Serum mercury concentration in relation to survival, symptoms, and diseases: results from the prospective population study of women in Gothenburg, Sweden

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A prospective population study of women in Gothenburg, Sweden was started in 1968–69 and comprised 1462 women aged 38, 46, 50, 54, or 60 years at baseline. Follow-up studies were carried out in 1974–75, 1980–81, and 1992–93. The baseline study included an extensive medical and dental examination. Serum mercury concentration (S-Hg) was determined in deep-frozen samples from all participants in 1968–69 and in a random subsample of sera from participants in 1980–81, about 20 years after the baseline examination. S-Hg was statistically significantly correlated with number of amalgam fillings at both examinations. Of 30 defined symptoms and 4 different clusters of symptoms, no one was independently correlated with S-Hg measured in the samples from 1968–69, while there was a negative statistically significant correlation with over-exertion and poor appetite in 1980–81. Blood hemoglobin and serum B-12 concentrations in 1968–69 were statistically significantly and positively correlated with S-Hg, while erythrocyte sedimentation rate and the serum concentrations of potassium and triglycerides were significantly and negatively correlated with S-Hg, also after including potential confounders. Blood hematocrit examined in 1980–81 was negatively correlated with S-Hg. When including potential confounders, serum IgA was also statistically significantly correlated with S-Hg, but not in univariate analysis. No statistically significant correlation was observed between S-Hg, on the one hand, and the incidence of diabetes, myocardial infarction, stroke, or cancer on the other, while a statistically significant negative correlation was observed with overall mortality when age and education were included as background variables. There were some correlations between biological variables and S-Hg, probably of no negative clinical significance, and we conclude that there is no association between disease and S-Hg on a population basis in middle-aged and older women. □ *Epidemiology; laboratory variables; mercury; morbidity; mortality; symptoms*

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Mercury vapor is released from dental amalgam fillings (1–6). Of the mercury vapor inhaled, about 80% is absorbed in the lungs (3). In populations with numerous amalgam tooth fillings, these are the major source of exposure to inorganic mercury (3), and each amalgam surface contributes with about 0.1–0.2 nmol/l to the serum mercury concentration (S-Hg), but the differences between individuals are considerable (7–10). Because of their release of mercury, dental amalgam restorations have been highlighted as a possible source of different health disturbances (4, 5, 11–14), and have been the root of vigorous debate, probably especially intensive in Sweden (15). The discussion also concerns possible interindividual differences in the release of mercury from amalgam restorations, sensitivity to toxic effects of mercury (16), and immunoresponse (17).

In previous studies relating symptoms and diseases to amalgam tooth fillings, we found no correlation between subjectively experienced symptoms (18), incidence of certain diseases or early death (19) or impaired laboratory variables (20), and the number of tooth surfaces of amalgam.

The purpose of this study is to go one step further and to analyze potential associations between symptoms and diseases on the one hand and S-Hg on the other.

Study population

In 1968–69 a randomized sample comprising 1462 women in the age strata 38, 46, 50, 54, and 60 years was medically examined in Gothenburg, Sweden (21). A dental examination was also performed, including panoramic radiography and color slides of the dentition (22). The participation rate was 90.1% in the medical part of the study and 87.4% in the dental part. The women were

Table 1. *P*-values for correlations between different symptoms and complaints in 1974–75, on the one hand, and the log of S-Hg in 1968–69, on the other, in a non-parametric permutation test without and with background variables (correlations where $P < 0.05$ are in bold)

Symptoms or complaints	No. of women in the analysis	Univariate analysis	Background variables: Age	Background variables: Age + education
Dizziness	1229	*f*	*f*	*f*
Eye complaints	1226	*f*	*f*	*f*
Hearing defects	1227	*f*	*f*	*f*
Headache	1229	*f*	*f*	*f*
General fatigue	1230	*f*	*f*	*f*
Sleep disturbances	1227	*f*	*f*	*f*
Nervous symptoms	1226	*f*	*f*	*f*
Sweating	1228	*f*	*f*	*f*
Breathlessness	1229	**0.004 (R)**	**0.006 (R)**	0.067 (R)
Chest pain	1230	*f*	*f*	*f*
Cough	1230	*f*	*f*	*f*
Irritability	1229	0.056 (R)	**0.045 (R)**	0.075 (R)
Over-exertion	1228	*f*	*f*	*f*
Reduced mental concentration capacity	1226	*f*	*f*	*f*
Restlessness	1226	*f*	*f*	*f*
Depressive symptoms	1228	*f*	*f*	*f*
Readiness to cry	1229	**0.016 (R)**	**0.020 (R)**	0.072 (R)
Reduced capability of relaxing	1228	*f*	*f*	*f*
Abdominal pain	1229	*f*	*f*	*f*
Indisposition	1229	*f*	*f*	*f*
Diarrhea	1230	0.19	0.19	*f*
Constipation	1228	*f*	*f*	*f*
Poor appetite	1230	0.143 (R)	0.164 (R)	*f*
Loss of weight	1228	*f*	*f*	*f*
Overweight	1228	*f*	*f*	*f*
Sensitiveness to cold	1227	*f*	*f*	*f*
Micturation disturbances	1229	*f*	*f*	*f*
Joints complaints	1229	*f*	0.10	*f*
Back complaints	1229	*f*	*f*	*f*
Leg complaints	1225	*f*	*f*	*f*

f = $P > 0.20$; (R) = reversed correlation, the symptom being decreased with increasing S-Hg.

medically re-examined in 1974–75 (23), and 89.1% of those examined in the first study took part in this second one. The third phase of the study was carried out in 1980–81 (24), which again included both a medical and a dental examination, and 78.9% and 72.7%, respectively, of the women who had taken part in the first study participated in this 12-year follow-up medical and dental study. Determination of S-Hg in serum samples from 1980–81 was for financial reasons confined to a random sample of 142 women from one of the age groups (women born in 1922).

In a 24-year follow-up carried out in 1992–93 (25), information from the participants, by telephone interview or letter, and from many of the non-participants was supplemented by data from the Swedish National Death Registry, from the Swedish Cancer Registry, and from hospital inpatient registers.

Non-participation analysis

Non-participation analyses were carried out in 1968–69 (22), 1980–81 (24), and 1992–93 (25). The only difference found between the participants and the non-participants in the first study was that there was an overrepresentation of single women among the non-participants. More non-participants than participants in the 1980–81 study were smokers at the time of the baseline study, but there were no differences in socio-economic status or prevalence of heart diseases, antihypertensive treatment, diabetes, history of neoplasms or body weight. Regarding the dental status among non-participants compared with the participants in 1980–81, a larger fraction in the former group were edentate at the time of the initial study, or had a lower total number of teeth and a lower total number of dental fillings (22, 24).

Methods

Dental examination

Number of teeth in dentate women and number of tooth surfaces filled with amalgam were calculated from a panoramic radiograph in 1968–69 and also in 1980–81. In

Table 2. *P*-values for correlations between laboratory variables studied in 1968–69, on the one hand, and the log of S-Hg, on the other, in a non-parametric permutation test without and with background variables (correlations where $P < 0.05$ are in bold)

Variables studied	No. of women in the analysis	Univariate analysis	Background variables: Age	Background variables: Age + education
Blood				
Hemoglobin	1397	**0.017**	**0.012**	**0.019**
Hematocrit	1393	*f*	*f*	*f*
Leukocytes	1375	*f*	*f*	*f*
Platelets	373	*f*	*f*	*f*
Glucose	1394	*f*	*f*	*f*
ESR*	1396	**0.004 (R)**	**0.010 (R)**	0.080 (R)
Serum				
TIBC*	1397	*f*	*f*	*f*
Creatinine	1397	*f*	*f*	*f*
Iron	1397	*f*	*f*	*f*
Chloride	1395	*f*	*f*	*f*
Potassium	1397	**0.044 (R)**	**0.037 (R)**	**0.035 (R)**
Sodium	1396	0.079	**0.025**	**0.044**
Calcium	1396	0.147	0.060	0.076
Cholesterol	1397	*f*	*f*	*f*
Triglycerides	1397	**<0.0001 (R)**	**<0.0001 (R)**	**0.0004 (R)**
Uric acid	1397	0.056	**0.022**	**0.026**
Alkaline phosphatase	346	*f*	*f*	*f*
Bilirubin	345	*f*	*f*	*f*
Protein	1397	*f*	*f*	0.089
B 12	596	**<0.0001**	**<0.0001**	**<0.0001**
IgA	596	0.153	0.1033	**0.033**
IgD	596	0.135	*f*	0.142
IgG	596	*f*	*f*	*f*
IgM	596	*f*	*f*	*f*
IgE	596	**0.037**	0.090	0.062
Urine				
Concentration capacity	1342	0.175	*f*	*f*
Protein	1393	*f*	*f*	*f*

f = $P > 0.20$; (R) = reversed correlation, variable decreasing with increasing S-Hg; *ESR = erythrocyte sedimentation rate; TIBC = total iron-binding capacity.

1968–69 the examination was also complemented by color slides of the dentition (22).

Information about symptoms

In the 1974–75 and 1980–81 studies, all participants answered a standardized self-administered questionnaire (18, 26) which included 30 questions about different symptoms or complaints (Table 1). The main question was: 'Have you had any of the following symptoms during the last three months? Try to answer the question even if you are in doubt!' Each complaint was registered separately.

Four multi-item scales have been constructed from clusters of these questions about symptoms and well-being (27). One of them reflects mental symptoms and another physical symptoms. The third scale in the study was constructed to reflect social well being, and comprised questions believed to reflect the broad concept of life satisfaction; the fourth scale was constructed to reflect satisfaction with both general and mental health. These four scales were used in this study.

Endpoints during the follow-up period

Myocardial infarction.—At least 2 out of the following 3 criteria had to be fulfilled in order for the diagnosis of myocardial infarction to be accepted: central chest pain, typical electrocardiographic changes, and serum transaminase elevation. For a fatal myocardial infarction, the diagnosis had to be stated on the death certificate.

Stroke.—If the stroke was a non-fatal diagnosis, a hospital admission record was required. If the stroke was fatal, there had to be signs consistent with a recent cerebrovascular accident at postmortem examination, or stroke had to be recorded on the death certificate as the major cause of death.

Diabetes.—Information about diabetes was obtained in an interview. Diabetes was accepted as a diagnosis when this diagnosis had been confirmed by a doctor. Additional and complementary information about diabetes was obtained from hospital inpatient registers. Furthermore, if the fasting serum glucose concentration was ≥ 6.0 mmol/l at the follow-up examinations, a clinical examination was

Table 3. *P*-values for correlation between laboratory variables studied in 1980–81 in one age group (women born in 1922), on the one hand, and the log of S-Hg in 1980–81, on the other, in a non-parametric permutation test without and with educational level as a background variable (correlations where $P < 0.05$ are in bold)

Variables studied in 1980–81	No. of women in the analysis	Univariate analysis	With background variable
Blood			
Hemoglobin	134	*f*	0.167 (R)
Hematocrit	134	**0.043 (R)**	**0.047 (R)**
Leukocytes	135	*f*	*f*
Platelets	134	*f*	*f*
Glucose	136	0.057 (R)	0.067 (R)
ESR*	135	*f*	*f*
Serum			
TIBC*	135	*f*	*f*
Creatinine	133	*f*	*f*
Iron	135	*f*	*f*
Chloride	116	0.062	0.058
Potassium	134	*f*	*f*
Sodium	134	*f*	*f*
Calcium	133	*f*	*f*
Cholesterol	134	*f*	*f*
Triglycerides	134	0.145 (R)	0.168 (R)
Uric acid	132	*f*	*f*
Alkaline phosphatase	135	*f*	*f*
Bilirubin	135	*f*	*f*
Protein	136	0.090	0.081
TSH*	128	*f*	*f*
Aspartate amino-transferase	135	*f*	*f*
Alanine amino-transferase	134	*f*	*f*
Antinuclear factor (ANF or ANA)	136	*f*	*f*
Agglutination-activator factor (AAF)	136	*f*	*f*

f = $P > 0.20$; (R) = reversed correlation, the variable increasing with decreasing S-Hg; *ESR = erythrocyte sedimentation rate; TIBC = total iron-binding capacity; TSH = thyroid stimulating hormone.

carried out, either by the population study team or by the participant's own doctor.

Cancer.—Cancer was accepted as a diagnosis if reported by the participant in an interview and confirmed by hospital records or reports from autopsy or pathoanatomical examinations, or if information about cancer was obtained from the Swedish Cancer Registry.

Mortality.—Information about women who had died was obtained from the Swedish National Death Registry. Further details about the definitions of endpoints have been given in a previous paper (19).

Serum sampling

In the 1968–69 study, about 150 g of venous blood from the cubital vein was sampled in 2 open glass tubes without anticoagulant (21). In 1980–81, the samples were collected in evacuated tubes. After centrifugation, serum was portioned into 3-ml polypropylene tubes and stored at −20°C until analysis. Samples collected from all the 1462 women in 1968–69 were analyzed for S-Hg. Of those collected in 1980–81, 142 samples were randomly selected from women born in 1922 and analyzed for S-Hg.

Mercury determination.—The determination of low levels of mercury in small sample volumes (0.3 ml) was possible due to development of a highly sensitive method involving wet digestion, preconcentration on a gold amalgamation trap, and cold vapor atomic absorption spectrometry (CV-AAS) (28). The samples were analyzed in 1992–93 and all in duplicate. They were rerun if the results of the two analyses differed by more than 1 nmol/l. More than 90% of the duplicate analyses differed by less than 0.5 nmol/l.

At least one reference sample was included in each run (Seronorm Trace Elements Whole Blood, Batch No. 904, from Nycomed, Oslo, Norway). The mean and standard deviation for our analyses was 17.0 ± 0.8 nmol/l ($n = 77$), while the recommended, but not certified, value was 20 nmol/l.

Other biochemical analyses.—The methods for determination of biochemical variables (Table 3) were in accordance with the routine methods of the Central Laboratory of the Sahlgrenska University Hospital in Gothenburg (20).

Statistical methods

Calculations were made by means of different procedures from the SAS computer program. The log S-Hg was

Table 4. *P*-values for the correlations between the incidences of different diseases and early death during a 24-year follow-up, on the one hand, and log S-Hg, on the other, when age and age + educational level are taken into account as background variables in a non-parametric permutation test (correlations where $P < 0.05$ is considered statistically significant are in bold)

			P-values, background variables	
Endpoints	No. at risk	Incidence	Age	Age + education
Myocardial infarction	1397*	87	0.102 (R)	*f*
Fatal myocardial infarction	1397*	39	0.089 (R)	0.144 (R)
Stroke	1395*	77	*f*	*f*
Diabetes	1386*	77	*f*	*f*
Cancer	1356*	208	*f*	*f*
Death	1397	253	0.066 (R)	**0.049 (R)**

f = $P > 0.20$; (R) = reversed correlation, the endpoint increasing with decreasing S-Hg; *cases before start of follow-up period are excluded.

normally distributed in the population, while the S-Hg distribution was skewed. The 10-log value for S-Hg was therefore used in the statistical analyses. Correlations were studied with Pitman's non-parametric permutation test (29). In adjusting for potential confounding factors (age and educational level), an extension of the Mantel-Haenszel procedure to permutation test was used. *P*-values < 0.05 were considered statistically significant.

Results

Age in relation to S-Hg

There was no correlation of statistical significance between the 10-log S-Hg and age, but when correlated with the rough figures of S-Hg, there was a statistically significant negative correlation ($P < 0.042$).

Number of amalgam fillings in relation to S-Hg

There was a statistically significant correlation between number of amalgam fillings and S-Hg in 1968–69 ($P < 0.0001$) as well as in 1980–81 ($P < 0.0001$). The number of amalgam fillings in all dentate women in 1980–81 was significantly correlated to number of amalgam fillings in the same women in 1968–69 ($P < 0.0001$, $r = 0.84$).

Symptoms and complaints in relation to S-Hg

Table 1 gives the *P*-values for the correlations between different symptoms and complaints as reported in 1974–75, on the one hand, and S-Hg in 1968–69, on the other. Statistically significant correlations were observed for breathlessness ($P = 0.004$, negative correlation) and readiness to cry ($P = 0.016$, negative correlation). When age was included as confounder, the statistically significant correlations remained. However, they disappeared when age along with educational level were included in the analysis. No correlations were found between the four clusters of symptoms and well being, described in the method section, and the S-Hg.

In 1980–81 the same correlation analyses were carried out between different symptoms and complaints and the S-Hg in the sample of women born in 1922. Over-exertion ($P = 0.04$, negative correlation) and poor appetite ($P = 0.017$, negative correlation) showed statistically significant correlations with S-Hg in the univariate analysis. The relationships remained when educational level and age were taken into consideration as background variables ($P = 0.033$ and 0.015 respectively, both negative).

Blood, serum, and urine variables in relation to S-Hg

Variables studied in both 1968–69 and 1980–81 (Tables 2, 3).— In the 1968–69 study, including all women, 5 variables were statistically significantly correlated with S-Hg. The correlation with blood hemoglobin concentration was positive, which means that a higher concentration of hemoglobin was associated with a higher S-Hg, while erythrocyte sedimentation rate (ESR) and serum concentrations of potassium and triglycerides were negatively correlated, meaning lower values for ESR, potassium, and triglycerides at higher S-Hg. All the statistically significant correlations in 1968–69 remained when the background variables were included in the statistical analyses.

Of the variables studied in 1980–81, only hematocrit was statistically significantly correlated with S-Hg, a negative correlation, which remained also when potential confounders were included in the statistical analysis. None of the variables showed a statistically significant correlation with S-Hg on both occasions.

Variables studied either in 1968–69 or in 1980–81 (Tables 2, 3).—For the variables studied only in 1968–69, there was a statistically significant correlation with S-Hg for serum concentration of B 12, which remained after adjustment for background variables. There was also a statistically significant correlation for serum IgE concentration ($P = 0.037$, positive correlation), but this statistical significance did not remain when background variables were included in the analyses. The serum IgA concentration was not statistically significantly correlated with S-Hg in the univariate analysis, but the correlation did become

significant when age and educational level were included as background variables ($P = 0.033$).

Endpoints during the follow-up period

During the 24 years, altogether 87 women developed myocardial infarction, and 39 of those died. During the same period, new signs of stroke were observed in 77 women, and diabetes developed in 77 women. During the 24-year follow-up period, 208 women had the diagnosis of cancer. A total of 253 women died during the period. Table 4 gives the *P*-values for statistical analyses between the incidences of different diseases and death, on the one hand, and S-Hg, on the other, after age and education level are taken into consideration as background variables. There was no statistically significant correlation between the different diseases studied and S-Hg ($P = 0.102$ with myocardial infarction, reversed correlation), but there was a statistically significant negative correlation between mortality and S-Hg ($P = 0.049$ when age and education were included as potential confounders). The negative correlation between mortality and S-Hg was not statistically significant until the potential confounders were included as background variables.

Discussion

The present study does not indicate any unfavorable influence of S-Hg on symptoms experienced, incidence of disease, or mortality in the general population. In 3 previous reports we have related number of amalgam fillings to different symptoms (18), incidence of early death and certain diseases (19), and to laboratory variables (20) without finding any adverse effects of amalgam fillings as far as these variables are concerned. When extending our analyses to include S-Hg, the only positive statistically significant correlations with symptoms and complaints were those observed between over-exertion and poor appetite, on the one hand, and S-Hg, on the other, both being negative, thus indicating a lower prevalence of the symptom with higher S-Hg.

Of special interest is the association between decreasing risk for overall mortality and increasing S-Hg, which was statistically significant when age and education level were included as background variables. Also the incidence of myocardial infarction was lower among those with the higher S-Hg, though the correlation was not of statistical significance. One possible reason for an association between S-Hg and a lower mortality could be a protective effect from fish consumption. We have recently shown that the concentration of methylmercury in serum is associated with fish consumption (7). Fish consumption is also associated with intake of polyunsaturated fatty acids, which are regarded as protective against myocardial infarction (30). Another possibility might be that subjects who are eager to restore their teeth also are careful with respect to lifestyle factors. However, our inclusion of education level as a background factor in the statistical analysis should, at least to some extent, allow for this potential confounding factor. As always when carrying out a large number of statistical analyses, the risk of chance significance must also be taken into consideration.

There was also a statistically significant positive correlation between serum B 12 concentration and S-Hg. Vitamin B 12 is assumed to be involved in the methylation of mercury (31). Thus, the result may reflect a role of vitamin B 12 in the metabolism of mercury, but could also reflect the fact that fish is a dietary source of both mercury and vitamin B 12.

There was a statistically significant correlation between serum IgE concentration and S-Hg in the univariate analysis, but the statistical significance disappeared when background variables were included in the analysis. A statistically significant correlation between serum IgA concentration and S-Hg was observed first when the background variables were included. In studies of rats, an activation of the immune system by mercury exposure has been observed (32, 33). After 12 weeks, rats with amalgam restorations showed a significant increase of immune-complex deposits and increased Hg concentrations in the kidneys as well as in other organs (33). However, in a study of 41 healthy 15-year-old schoolchildren, there was no relationship between the Hg concentration in plasma and IgE or IgA, nor was there any significant influence of the number of amalgam surfaces on the immune factors tested (34). In a recent study of 77 Swedish adolescents (35), no statistically significant association between IgE levels and Hg concentration in blood was found, but there was a tendency ($P = 0.10$) in the same direction as in the present study. IgA is responsible for mucosal immunity and is thus the first line of defense for the majority of infections. The fairly weak association between serum IgA concentration and S-Hg in the present study may be a chance finding, but it could also indicate an immunological response to mercury from amalgam fillings. However, from our data, we cannot reveal any impact of clinical significance of mercury uptake from amalgam fillings, as reflected by S-Hg or number of fillings (20).

We conclude that there were some associations between biological variables (serum concentrations of IgA and B 12) and S-Hg. Our main conclusion from our prospective population study, however, is that it gives no support for an unfavorable influence of the S-Hg on experienced symptoms, mortality, or incidence of diseases in a general population of middle-aged or older women.

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