After adjusting for gender, age and complaint intensity reported in Questionnaire 1, changes in intra-oral and general health complaints remained significantly different, and changes in extra-oral health complaints remained not significantly different (Table 3). Results from intention-to-treat comparisons were in general similar to the results from per-protocol analyses (Table 3). Results from analyses based on data from the reference group after *post hoc* application of exclusion criteria showed no major differences compared with the analyses using all 13 participants from the initial reference group. Unadjusted per-protocol differences in changes in index scores between the treatment group and the reference group after application of exclusion criteria were 8.3 (95% CI: 1.2 to 15.3, *P* = 0.024), 3.6 (95% CI: -3.7 to 10.7, *P* = 0.320) and 19.9 (95% CI: 8.1 to 31.7, *P* = 0.002) for the intra-oral, extra-oral and general indices, respectively.

Table 3. Comparisons of changes in health complaints in the treatment group and the reference group. Per-protocol (PP) and intention-to-treat (ITT) comparisons of changes in health complaints from Questionnaire 1 to the 3-year follow-up in the treatment group and Questionnaire 3 in the reference group. Mean changes in index scores and mean differences in changes in index scores (mean changes in the treatment group minus mean changes in the reference group) are given

	<i>n</i>	Difference Questionnaire 1- to 3-year follow-up [†]		Unadjusted differences in changes in index scores [‡]			Adjusted difference in changes in index scores [§]		
		Mean [¶]	95% CI	Mean	95% CI	<i>P</i> -value*	Mean	95% CI	<i>P</i> -value*
Intra-oral index									
Treatment group (PP)	19	3.7	0.5 to 6.9						
Reference group (PP)	13	-4.2	-11.6 to 3.1						
Treatment-reference (PP)				7.9	1.1 to 14.7	0.024	8.1	1.9 to 14.2	0.012
Treatment group (ITT)	20	3.5	0.4 to 6.6						
Reference group (ITT)	20	-0.6	-6.4 to 5.2						
Treatment-reference (ITT)				4.1	-2.3 to 10.5	0.200	6.9	1.3 to 12.4	0.016
Extra-oral index									
Treatment group (PP)	19	1.5	-2.8 to 5.8						
Reference group (PP)	13	-1.8	-7.9 to 4.3						
Treatment-reference (PP)				3.2	-3.7 to 10.2	0.346	5.5	-0.4 to 11.4	0.066
Treatment group (ITT)	20	2.0	-2.2 to 6.2						
Reference group (ITT)	20	-0.6	-4.8 to 3.6						
Treatment-reference (ITT)				2.6	-3.1 to 8.3	0.365	4.3	-1.6 to 10.3	0.145
General index									
Treatment group (PP)	19	9.7	4.4 to 15.0						
Reference group (PP)	13	-8.7	-21.4 to 4.0						
Treatment-reference (PP)				18.4	6.8 to 30.0	0.003	17.4	5.8 to 29.0	0.005
Treatment group (ITT)	20	10.1	5.0 to 15.2						
Reference group (ITT)	20	-2.3	-13.1 to 8.5						
Treatment-reference (ITT)				12.4	0.9 to 23.9	0.036	14.2	2.4 to 26.0	0.020

*Level of significance: $P < 0.05$.

[†]For the reference group, data from Questionnaire 3 were used.

[‡]Independent-sample *t*-test comparing changes in index scores in the treatment group and the reference group.

[§]Analysis of covariance of changes in index scores in the treatment group and the reference group, adjusted for gender, age and health complaints from Questionnaire 1.

[¶]Positive values indicate reduced health complaints, and negative values indicate increased health complaints.

Changes in health complaints in the treatment group

In the treatment group, there were significant reductions in mean index scores for intra-oral and general health complaints from Questionnaire 1 to the 3-year follow-up (Table 3). The reduction in mean index scores for extra-oral health complaints in this period was not significant. Intention-to-treat analysis showed similar results as the per-protocol analysis (Table 3). In the repeated measures analysis (Table 4), data from the pre-treatment examination and all follow-ups were included. Per-protocol repeated measures analysis showed significant overall effects of time for all three index scores. Plots of intra-oral, extra-oral and general index scores from Questionnaire 1 against index scores at 3-year follow-up are given in Fig. 3.

Changes in health complaints in the reference group

In the reference group, there was a slight, but not statistically significant, increase in mean index scores for intra-oral, extra-oral and general health complaints from Questionnaire 1 to Questionnaire 3 (Table 3). Intention-to-treat analysis showed no significant changes in mean index scores from Questionnaire 1 to Questionnaire 3 (Table 3). Data from Questionnaire 2 were included in the repeated measures analysis (Table 4). Per-protocol analysis of changes in mean index scores over time showed a significant overall effect of time for general health complaints. Plots of intra-oral, extra-oral and general index scores from Questionnaire 1 against index scores from Questionnaire 3 are given in Fig. 3.

Table 4. Repeated measures analysis of changes in health complaints over time. Per-protocol (PP) and intention-to-treat (ITT) repeated measures analysis of changes in health complaints in the treatment group and the reference group. Mean index scores, standard deviations (s.d.) and *P*-values for within-group changes over time are given

		Questionnaire 1	Pre-treatment examination	3-month follow-up	1-year follow-up [†]	3-year follow-up [‡]	<i>P</i> -value*
	<i>n</i>	Mean (s.d.)	Mean (s.d.)	Mean (s.d.)	Mean (s.d.)	Mean (s.d.)	
Treatment group							
Intra-oral index (PP)	18	8.6 (6.9)	6.6 (3.8)	6.7 (4.5)	4.7 (5.2)	5.2 (3.8)	0.026
Intra-oral index (ITT)	20	8.4 (6.6)	6.8 (3.7)	6.4 (4.5)	4.8 (5.0)	4.9 (3.8)	0.015
Extra-oral index (PP)	18	6.7 (8.8)	6.7 (7.1)	5.7 (6.4)	2.4 (3.2)	4.8 (4.3)	0.004 [§]
Extra-oral index (ITT)	20	6.9 (8.4)	6.8 (6.8)	5.6 (6.3)	2.8 (3.8)	4.9 (4.4)	0.009 [§]
General index (PP)	18	41.4 (16.4)	42.9 (21.3)	39.0 (24.3)	32.1 (19.2)	31.6 (14.5)	0.001
General index (ITT)	20	41.5 (16.0)	42.7 (20.4)	37.9 (23.2)	31.6 (18.5)	31.4 (13.9)	<0.001
Reference group							
Intra-oral index (PP)	12	11.0 (12.0)	n.a.	n.a.	10.8 (12.8)	15.4 (13.4)	0.245 [§]
Intra-oral index (ITT)	20	13.0 (12.0)	n.a.	n.a.	11.3 (12.4)	13.6 (12.2)	0.246 [§]
Extra-oral index (PP)	12	10.8 (10.6)	n.a.	n.a.	9.4 (11.4)	12.5 (12.6)	0.179 [§]
Extra-oral index (ITT)	20	11.0 (9.3)	n.a.	n.a.	10.0 (10.0)	11.6 (10.8)	0.259 [§]
General index (PP)	12	43.1 (18.1)	n.a.	n.a.	38.3 (23.3)	49.5 (28.5)	0.004 [§]
General index (ITT)	20	47.3 (21.2)	n.a.	n.a.	41.3 (25.2)	49.6 (27.3)	0.004 [§]

n.a., not applicable.

**P*-value from analysis of variance for repeated measures.

[†]For the reference group, mean index scores from Questionnaire 2 were used.

[‡]For the reference group, mean index scores from Questionnaire 3 were used.

[§]Wilks' Lambda.

Mercury concentration in serum and urine

There was a significant decrease in mercury concentration in serum and urine following the removal of amalgam fillings. After removal of the fillings, the mean serum concentration was reduced to half the concentration at pre-treatment, and the mean concentration in urine was reduced to about one-fourth of the pre-treatment concentration (Fig. 4).

Changes in health complaints related to changes in mercury concentration in serum

Secondary explorative analyses of correlations between reduction in mercury in serum and reduction in health complaints 3 years after treatment showed positive but not significant correlations. Pearson correlation coefficients were 0.320, 0.193 and 0.127 for correlations between reduction in mercury in serum and reduction in intra-oral, extra-oral and general indices, respectively. Corresponding *P*-values were 0.182, 0.428 and 0.604 ($n = 19$), leaving no statistically significant support for mercury as a cause of the complaints.

Adverse events

Seven participants in the treatment group experienced increased health complaints in connection with removal of amalgam fillings. Laboratory tests of blood samples collected within a few days after the treatment session showed values within reference intervals. Health complaints reported in connection with amalgam removal were gastric pain, pain in joints and muscles, oral ulcers, sore throat, pain in legs, hands and feet, dizziness, tachycardia, nausea, diarrhoea, depression, fatigue, chills, burning sensations in the face, cold hands, increased blood pressure and submandibular lymphadenopathy. The increase in complaints was transient and disappeared within a week or two.

Discussion

The aim of this study was to investigate long-term changes in subjective health complaints after the removal of all amalgam fillings in a group of patients who attributed health complaints to amalgam fillings. The main finding was that the long-lasting reductions

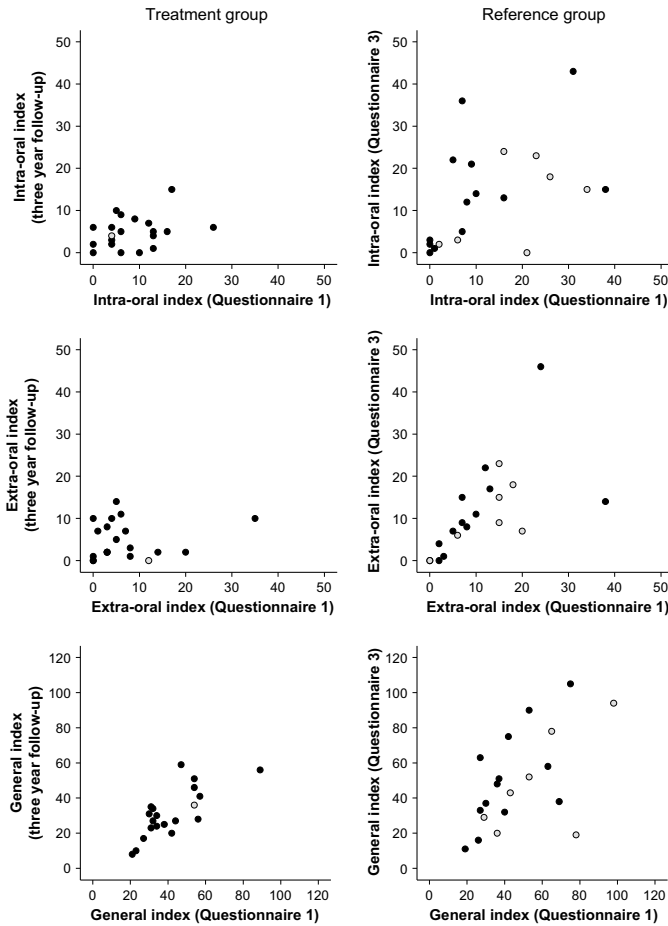


Fig. 3. Individual index scores from 3-year follow-up and Questionnaire 3 plotted against scores from Questionnaire 1. Index scores for intra-oral, extra-oral and general health complaints from treatment group (left column) at 3-year follow-up plotted against index scores before amalgam removal (Questionnaire 1). For the reference group (right column), index scores from Questionnaire 3 were plotted against index scores from Questionnaire 1. Data from intention-to-treat analyses (last value carried forward) are marked with grey dots in the diagrams. Results from statistical analyses of data are given in Table 3.

in intra-oral and general health complaints in the treatment group were significantly different from the change in the reference group, in which there were no long-lasting reductions.

In the treatment group, intra-oral and general health complaints were significantly reduced 3 years after completed replacement of amalgam fillings. Reductions in subjective health complaints after replacement of amalgam fillings have also been found in previous studies (24, 25). The reference group received no intervention, and no improvement in health complaints was found. This is in agreement with data from patients with health complaints attributed to dental restorations, mainly dental amalgam, who did not change the restorations to other materials (8).

It is necessary to consider several factors that may have influenced the results. First, there has been a reduced exposure to mercury in the treatment group. Previous studies have established that people with amalgam fillings have higher concentrations of mercury in blood, plasma, urine and body organs than people without amalgam fillings (12, 15, 17–19, 31). The finding of reduced levels of mercury in serum and urine in the present study is in agreement with data from several studies showing that replacement of amalgam fillings leads to reduced levels of mercury in blood, plasma and urine (14, 32, 33). Despite this, studies investigating the relationship between amalgam fillings and reported health complaints have not found positive correlations between number of amalgam fillings and

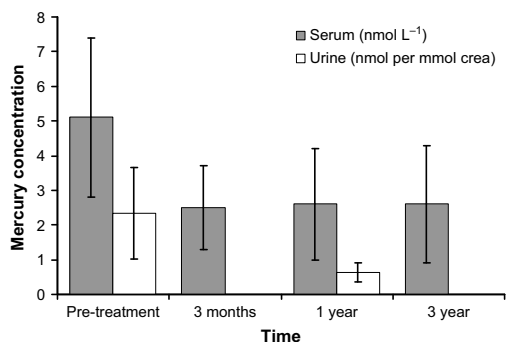


Fig. 4. Mean mercury concentration in serum and urine at pre-treatment examination and at follow-up after removal of amalgam fillings. Mean mercury concentration (and s.d.) in serum (nmol L⁻¹) and urine (nmol per mmol creatinine) at pre-treatment examination and at follow-up after removal of amalgam fillings. Mercury concentration in both serum and urine was significantly reduced after amalgam removal ($P < 0.001$, and $P = 0.004$, respectively).

number of reported complaints (9, 18), indicating that if there is a causal relationship between amalgam fillings and health effects, there is not a simple dose-response relationship between exposure to amalgam fillings and reported health complaints. In a recently published study on health effects after removal of amalgam fillings (34), correlations between amalgam-filled surfaces and symptom scores were not statistically significant. However, positive moderate correlations were found between mercury levels in both plasma and urine and subjective health complaints, and between reductions in mercury levels in these media and reductions in subjective health complaints (34). In the present study, we found positive but not significant correlations between reduction in mercury concentration in serum and reductions in subjective health complaints, which may be in agreement with the analyses presented in (34). It is possible that some individuals are highly sensitive to mercury from dental amalgam and may benefit from reduced exposure (35).

The reference group received no treatment and was only followed up by questionnaires sent by post. This makes it difficult to untangle the effects of the general care associated with amalgam replacement and follow-ups in the treatment group from the effects of the amalgam replacement itself. Follow-ups in the treatment group were carried out by health personnel with both time and motivation to listen to and understand

the patients' experiences. This may have contributed to the reduction in reported subjective health complaints as patient-centred communication has been shown to be associated with improved patient health outcomes (36, 37). In addition, participants in the treatment group no longer had to worry about possible adverse effects from their amalgam fillings. This may also have played a part in the reduction in health complaints as worry has been found to lead to increased monitoring of complaints, which again may lead to an increased feeling of ill health (38). Even so, replacement of amalgam fillings will usually take place in a treatment context where factors like these are present and, thus, potentially might influence the treatment results. Participants' belief in amalgam replacement as an effective treatment (39) and gratitude in relation to having the replacement covered by project funds could possibly have resulted in a response bias towards reporting reduced health complaints. However, it is not likely that the participants would remember how they responded to the scales in the questionnaires several years ago. Factors mentioned above are linked to components related to placebo (expectations, conditioning, learning, memory, motivation, somatic focus, reward, anxiety reduction and meaning), as defined as a genuine psychobiological event attributable to the overall therapeutic context (40). In this context, it is also possible that for some patients, the presence of amalgam fillings has been associated with a nocebo effect. Removal of amalgam fillings could therefore result in a discontinuation of this effect and consequently lead to a reduction in reported health complaints.

Reduction in intra-oral health complaints may have been influenced by general effects of the dental treatment received during the amalgam replacement process. It does, however, seem unlikely that an effect of a generally improved dental health should be prominent 3 years after completed replacement, given that patients with need for complicated dental rehabilitation were excluded from the treatment group and that the removed amalgam fillings were described as sound and well-functioning.

Participants included in this study were recruited from patients referred to the Dental Biomaterials Adverse Reaction Unit. Consequently, participants are not representative of all patients with health complaints attributed to amalgam fillings. Not all patients with health complaints attributed to dental amalgam are

referred to this unit. Some patients are directly treated by their own dentist or general practitioner or seek help from practitioners of alternative medicine. Despite lack of objective signs of adverse reactions to dental amalgam, some patients nevertheless have all their amalgam fillings removed of their own accord because they are concerned about possible adverse effects of mercury released from amalgam fillings. The participants included in this study had not removed all amalgam fillings, either because they accepted that there were no indications for amalgam removal or because they did not have the financial means necessary for amalgam removal. Thus, the treatment group is not directly comparable with patients who remove amalgam restorations of their own accord (23).

The study was designed as a before-and-after study with a comparison group (reference group). Comparisons between the reference group and the treatment group must be interpreted with caution. Even though power calculations showed acceptable power of the study, the sample size is small and the results should be considered in context with results from comparable studies (8, 24, 25, 41). A larger sample size could provide more precise estimates and less-wide confidence intervals. In addition, there may be unknown factors that influence reporting of health complaints over time in the groups. Another limitation could be that as the outcome is based on the participants' reporting of health complaints, the study is open for response bias in both the treatment group and the reference group.

In the treatment group, all 20 participants completed replacement of amalgam fillings, and 19 of the participants were able to attend the 3-year follow-up. In the reference group, seven of the 20 participants were lost to follow-up or excluded because of completed removal of amalgam fillings (Fig. 1). The response rate in the reference group was influenced by the fact that only two reminders, by letter, is allowed by the Regional Committee for Medical Research Ethics. This is in line with the standards used by the Norwegian National Committee for Medical and Health Research Ethics. As there were no major differences between the results from the per-protocol analyses and the intention-to-treat analyses, we assume the potential bias from non-random dropout of participants or exclusion of 'protocol violators' (participants in the reference group who removed amalgam during the study) had no major impact on the result.

Exclusion criteria were initially not applied in the reference group. The clinical examination necessary to fully apply these criteria could potentially lead to a renewed focus on amalgam fillings as a possible cause of ill health, thus increasing the risk of participants in the reference group initiating amalgam removal of their own accord. As no intervention was planned for the reference group, the participants were not asked to undergo a clinical examination. The patients excluded from the treatment group were, based on their responses to Questionnaire 1, quite similar to the treatment group and the reference group, with the exception of per cent on sick leave or disability pension. For this variable, exclusion of the 10 patients resulted in a more equal occupational status for the treatment group and the reference group (Table 2). Changes in health complaints in the treatment group were compared with changes in both the initial reference group and changes in the reference group after *post hoc* application of exclusion criteria. No major differences were found between the two comparisons. However, as there was no clinical pre-treatment examination of patients in the reference group, there could still be differences between the groups. The bias from differences between the groups at study start is expected to be limited.

Treatment of patients with subjective health complaints attributed to amalgam fillings should only be considered after a thorough medical and dental examination has been carried out and other causes for the complaints have been eliminated or adequately treated (42). The results from the present study, and other studies investigating the effects of amalgam replacement, indicate that replacement of amalgam fillings is associated with reductions in subjective health complaints at group level. The mechanisms behind this are not known, and other treatment options than amalgam replacement should also be considered. In a recent randomised clinical trial, all investigated treatments (amalgam removal, amalgam removal plus biological detoxification and health promotion without amalgam removal) resulted in clinically relevant reductions in health complaints (25). When considering replacement of intact amalgam fillings, potential benefits must be balanced with risks associated with the dental treatment (e.g. tooth fractures or endodontic complications). When removing amalgam fillings, measures should be taken in order to minimise exposure to mercury for both patients and dental personnel (29, 42).

The results from the present study indicate that the replacement of amalgam fillings was associated with reductions in subjective health complaints at group level. The mechanisms behind this remain to be identified. Reduced exposure to mercury, patient-centred treatment and follow-ups, and elimination of worry are factors that may have influenced the results. In this study, we investigated changes in index scores. More knowledge is needed about changes in specific complaints included in the index scores after replacement of amalgam fillings, and a characterisation of the treatment group in this respect is warranted.

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EMPIRICAL STUDY

Patients' experiences of changes in health complaints before, during, and after removal of dental amalgam

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Abstract

In this article, we explore how patients with health complaints attributed to dental amalgam experienced and gave meaning to changes in health complaints before, during, and after removal of all amalgam fillings. We conducted semistructured qualitative interviews with 12 participants from the treatment group in a Norwegian amalgam removal trial. Interviews took place within a couple months of the final follow-up 5 years after amalgam removal. Using the NVivo9 software, we conducted an explorative and reflective thematic analysis and identified the following themes: Something is not working: betrayed by the body, You are out there on your own, Not being sure of the importance of amalgam removal, The relief experienced after amalgam removal, and To accept, to give up, or to continue the search. We discuss the findings in the context of patients' assigning meaning to illness experiences.

Key words: Health, health seeking, illness experiences, dental amalgam, assigning meaning, reflexivity, thematic analysis

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The meanings given to symptoms and distress can transform suffering. Meaning—any meaning—serves to turn back the tide of chaos and bafflement that confronts us in affliction. Given specific meaning, illness becomes metaphor—a rhetorical resource to be used to explore and communicate the wider significance of our predicament. (Kirmayer, 1994, p. 183)

Patients suffering from health complaints which cannot be fully explained by the doctors' findings might find it difficult to assign meaning to their illness experiences (Kornelsen, Atkins, Brownell, & Woollard, 2015; Madden & Sim, 2006). How can they understand the experienced pain and discomfort when the biomedical “stamp of approval”—a diagnosis—is apparently not within reach? How can they justify not being able to partake in activities as they did previously when their suffering remains unconfirmed by the medical system?

It is well known that mercury vapor released from amalgam fillings can be inhaled and absorbed into the bloodstream (Clarkson, Magos, & Myers, 2003). Some patients fear their health complaints might be caused or aggravated by mercury released from their amalgam fillings (Sjursen et al., 2014; Tillberg et al., 2005). Patients who attribute health complaints to their dental amalgam fillings are a heterogeneous group. Common to all of them is that they suffer from unexplained or partially explained health complaints that they believe are caused or aggravated by their amalgam fillings. For some, only one or a few local complaints such as taste disturbances, dry mouth, and intraoral pain are attributed to the dental amalgam. The majority describe a number of both local and general health complaints involving several organ systems. Tiredness, headaches, pain in muscles and joints, and problems with memory and concentration are among the most frequently reported complaints (Langworth, Björkman, Elinder, Järup,

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& Savlin, 2002; Lygre, Gjerdet, & Björkman, 2005; Vamnes, Lygre, Grønningsæter, & Gjerdet, 2004). For some patients, contact allergic reactions might be present, and removal of amalgam fillings in contact with such lesions is generally recommended (Issa, Brunton, Glenny, & Duxbury, 2004; Lygre, Gjerdet, & Björkman, 2004). For the majority of patients with health complaints attributed to dental amalgam, no objective signs of adverse reactions can be observed (Langworth et al., 2002; Vamnes et al., 2004). Nevertheless, one cannot preclude the possibility that dental amalgam could have deleterious effects on the health of highly susceptible people (Needleman, 2006; US Food and Drug Administration, 2009). This poses the following dilemma: Even though there is not sufficient evidence to lend scientific credibility to an amalgam syndrome diagnosis, standard safety margins are lacking, thus making it impossible to rule out that, for some people, amalgam might be associated with a risk of negative health effects (Richardson et al., 2011).

Studies investigating changes in general health complaints after removal of amalgam fillings have found reductions in health complaints (Lygre et al., 2005; Melchart et al., 2008; Nerdrum et al., 2004; Sjørusen et al., 2011), but not to the levels found in the general population (Lygre et al., 2005; Nerdrum et al., 2004). The observed reductions in health complaints might be interpreted as effects of patients being seen and heard, improved dental conditions, the natural variation in the course of the complaints, reduced exposure to mercury, as well as placebo effect and discontinued nocebo effect (Melchart et al., 2008; Nerdrum et al., 2004; Sjørusen et al., 2011). Because of difficulties in masking whether patients have their amalgam fillings removed or not, randomized clinical trials of the effects of amalgam removal are likely to be influenced by participants' expectations.

In previous studies, patients' experiences have seldom been explored on their own terms. In a focus group study from New Zealand (Jones, 2004) with 35 participants having amalgam-related complaints, participants described experiencing psychological problems such as memory loss and mood swings that they believed were related to their amalgam fillings. They also described experiencing psychological problems, such as loss of social support and considering suicide, that they related to suffering from symptoms that were not easily diagnosed and thereby often treated as indicating hypochondriac tendencies. Of the participants who had removed all amalgam fillings, the majority reported improved health; some even to the extent of full recovery (Jones, 2004). In a Swedish interview study (Stahlnacke &

Soderfeldt, 2013) of persons who attribute health problems to dental filling materials, mostly dental amalgam, the participants described a variety of long-lasting health problems that they believed were caused by dental amalgam. Replacement of dental materials was the main treatment for these problems, and the majority of the participants reported having had good experiences with health professionals, although some negative encounters were also reported (Stahlnacke & Soderfeldt, 2013).

When patients suffer from health complaints that cannot be easily explained, both patients and health personnel find themselves in a situation where the normal expectations of the medical encounter cannot be met. To be better able to meet the patient where he or she is, it is important that health personnel take the time to learn more about how patients interpret and give meaning to their health complaints. Patients experience and give meaning to health complaints in their everyday life, and it is therefore important to know how the patients' thoughts, obligations, past experiences, and perceptions of the future interact with the perceived pain and discomfort. Consequently, for patients with health complaints attributed to dental amalgam, it is not only necessary to bridge the gap between the medical and dental aspects, it is also necessary to bridge the gap between how the complaints are understood in the physician's/dentist's office and how they are understood and experienced in the context of the patient's everyday life.

In a previous article (Sjørusen et al., 2014), we explored how patients came to attribute their unexplained health complaints to dental amalgam. In this article, our aim is to explore how the same patients experienced and gave meaning to changes in health complaints before, during, and after amalgam removal.

Method

Participants

Participants were recruited from the intervention group in a Norwegian amalgam removal trial (Sjørusen et al., 2011). To be eligible for participation in the intervention group of the trial, participants had to fulfill the following criteria: initially referred to a specialty unit for examination of health complaints attributed to dental amalgam; no signs of contact allergic reactions to dental amalgam and thereby not recommended for removal of amalgam fillings; amalgam fillings still present; health complaints from at least three organ systems; mercury level data available from initial examination; no allergy to resin-based dental materials; no need for complicated

dental therapy; and no severe medical disorders/food allergies/psychological difficulties.

The 20 participants in the intervention group had all their amalgam fillings replaced with other restorative materials by their regular dentists. Amalgam fillings were removed according to guidelines ensuring minimal exposure from mercury (Dental Biomaterials Adverse Reaction Unit, 2002). The cost of the amalgam removal was covered by project funds for the amalgam removal trial. Follow-ups took place approximately 3 months and 1, 3, and 5 years after the participants had completed the removal of all their amalgam fillings. At the 5-year follow-up, 12 (seven women and five men) of the participants were invited to participate in qualitative research interviews. All accepted, and interviews were scheduled accordingly. At the time of the interviews, age range of the participants was from 45 to 65 years (mean age 54.4 years). After the completion of the 12 interviews, we were able to identify both convergent and divergent experiences in our data material. As we did not have the impression that the last interviews brought to light new themes, we decided to stop recruiting participants at this point.

Sampling method

We used a purposive sampling procedure to recruit participants from the intervention group in an amalgam removal trial to explore how they experienced and gave meaning to changes in health complaints before, during, and after amalgam removal. By choosing this sampling procedure, we were able to obtain a homogenous sample with regard to all participants having had their amalgam fillings removed. When it came to the demographic characteristics, participants were selected to ensure that a diverse age range and both sexes were represented.

Researchers

The interview study was carried out as a cross-disciplinary collaboration between three psychologists, two dentists, and one operating nurse. Together we have varied clinical experience, as well as a diverse experience with both qualitative and quantitative research methods.

Data collection

To lay the basis for an open exploration of participants' experiences of changes in health complaints and how they assigned meaning to these, we chose to carry out semistructured, exploratory, in-depth interviews. The first author, in close cooperation with the

fifth author, carried out all interviews. Neither had been present at the follow-ups, and the interviews were held at a different location than the follow-ups. After each interview, the first and fifth author adjusted the interview guide that had been initially developed by all the authors. The interviews were videotaped. Mean duration of the interviews was 60 min (range 32 min to 2 h 9 min).

Analysis

By reading and comparing the individual accounts, we wanted to identify similarities and discrepancies in the ways in which the participants experienced and gave meaning to changes in health complaints before, during, and after amalgam removal. We conducted an explorative and reflexive thematic analysis (Binder, Holgersen, & Moltu, 2012; Braun & Clarke, 2006), which can be summarized as follows: (a) the first author transcribed all interview recordings verbatim, (b) to get a basic sense of patterns in the participants' experiences, all authors read through the written material separately, (c) to establish meaningful themes, each author discussed the material with the first author, (d) the first author organized the text material, with the assistance of the NVivo9 software (QSR International Pty Ltd., 2010), into "nodes" in accordance with these themes, (e) in cooperation with the coauthors, the themes were additionally refined and condensed into the presented findings, and (f) examples and quotes were selected to illustrate how patients experienced and gave meaning to changes in health complaints. To strengthen the transparency of the analysis, we presented thick descriptions and used quotes that exemplify the themes (Denzin, 2001; Geertz, 1973; Ponterotto, 2006).

Ethical concerns

Participants received written and verbal information about the interviews at the time of the 5-year follow-up, and all included participants signed a consent form. Before they entered the interview room, the participants were reminded that the interviews were going to be videotaped. The Regional Committee for Medical and Health Research Ethics in Western Norway, and the Norwegian Social Science Data Services approved the study. To safeguard the anonymity of participants, findings are presented without identifying details.

Findings

In our analyses of how patients experienced and gave meaning to changes in health complaints before,

during, and after amalgam removal, we found the following themes to be of importance:

- a. Something is not working: betrayed by the body.
- b. You are out there on your own.
- c. Not being sure of the importance of amalgam removal.
- d. The relief experienced after amalgam removal.
- e. To accept, to give up, or to continue the search.

Something is not working: betrayed by the body. The starting point for all participants was the experience of something not working inside their bodies. Some had struggled with health complaints from an early age, whereas others experienced onset of complaints as adults. The majority of the participants described the onset of complaints as gradual, but some pinpointed more distinct starting points for the health complaints they attributed to dental amalgam. Several of the participants already had—or went on to receive—other diagnoses explaining part of their complaints; nevertheless, they felt that something remained unexplained. Participants' complaints differed in kind, number, and intensity. The following complaints were mentioned most often: pain in muscles and joints, headaches, memory problems, tiredness, gastrointestinal symptoms, and intraoral health complaints. For some, the discomfort and impairment were limited to a few distinct complaints; for others, it was the sum of the complaints—more than the separate complaints in themselves—that posed the main burden. Some participants were puzzled by the way the complaints made them feel “beside themselves” or “out of it.”

I was in so much pain, and I also felt, for a while, that I had such a poor memory (sighs). I cannot say if that was because of stress caused by having to fight the pain, but I did feel “out of it” in a way. I really did.

Some described their bodies as being overly sensitive to many different things to a degree that some even felt betrayed by their bodies. They found it necessary to avoid certain foodstuffs, such as wheat and/or sugar, and some also developed respiratory reactions and headaches from certain odors such as perfume and paint. One participant described some of her puzzling complaints and asked, “What causes it? Why did it happen? Was it because of my strange body? Who knows?” Another participant seemed saddened that her body was not working as well as others' appeared to function. Because of her complaints, she was only able to keep a part-time job, and

even then, she often felt exhausted and in pain after work. Several described how the health complaints had negative consequences for their social life. They recounted the various ways the complaints and, in particular, the depleted energy levels and nausea caused by the pain limited their ability to keep up with family life and professional obligations. They felt they could not perform as well, or at least not as effortlessly, as others seemed to be able to do. Despite having families that gave them support and understanding, several described a profound feeling of sadness related to not being able to be the spouse/parent they wanted to be. Several also felt that their relationship with friends and colleagues suffered because of their complaints. They seldom had the energy to meet people socially, and when in pain, they had to pull themselves together to avoid responding more harshly than they wanted to in tense situations. All participants worked hard to ensure that they did not lash out and hurt the people around them, and most of the time they thought they succeeded with this. This was very important to all of them, and the occasional slip-up was not taken lightly.

If it only affected oneself, it would be more than terrible, but it gets even worse if it hurts others. And sometimes it ends up in a way that one is not able to be the person one would like to be.

It became important not only for them but also for the significant people in their lives, to search for a way to understand and hopefully cure the complaints.

You are out there on your own. The majority of the participants in our sample said that they had been actively trying to find explanation for their complaints. Several were disappointed by how little the medical profession had to offer when it came to health complaints in the absence of corresponding objective findings.

I'm not quite able to sort it out, and the doctors are not very good at helping with these things when they do not find anything specific. ... So in a way, you have to sort it out on your own.

In addition to seeking help from physicians and dentists, participants also had consulted physiotherapists, chiropractors, and practitioners of alternative medicine. For some participants, this had yielded immediate and striking results, such as the case of one participant, who consulted a healer because of a locked temporomandibular joint.

Then I saw a healer for the first time, and I have never experienced anything so strange. I mean, he didn't even touch me, but it creaked and groaned and after that, I have been able to open my mouth wide.

A few of the participants who had consulted practitioners of alternative medicine had developed quite close relationships with some of them. In addition to the treatment *per se*, it seemed that these therapists filled an important role as emphatic listeners and givers of advice relating to many aspects of the participants' lives. Other participants only sought treatment when they needed help to manage specific complaints. They tried to limit the number of treatment sessions as these were described as expensive and time consuming. There were also participants who had spent a considerable amount of time, energy, and money on treatments that were described as having from minor effect to no effect at all.

Participants had also made other changes in their lives, hoping to diminish their health complaints. Several had tried different diets, sometimes through trial-and-error, and other times on advice given at rehabilitation centers or by practitioners of alternative medicine. For most, the results were promising at first, but the beneficial changes did not last over time. Several participants, however, did continue to avoid or limit the intake of certain food types as they experienced this to be somewhat helpful. Most of the participants had also modified their work situation. Some had started working reduced hours, some had changed to jobs that were less physically taxing, and some had started saying "no" more often at work. One participant said that the questions the project's physician had asked her at the pretreatment examination led her to take a closer look at the way she was living her life, and she had realized that she needed to make more room for herself in her own life.

Participants varied as to how and when dental amalgam was suspected to be a possible cause for their body not working properly (Sjursen et al., 2014). When they first contacted the specialty unit, there was considerable media coverage of possible harmful effects of dental amalgam, and all participants acknowledged having heard about this possible connection through the media or through accounts from friends and acquaintances. In addition, they had all experienced something that made the link between dental amalgam and health complaints seem personally relevant. For some, dental amalgam ended up as the only plausible explanation remaining after they had tried everything else; for others, dental amalgam was thought to be only one of many factors influencing their health. Common to all participants was a strong desire to have the amalgam removed once the

attribution of health complaints to dental amalgam was made.

Not being sure of the importance of amalgam removal.

Participants said that they were very happy to be given the opportunity to have all amalgam fillings removed through participation in the clinical trial. Several pointed out that they would otherwise not have been able to afford such extensive dental treatment. Many of the participants emphasized that they had felt well taken care of both by their dentist and by the personnel at the specialty unit during follow-ups. To limit patients' exposure to mercury, a protective sheet (rubber dam) made from silicone was used during amalgam removal. Several of the participants said this made them feel well-protected. A few patients had experienced illness episodes after treatment sessions. Two of the patients who had experienced adverse reactions said that they felt worse after treatment sessions when the rubber dam had been difficult or impossible to place.

When responding to the opening question: "Have you experienced any changes in health complaints or quality of life after the amalgam removal?" nine participants said that they had experienced changes for the better. One participant said she was unable to answer this question because she had been in a very demanding life situation at the time of the amalgam removal. Two men answered no to this question. They had both received other diagnoses and no longer suspected that dental amalgam was the cause of their complaints. The participants who had experienced changes for the better were somewhat hesitant when it came to identifying the amalgam removal as a direct cause for the changes. After they described the perceived changes in health complaints, they usually tried to sort out which changes they thought were caused by the amalgam removal and which were more likely to have been brought on by other changes in their lives.

Well, what I think is that I don't really know what (pause). I think that the amalgam removal at least has had an effect on my mouth and the pain I had there. But I (pause) when it comes to the other complaints, I think that it is kind of impossible to know if it is [the amalgam removal] that has made me better or if it is other things. I have tried a lot of different things. I have had different treatments, and I have changed my diet, you know, and I have started to take Omega-3 supplements, which is also supposed to be good for the joints, for instance. So, I really have done other things as

well, and I really can't say if it is the teeth or if it is the other things or if it is (pause). I find this to be very difficult.

Participants thought that the new white fillings were much nicer looking than the old black fillings, and some of the participants said that they felt their oral condition had greatly improved after the amalgam removal. Two participants reported that a taste disturbance (metallic taste) had disappeared and they were reasonably certain that this was because the amalgam had been removed. One participant had to replace several of the new fillings due to new caries lesions. Participants found it easier to connect reduced intraoral health complaints, such as reduced pain and smarting in the gingiva, to the amalgam removal, than to connect the more general health complaints to the removal.

When it came to the general health complaints, all participants were quick to point out that both the initial complaints and the subsequent changes might have been influenced by changes in life situation, work conditions, and so forth. Several of the participants used phrases like "but, of course, this could also have been influenced by the stress caused by. . . ." They also emphasized that they had been trying several treatment options both before and after the amalgam removal, and several of the women pointed to menopause as a possible explanation for reductions of some health complaints. Some of the participants had previously taken care of elderly parents, whereas other participants had this responsibility at the time of the interview. Some had gone through a divorce or a painful breakup after the amalgam removal and said that this had also influenced their health and general well-being. At the time of the interview, several participants were in demanding life situations that negatively affected their health, and several described how fluctuations of other medical conditions, both previously known and recently diagnosed, made it difficult to assess which changes were directly related to the amalgam removal.

The relief experienced after amalgam removal. Despite the uncertainties described in the last theme, the majority of the participants concluded that they were in a much better place in their lives at the time of the interview than they had been before the amalgam removal. With the exception of the two men who said they had experienced no changes in health complaints after amalgam removal, all participants believed that the amalgam removal was partially responsible for their feeling better.

This amalgam removal, I do believe it has had an effect, together with all the other things. But I

would have to have psychic abilities to know exactly how. As I have told you, there are still periods in which I feel quite poorly and beside myself, but I do feel much better now. I really do.

All participants, including the participant who had experienced several new caries lesions after the removal, seemed relieved that they no longer had any amalgam fillings in their teeth. For many of the participants, this relief appeared to be associated with being able to cross a worry off a list.

Participant (P): Well, I was very relieved that I could have them removed. . . . Because, at that time, I was very focused on what was causing me to be not as healthy as others, and this was something I wanted to try to (pause) that it might help me get better. So it was certainly a plus to get rid of it. At least I did not have those anymore, and I had kind of excluded something (laughs). It was a little bit like that.

Interviewer (I): Yes, it felt good to

P: You know, some (pause). There are many people with the same complaints that I have had who are talking about amalgam and such. So it is possible that if I still had those fillings left, I could have been constantly thinking "Yes, it really could be those fillings keeping me from feeling well." But it is not like that anymore, is it?

For almost all participants, there was a distinct change in emotionality and tone when asked how they would have felt if they still had one amalgam filling left. All responded that they would have had it removed and emphasized that they would not have been happy at all. This stood in stark contrast to the calm replies of some who had stated that they had never been totally sure of the connection between amalgam and health complaints to begin with, and who conveyed in other parts of the interview a quite sophisticated understanding of health as being multifactorially determined. This uncertainty related to the importance of the amalgam removal stood almost paradoxically in contrast to the absolute certainty, even 5 years after removal, that it was important to get rid of all amalgam fillings.

To accept, to give up, or to continue the search. Despite feeling better, as reported by the majority of the participants, none of them had become symptom-free after the amalgam removal. They reacted to this in different ways. For some, there seemed to be a change in the urgency to seek answers. A few even thought that they were moving toward accepting their health

complaints, or at least toward accepting that their complaints could never be fully explained.

Well, in a way I have accepted that I will always have some complaints. I am not like I used to be when I thought that if only I could find the right solution, then I would also get cured. I have kind of given up on that. It is more about finding the best possible way to live with [the complaints].

For some participants, this was associated with growing older and accepting complaints as something to be expected with advancing age. For others, the acceptance seemed to be more a consequence of the limited success of previous attempts at finding answers. The quest for an answer comes at a cost, as reflected in the theme, "You are out there on your own." In addition to the time and energy spent, there is also an emotional toll entailed in getting your hopes up and then being disappointed repeatedly. The process toward acceptance was described as containing both elements of relief, in that they could ease up on the search for an answer, and sadness at having to let go of their hope for a cure. One participant who suffered from daily pain and personal limitations caused by a diagnosed disease very firmly stated that she preferred a growth perspective to a pain-coping perspective. She did not want to dwell on her pain and would much rather participate in creative-outlet courses instead of pain management courses. She had tried both of these and had experienced that creative and artistic courses enhanced her quality of life to a much greater extent than did pain management courses. For several of the participants, the search for an answer continued. Even some of the participants who talked about accepting their health complaints kept the door open for other explanations. There were also participants who regarded the new filling materials with some skepticism.

And now I just heard that they have started talking about the new filling materials, the white ones, you know. Because there are people who react to those as well, you know. I have almost nothing like that, because I mostly have, uhm, porcelain crowns, you know. That was a conscious choice I made at the time. However, I have no idea what they used to cement the crowns.

The not-knowing part of their health complaints seems to have made acceptance and management of the complaints difficult. The majority of the participants had other diagnoses, or went on to receive other diagnoses, explaining part of their health complaints.

When describing the management of these complaints, including potentially life-threatening adverse reactions to prescribed medication, participants seemed less emotionally engaged than when describing suffering from the complaints they could neither explain nor knew how to treat.

Discussion

The opening phrase in the interviews was formulated along the lines: "The main focus for this interview is possible changes in health complaints and quality of life after amalgam removal. However, we do know that things in life are connected, so we are interested in the big picture." We thereby opened for a broad understanding of what was meant by "after amalgam removal" because "after" could be understood either as "in the period following" or as "caused by." In their answers, participants seemed to alternate between these interpretations. When they became aware of this, they tried to sort out what was reasonable to connect with the dental amalgam and what might be related to other things. Most participants stressed how difficult these were to untangle and how it was impossible to make strong claims. Through the participants' descriptions, a pattern emerged of "searching for an answer, trying out a solution, and evaluating the effect." The majority of the participants described having been through similar circular procedures of searching for an answer, trying out a solution, and evaluating the effect before the amalgam removal, and some described having started on new searches after the removal.

When drawing conclusions, one is always at risk of accentuating some aspects of participants' experiences over others. In our interview material, the energy and drive the participants put into their search for a diagnosis and a cure really stand out. It could be argued that this automatically follows from the experienced discomfort; however, the participants seemed to invest the same drive and energy in taking care of their families and their work obligations. The majority of the participants seemed to hold themselves to quite high standards and they expressed both sadness and frustration over not being able simply to "pull themselves together." Through these descriptions, we were able to glimpse a sense of despair and chaos; however, this was often quickly brushed aside with a curt laugh, a joke, or a shift in focus.

According to Cassell (1982, p. 640), "suffering occurs when an impending destruction of the person is perceived; it continues until the threat of integration has passed or until the integrity of the person can be restored in some other manner." In more general terms, Cassell defined suffering as "the state of severe distress associated with events that threaten

the intactness of the person” (Cassell, 1982, p. 640). Consequently, it is not only the pain and the health complaints in and of themselves that are important, but also the perceived implications these have for the individual’s everyday life, hopes for the future, and sense of self. In our interview material, the “threat to the intactness of the person” seems mostly to have been associated with participants’ being unable to fulfill their obligations as employees and family members.

Despite this complexity, we find that “pain” and “suffering” are often used interchangeably in everyday language. This is not a trivial distinction and to treat it as such can potentially lead to more suffering. According to Loeser (2000), it is the suffering, and not the pain, that motivates people to seek medical care. Nevertheless, it is usually the pain, or the health complaints, which are addressed by both the patient and the physician. If patients seek relief for their suffering, which they perhaps are not even able to distinguish from their pain, and doctors are trained to diagnose and treat pain and/or health complaints, it is hardly surprising that patients with unexplained health complaints often describe their encounters with the medical profession as far from satisfactory.

As argued by Kirmayer (1994, p. 183), suffering can be transformed by the meanings given to the experienced symptoms and distress. In continuation of this, he says that to be effective—that is, “to carry private conviction and rhetorical force” (p. 184)—the illness meaning must be perceived as having some sort of authority. Within a biomedical understanding of illness and disease, authority is generally granted through a diagnosis. As summarized by Jutel (2010, p. 229), a “medical diagnosis explains, legitimizes, and normalizes.” In the absence of a diagnosis, patients are denied an explanatory framework through which they can understand, and potentially give meaning to, their complaints. It should therefore not come as a surprise that many patients consider a diagnosis as a prerequisite for finding meaning and restoring “the integrity of the person” (Cassell, 1982, p. 640). For many patients, including our patient group, a single diagnosis by which all complaints can be explained cannot always be obtained. This leaves the patients with more unknowns than answers: Where are they supposed to direct their energy? Can they trust that their complaints will stay more or less stable, or do they have to anticipate getting worse? Should their efforts be focused on adapting and coping, or should they continue searching for an explanation and a cure? How can they integrate their sense of self with their (new) everyday life?

One thing that seemed to be of importance for all our participants, with all their similarities and

differences, was the fact that they were all very happy to have had all their amalgam fillings removed. They were, however, unwilling to state unequivocally that they had become better because of the amalgam removal, and the majority seemed to lean toward the hypothesis that amalgam removal played a part along with all the other changes in their lives. Participants sometimes during the interviews referred to more simplistic convictions; these were, however, quickly contrasted with more complex and open-ended explanations. Different explanations seemed to be accompanied by different levels of emotions and rationales. Some of the most important aspects of the amalgam controversy are perhaps found in the difference between the rational understanding of multifactorial explanations of health and the emotional activation seen when a participant imagines having one amalgam filling left. This underscores how important it is that both researchers and health personnel learn more about how patients think, act, and feel regarding these questions.

Several of the participants in our sample seemed to construe the amalgam removal as a prerequisite enabling them to start the process of accepting their health complaints. Without it, they feared they would have continued to worry that their amalgam fillings stood between them and good health. Nevertheless, our participants were also quick to point out that for most of their health complaints, they could not be certain that these were causally linked to their amalgam fillings. It is reasonable to assume that the emotional side of the question “Are my amalgam fillings making me ill?” is often left out of the medical encounters, or perhaps it is only answered by referring to statistics and probabilities. Even though health personnel and researchers might find comfort in, and take guidance from the evidence indicating that dental amalgam is a safe treatment option at group level; the same evidence, with its corresponding statistical and clinical uncertainties, does not necessarily sound equally convincing to the patients who are trying to figure out whether it is true for their lives.

For some patients, it would perhaps be beneficial to be able to address these issues based not only on general probabilities but also on the direct consequences the complaints and the uncertainties linked to the dental amalgam have in their life. It is our strong belief that taking the time to address this would be an important step toward addressing not only the pain but also the suffering and fear related to the pain. For some patients, this could result in their being better able to live with their health complaints and the uncertainties related to the origin and prognosis of the complaints. For other patients, the worry deriving from their dental amalgam could potentially still have a too negative impact on their quality of life.

When considered in light of stories of successful recoveries in the media, patients' continued wish to have their amalgam fillings removed does not appear unreasonable. Several studies have reported that patients experience improved health after amalgam removal (Lygre et al., 2005; Melchart et al., 2008; Nerdrum et al., 2004; Sjursen et al., 2011). This has also been described in the qualitative studies performed within this field (Jones, 2004; Stahlacke & Soderfeldt, 2013). It has been difficult, however, to pinpoint the exact causes for the reported health improvements, and the patients' health complaints have not been reduced to such an extent that they have reached the levels of health complaints found in the general population.

The fact that we do not fully understand the reason for the reported improvements is perhaps most disconcerting for the researchers and the health professionals. For many patients, a subjective perception of reduced health complaints will have its own value irrespective of the mechanisms involved. In continuation of this, it could be argued that it should be easier for patients to have all their amalgam fillings removed. However, removal of dental amalgam should never be considered a treatment if other possible causes for the complaints have not yet been ruled out (Norwegian Directorate of Health, 2008). In addition, there will always be risks associated with removing sound dental amalgam fillings. These risks must be appropriately described by the dentist before amalgam removal is initiated (Norwegian Directorate of Health, 2008).

Reflexivity, scope, and limitations

The cross-disciplinary approach of this study enabled us to look at the patients' experiences from different clinical angles; however, there is also a risk that our clinical stance could overshadow the perspectives of the patients. At the participants' first examination at the specialty unit, no objective findings (i.e., contact allergic reactions) of adverse reactions to dental amalgam were found, and it was not recommended that the participants have their dental amalgam removed. This also meant that they could not have the cost of the amalgam removal covered by social security. In the interviews, the participants expressed a strong wish to have their fillings removed, but except for making sure that defective fillings were replaced with other materials than dental amalgam, no one had initiated a full amalgam removal on their own. This could be because they were relatively reassured by the examination and the advice from the specialty unit, or it could be because of lack of financial means. From the interviews, we get the impression that both explanations play a part. Therefore, we have to

assume that our participants were not among the most strongly convinced anti-amalgam patients, and our findings have to be interpreted accordingly.

When interpreting our findings, it is also important to take into consideration that the participants had taken part in a treatment study for which the aim was to investigate the effects of amalgam removal, and that they were told in advance that changes in health complaints after amalgam removal would be the topic in the interviews. To reduce the impact of links to the clinical trial, interviews were carried out at a different location than the follow-ups. Moreover, the interviewer had not been part of the follow-ups. It soon became clear that the interviewer was nevertheless considered a member of the specialty unit.

The participants might also have reacted to subtle cues from the interviewer, perhaps unintentionally prompting multifactorial explanations at the expense of other explanations. The fifth author, who listened in on the interviews, had the impression that different explanations were met with equal interest. The participants, however, might have experienced this differently. It is reasonable to assume that the topic and context of the interviews might have accentuated our finding that patients seemed to be more worried about the health complaints that they could not explain and which could potentially have been caused by the dental amalgam, than by pain and health complaints caused by other diagnosed medical conditions.

Interviews were performed 5 years after removal of dental amalgam. The explanations and descriptions given in the interviews would have been different if the interviews had taken place before or shortly after the amalgam removal. However, the aim of the exploration presented in this article was to learn more about how participants experienced and gave meaning to changes in health complaints before, during, and after amalgam removal, and not to obtain an exact chronological description of every experience. The stories related by the participants are the stories they live with, the stories through which they remember and give meaning to their experiences.

Conclusion

If patients' experiences 5 years after amalgam removal can be summarized in a single sentence, the following might be appropriate: "The dental amalgam was certainly important to get rid of, but it is uncertain how important the removal was for the experienced changes in health complaints." Patients were very happy to have had all their amalgam fillings removed, but they did not believe that they could credit all the positive changes to the amalgam removal. Nevertheless, several of the participants said that the

amalgam removal had been very important because it meant that they could cross this particular worry off the list. For some participants, this also meant that they thought they might be moving toward a personal acceptance of their health complaints.

Ethics and consent

The project was approved by Regional Committee for Medical and Health Research Ethics in Western Norway (REK III nos 24.01 and 2007/10173-ARS), and the Norwegian Social Science Data Services (NSD 19306).

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Appendix

Appendix

Search strategy for Table 1

The search strategy for identifying prospective studies investigating the effects of amalgam removal on general health complaints was based on the following criteria:

- Study group:
 - Patients with general health complaints attributed to dental amalgam
- Prospective study:
 - Measurements of general health complaints from both before and after amalgam removal
- Control group:
 - Changes in health complaints in the amalgam removal group should be compared with changes in health complaints in a relevant control group, preferably with changes in health complaints in patients with health complaints attributed to dental amalgam who did not replace their amalgam fillings

The following search criteria were used to search the PubMed database:

(amalgam [All Fields]) AND (removal [All Fields]) AND (health [All Fields]) AND (follow-up [All Fields] OR longitudinal [All Fields]) NOT (caries [All Fields] OR lichenoid [All Fields])

The search, which was concluded at May 15, 2016, resulted in 12 hits. Three of these references had no comparison group (Begerow, Zander, Freier, & Dunemann, 1994; Prochazkova, Sterzl, Kucerova, Bartova, & Stejskal, 2004; Stejskal et al., 1999) one was a review (Levey, Carson, & Innes, 2015) and three of the references were papers included in the thesis (Paper I, II and IV). Thus, five publications were included in Table 1. The paper by Tillberg et al. (2005) was not detected by the PubMed search, but was included even though their study group also included participants with health complaints attributed to other dental materials. The majority of the participants in the study were however initially referred for health complaints attributed to their amalgam fillings.

Questionnaire regarding current health complaints*

**translated from Norwegian*

Name:

Address:

Year of birth: Month:.....Day:.....

A number of different symptoms are listed on the next pages. Please indicate how you have recently experienced the intensity of each symptom by marking an X on the horizontal lines.

Example:

I-----X-----I
0 1 2 3 4 5 6 7 8 9 10

No complaints

Worst possible complaints

Complaints associated with lips/face/jaw:

Facial burning sensation: I-----I
0 1 2 3 4 5 6 7 8 9 10
No complaints Worst possible complaints

Facial pain/tenderness: I-----I
0 1 2 3 4 5 6 7 8 9 10
No complaints Worst possible complaints

Facial stiffness/paresthesia: I-----I
0 1 2 3 4 5 6 7 8 9 10
No complaints Worst possible complaints

Facial skin problems: I-----I
0 1 2 3 4 5 6 7 8 9 10
No complaints Worst possible complaints

Pain from temporomandibular joints: I-----I
0 1 2 3 4 5 6 7 8 9 10
No complaints Worst possible complaints

Other complaints: I-----I
0 1 2 3 4 5 6 7 8 9 10
No complaints Worst possible complaints

Please describe "other complaints":

.....

General complaints associated with:

Pain from muscles and joints: I-----I
0 1 2 3 4 5 6 7 8 9 10
No complaints Worst possible complaints

Gastrointestinal symptoms: I-----I
0 1 2 3 4 5 6 7 8 9 10
No complaints Worst possible complaints

Cardiovascular symptoms: I-----I
0 1 2 3 4 5 6 7 8 9 10
No complaints Worst possible complaints

General skin problems: I-----I
0 1 2 3 4 5 6 7 8 9 10
No complaints Worst possible complaints

Visual disturbances I-----I
0 1 2 3 4 5 6 7 8 9 10
No complaints Worst possible complaints

Symptoms from ear/nose/throat I-----I
0 1 2 3 4 5 6 7 8 9 10
No complaints Worst possible complaints

Other complaints: I-----I
0 1 2 3 4 5 6 7 8 9 10
No complaints Worst possible complaints

Please describe "other complaints":

.....

Other complaints:

Fatigue: I-----I
 0 1 2 3 4 5 6 7 8 9 10
 No complaints Worst possible complaints

Dizziness: I-----I
 0 1 2 3 4 5 6 7 8 9 10
 No complaints Worst possible complaints

Headaches: I-----I
 0 1 2 3 4 5 6 7 8 9 10
 No complaints Worst possible complaints

Memory problems: I-----I
 0 1 2 3 4 5 6 7 8 9 10
 No complaints Worst possible complaints

Difficult to concentrate: I-----I
 0 1 2 3 4 5 6 7 8 9 10
 No complaints Worst possible complaints

Anxiety/depression I-----I
 0 1 2 3 4 5 6 7 8 9 10
 No complaints Worst possible complaints

Other complaints: I-----I
 0 1 2 3 4 5 6 7 8 9 10
 No complaints Worst possible complaints

Please describe "other complaints":

.....

Interview guide – semistructured interview*

**translated from Norwegian*

General briefing at the start of the interview: Mention that things affect one another and that changes in one field can result in changes in another. We are interested in hearing about changes associated with amalgam replacement, but also about other changes during recent years.

Changes in health complaints

The main focus of the interview is on any changes that you may have experienced (health complaints and life quality) after amalgam replacement.

Have you noticed any change(s)?

Can you tell me something about the complaints you have had? How did they affect your daily life?

Health complaints can have an impact in various ways on how we perceive our body.

Can you tell me something about how your complaints have been affected in terms of:

Sleep

Appetite

How your body feels – any feeling of tension, restlessness, listlessness?

How did you first notice a change?

Tell me specifically what is different on an ordinary day.

How do you experience your early morning/morning/afternoon/evening/night now in comparison with before?

Work tasks and relationships with colleagues

Have the changes affected how you feel at work/in terms of the work tasks you normally perform?

If yes:

Can you describe these changes?

If the informant does not answer spontaneously, ask:

If the changes have affected whether you can get things done

How the changes have affected your relationship with your colleagues at work

Family and friends

Would you say that the changes have affected your relationship with your family and friends?

If yes:

Can you describe these changes?

If the informant does not answer spontaneously, ask:

How the changes have affected your relationship with children

How the changes have affected your relationship with your partner/spouse – your closeness and sexual relations

How the changes have affected your relationship with friends

Leisure activities

Would you say that the changes have affected how you feel about leisure activities?

If yes:

Can you describe these changes?

If the informant does not answer spontaneously, ask:

How the changes have affected your feeling about doing routine housework

About participating in leisure activities

About physical exercise

Emotions

Health complaints will often affect us emotionally. Have you experienced that the changes have also affected how you feel on a normal day?

If yes:

Can you tell me about these changes?

If the informant does not answer spontaneously, ask about:

Frustration

Being able to speak your mind

Shame and/or guilt

Sadness

Anxiety/feeling of security

Happiness

Curiosity and exploratory inquisitiveness

Have the changes affected how you think about yourself?

If yes:

Can you tell me about these changes?

If the informant does not answer spontaneously, ask about:

Your belief in being able to accomplish things

Your feeling of self-esteem

Your thoughts about your future

Reflections

What was your reaction when you found out that your complaints might be associated with amalgam?

What were your experiences when your amalgam fillings were replaced?

What has been useful and positive in your experience of the amalgam replacement?

In relation to the replacement itself?

In relation to the contact with the Adverse Reaction Unit?

How is it/has it been to live with health complaints that people have so many strong opinions about?

In the media, in the health services and among family members and friends?

Concluding question:

"We are getting close to the end of the interview. We have touched on many different subjects, but there may well be things that you wonder about or thoughts you may have that I should have asked you about?"

Erratum

Paper I: page 838, in the last sentence in the caption to Table 1: “September 2000” is corrected to “September 2002”.

