*BioMetals* **15:** 189–195, 2002.



# Relationship between mercury concentration in blood, cognitive performance, and blood pressure, in an elderly urban population

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Received 19 November 2001; accepted 24 November 2001

*Key words:* blood pressure, BMI, cognitive function, elderly, mercury, Public Health

**Abstract**

Concentration of mercury (Hg) in whole blood in an elderly urban population with a mean age of 87 years was studied in relation to cognitive function, arterial blood pressure (arterial BP), age, gender, body mass index (BMI) and smoking habits. This population-based study consisted of 106 subjects both males and females. Clinical assessment of the subjects included medical and social history, physical and neurologic examination and assessment of cognitive functions with Mini-Mental State Examination (MMSE). Information on use of all potentially antihypertensive drugs was collected. Whole blood from 106 subjects were collected and analysed for mercury by Cold Vapour Atomic Absorption Spectrometry (Milton Ray ASS-CV) with Seronorm Trace Element as matrix matched quality control. Males and females did not differ in blood-mercury (B-Hg) concentrations or in any of the other studied variables. B-Hg concentrations did not differ between smokers and non-smokers. Females were treated more often than males with antihypertensive drugs. There was no relation found between B-Hg concentration and cognitive function, arterial BP, age, gender or BMI. In conclusion, no relations were found between B-Hg concentrations and the studied variables.

*Abbreviations: AD*–Alzheimer's disease; *BMI*–body mass index; *CNS*–central nervous system; *BPd*–blood pressure diastolic; *BPs*–blood pressure systolic; *F*–female; *M*–male; *Hg*–mercury; $Hg^0$–elementary mercury; $Hg^{2+}$–mercuric mercury; *MeHg*–methylmercury; *IEM*–Institute of Environmental Medicine; *SM*–smoker; *SS*–stopped smoking; *NS*–nonsmoker.

## Introduction

Exposure to mercury may give rise to neurobehavioral disorders (WHO 1989, 1990, 1991). An issue of public health concern and with great relevance to risk assessment is the potential for mercury to induce delayed neurotoxicity years after cessation of exposure or as a result of low-level exposure over a large portion of the lifespan. As the normal brain ages there is a decrease in numbers of neurones in certain regions as well as a decline in neurotransmitter levels and repair mechanisms. If this process were accelerated by chronic or historic exposure to a neurotoxicant, the effect would be a further decrease in functional capacity from that typically observed during ageing. The possibility of an interaction between ageing and exposure to neurotoxic agents was postulated almost three decades ago (Weiss *et al.*1975) and it has been raised repeatedly since (Office of Technology Assessment 1990; Weiss 1990).

There are both epidemiological and experimental evidence indicating that an exposure to the environmental contaminant methylmercury (MeHg) can produce delayed neurotoxicity largely characterised by abnormalities in motor function and impairment in visual, auditory and somatosensory systems (Tsubaki & Irukayama 1977; Rice 1996; Rice & Hayward 1999; WHO 1989, 1990).

Several reports have also noted elevated mercury (Hg) levels in post mortem brain tissue from patients with Alzheimer's disease (AD) (Ehmann *et al.* 1986; Thompson *et al.*1988) and in plasma of AD patients (Basun *et al.* 1991; Hock *et al.* 1998). Cognitive impairment in children, following exposure of MeHg *in utero*, have been reported from several epidemiological studies (Kjellstrom *et al.* 1986, 1989; Clarkson 1997; Davidson *et al.* 1995, 1998; Grandjean *et al.* 1997, 1998, 1999; Steuerwald *et al.* 2000). These data are today being used in risk assessment, identifying 'safe levels' of environmental MeHg exposure. Delayed neurotoxicity resulting in cognitive impairment is less well studied and data available for aged people with regard to concentration of toxic metals in blood are scarcely seen in the literature. There is a need for increased knowledge regarding kinetics and biological parameters in elderly people (WHO 1993). Mercury exists as many species, each with a different metabolism and kinetics including specific critical effect and biological half time. Elementary mercury ($Hg^0$) and MeHg readily cross the blood-brain barrier (NRC 2000). In the central nervous system (CNS) the demethylated mercury accumulates in the form of mercuric mercury ($Hg^{2+}$). Inorganic mercury, predominantly $Hg^{2+}$, in blood does not pass the blood-brain barrier and accumulates mainly in the kidneys (WHO 1989, 1990, 1991). The major mechanism of mercury toxicity is thought to be the high affinity of $Hg^{2+}$ for sulfhydryl groups, resulting in severe inhibition of critical enzymes essential for different biochemical pathways. Swedish people are exposed to MeHg mainly through eating contaminated fish. While exposure to $Hg^{2+}$, in people not occupationally exposed, mainly comes from dental amalgam fillings. In Sweden, 10-50 nmol Hg/l whole blood is used as normal range in riskassessments due to mercury exposure. The consumption of Hg-contaminated fish can though produce substantial individual variations in the concentrations of Hg present in the blood. Depending on previous levels and type of Hg exposure as well as individual characteristics, half-life of Hg in blood varies in the range of approximately 50-120 days (Birke *et al.* 1972; Sherlock *et al.* 1984). The half-life of the whole body-burden is estimated to be 70-80 days (Aberg 1969; Miettinen 1973).

Smoking is not considered an important exposure route for mercury in a similar way as for cadmium due to the cadmium in tobacco.

The study population, in this present study, consisted of elderly ($\geq$ 81 years) urban people selected from an ongoing prospective cohort-study called The Kungsholmen project (Fratiglioni *et al.* 1991, 1992).

The aim with this present study was to describe mercury levels in blood in an elderly population and the relation to cognitive function, arterial blood pressure (arterial BP), age, gender, body mass index (BMI) and smoking habits.

## Subjects, material and methods

### *Study subjects*

From a longitudinal population-based cohort study on ageing and dementia, The Kungsholmen project (Fratiglioni *et al.* 1991, 1992), a sub-sample of 106 (58 females-F, 48 males-M) subjects were assessed (1994–1996), in the present study, for total blood-mercury (B-Hg) concentrations, cognitive function, arterial-BP, anti-hypertensive drug treatment, BMI and smoking habits. The Kungsholmen project started in 1987 (Figure 1). In summary, the study population included all persons ($n = 2.368$) born in 1912 and before, and living (at home or institution) in the Kungsholmen district of Stockholm, Sweden in October 1987. The project aimed to study multiple psychosocial, medical and biochemical variables, whereas toxic metals, including mercury, was one part of the biochemistry arm. The study consisted of three phases. In phase I (October 1987–September 1989) 1,810 (76%) out of 2,368 subjects were assessed with a cognitive test, the Mini-Mental State Examination (MMSE) (Folstein *et al.* 1975) translated into Swedish. The cut-off point 23/24 was used to discriminate between individuals suspected (MMSE $\leq$ 23) and non suspected (MMSE $\geq$ 24) demented. Phase I also included clinical assessment with physical and neurologic examination, laboratory testing, social and medical interview. Subjects with suspected dementia, *i.e.*, cases and a comparable random sample of non-cases from phase I, entered phase II (January 1988–December 1989). In phase II a final diagnoses of dementia was reached, through clinical examination, family interview and laboratory tests. In phase III (November 1990–January 1992) the whole study population was re-examined for possible new cases of dementia. A follow-up (phase IV) was performed in 1994–1996, where 804 (out of 1,810) subjects were re-examined following the scheme in phase I. From the 804 subjects a sub-sample ($n = 157$) was chosen for further examination of dental status. The 106 subjects in this present study was chosen from

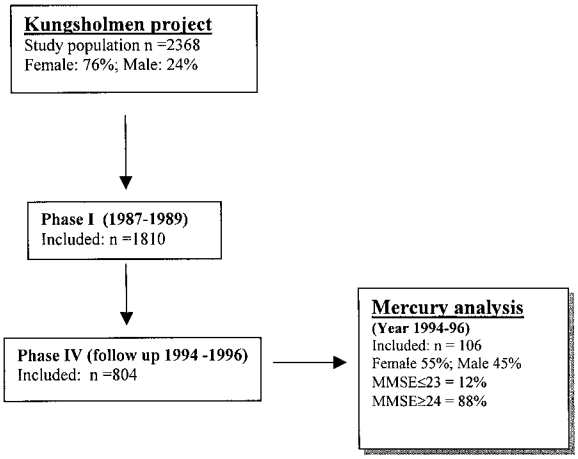


*Fig. 1.* The Kungsholmen project.

this sub-sample ($n = 157$). To get an even distribution, according to MMSE score, gender and age (in that order), in our study population, the subjects was chosen selectively for the assessment of total B-Hg concentrations. Other relevant assessments in this study were as follows: cognitive function tested with MMSE; BP (systolic-BPs and diastolic-BPd) measured with a mercury sphygmanometer with the subject in sitting upright position, after 5 min of rest; any use, two weeks preceding the baseline interview, of any antihypertensive drugs (codes: CO2, CO3, CO7 and CO8 of the Anatomical Therapeutic Chemical (ATC) classification system), was recorded; smoking habits divided in smokers (SM), previous smokers (SS), *i.e.*, stopped smoking <10years ago and non-smokers (NS); body weight (kg) and height (m) which was used to calculate BMI (kg/m$^2$); gender and finally age at the time of assessment. All assessments, for each subject, were at one point in time.

There was an informed consent and approval by the local Ethical committee KI: 90:251.

## Material and methods

### *Mercury assay*

#### *Blood-samples*

During phase IV of the Kungsholmen project blood was collected for metal analysis. 10ml blood was drawn from all subjects, following a strict protocol (Basun *et al.* 1994; Nordberg *et al.* 2000 a, b), and collected in tubes containing Sodium-Heparin. The tubes were stored at 4 °C during the day of sampling. To avoid contamination in future handling of the samples, the heparinized blood was evenly split into three acid-washed polyeten tubes. The tubes were frozen at −20 °C for one week and then transferred to −80 °C and stored at the Institute of Environmental Medicine (IEM) until taken for further analyses.

#### *Mercury analysis*

During two time-periods, November 1997 and July 1998, a total of 106 frozen blood-samples, representing 106 subjects, were collected and analysed for total Hg content. The analyses were performed by Analytica AB[1] Stockholm, Sweden, a commercial, accredited laboratory with an accredited method for analysing total Hg content in blood. The frozen blood samples were collected at IEM and transported to Analytica AB within 1h in a coldbox with frozen iceblocks below 0 °C. At Analytica AB the samples were stored at −20 °C low temperature for a few days before analysis. Cold vapour atomic absorption spectrometry (Milton Roy AAS-CV unit) was used to determine the B-Hg concentrations. A half millilitre of blood was analysed, in duplicates, after treatment with $SnCl_2$. Seronorm Trace Element was used as a matrix matched quality control. The concentration of the calibration standard was 500 nmol Hg/l and standard was added to every fifth sample. Accredited lower limit was 10 nmol Hg/l for both analyses (1997, 1998). Coefficient of variance (CV) was in 1997, 8% at 40 nmol Hg/l and 17% at 15 nmol Hg/l, and in 1998 10% at 40 nmol Hg/l. In 1997 the quantification limit (LOQ = 10× SD-blank) was 8.2 nmol Hg/l and the detection limit (LOD = 3× SC-blank) was 2.5 nmol Hg/l.

#### *Statistical analysis*

Various statistical methods were used. Comparison between groups were done with Student's $t$-test and with a $\chi^2$ test. Linear correlation was used to study the relationship between Hg and all the other variables. Out of 106 subjects, five subjects demonstrated B-Hg concentrations exceeding 28 nmol/l. These subjects were defined as outliers and excluded from the statistical analysis along with three subject with B-Hg concentrations below RDL (6× SD of standard). Statistical significance was set at $P < 0.05$.

[1]Present name SGAB. Accredited by the Board for accrediting and technical control (SWEDAC) in accordance with Swedish law. And in compliment with the demands in SS-EN 45001 (1989), SS-EN 45002 (1989) and I80/IEC Guide 25 (1990:E).

## Results

When plotted, BMI, BPs and BPd appeared approximately normally distributed. B-Hg concentrations were shifted towards lower levels when considering outliers, otherwise approximately normally distributed. MMSE scores were shifted towards higher scores. Information on B-Hg concentrations, MMSE-scores, BPs, BPd, antihypertensive drugs use and age were known for all the subjects ($n = 106$). BMI was calculated for 103 subjects and smoking habits were known for 105 subjects.

Mean ± SD B-Hg concentration was 17 nmol/l ± 11 (range 2–80 nmol/l). 101 subjects had B-Hg levels ≤ 28 nmol/l, the remaining 5 subjects showed extreme B-Hg levels (outliers) compared to the rest of the population (4 male: 42, 55, 60 and 80 nmol/l and one female: 54 nmol/l). None of these 5 subjects demonstrated a MMSE score below 25. These outliers were excluded from the statistical analysis along with three subjects, one male and two females, with B-Hg concentrations below 5 nmol/l, corresponding to approximately 6 × SD of the standard (RDL). MMSE score, mean ± SD: 27 ± 3 (range 17–30). 13 (12.3%) subject (7 F, 6 M) demonstrated a MMSE score less than 24. Age, mean ± SD: 86.7 ± 3.4 years (range 81–94). BPs, mean ± SD: 160 mmHg ± 24 (range 100–220) and BPd: 79 ± 12 (50–110). Out of 106 subjects, 31 F (53%) and 14 M (29%) used antihypertensive drugs. The use of more than one kind of antihypertensive drug occurred in 61% and 29% of the treated females and males respectively. BMI, mean ± SD: 23 ± 3 (range 16–30). Smoking habits: 79 NS (44 F (77%), 35 M (73%)), 14 SS (8 F (14%), 6 M (12.5%)) and 12 SM (5 F (9%), 7 M (14.5%)). Demographic and clinical data are summarised in Table 1.

There were no statistically significant differences between males and females in any of the studied variables: MMSE score ($P = 0.62$), B-Hg ($P = 0.19$); BPs ($P = 0.45$); BPd ($P = 0.19$); age ($P = 0.06$); BMI ($P = 0.56$) and smoking habits ($\chi^2 = 0.88$, df $= 2$, $P = 5.99$).

Anti-hypertensive drug treatment differed between gender. The females were treated to a significantly higher degree than the males ($\chi^2 = 18.9$, df $= 1$, $P = 3.84$). No linear correlation were found between B-Hg concentration and age ($r = 0.045$), BMI($r = -0.063$), BPs ($r = -0.1371$), BPd ($r = -0.1637$) or MMSE score($r = 0.1373$). The results from comparing B-Hg *vs*. BPs, BPd, MMSE and BMI remained non-correlated after stratifying for subjects with and without antihypertensive treatment. Our selected study-population ($n = 106$) represented 4.5% of the initial cohort ($n = 2.368$), 5.9% of the subjects initially included in phase I ($n = 1.810$) and 13.2% of the 804 subjects participating in the follow-up. The study-population differed significantly from the total follow-up population in phase IV, in having a higher sex ratio (F:M), a higher BPs and BPd and lower prevalence of C03 (diuretic) drug treatment.

## Discussion

In this cross-sectional study of elderly urban people no relations were found between B-Hg levels and cognitive performance, arterial BP, age, BMI or smoking habits. Males and females did not differ significantly in any of the studied variables. There were however differences in antihypertensiv drug- treatment (including diuretics) between gender. This might have influenced elimination rate of B-Hg differently in the male and female groups. Except for the highest four outliers, the B-Hg concentrations (17 nmol/l ± 11) were within the normal range (10–50 nmol/l) used in Sweden for risk-assessment after acute exposure. All the B-Hg concentrations were also clearly below concentrations known to cause acute (> 1000 nmol/l) or chronic (> 175 nmol/l) neurotoxicity (WHO 1990). The mean B-Hg was in the same range as reported for patients suffering from AD demonstrating significantly higher B-Hg levels than the control groups. Basun *et al.* (1994) reported a mean ± SD: 14.7 ± 6 nmol/l in 12 AD patients and Hock *et al.* (1998) reported B-Hg levels, in AD patients with early onset mean ± SE: 16.6 ± 3.6 nmol/l and late onset 13.2 ± 1.9 nmol/l.

No findings in this study support any relation between Hg concentrations in blood and neurotoxicity (in the form of declining cognitive function) or arterial BP. Half-life of B-Hg is, however, relatively short compared to the probable long latency period involved when low dose mercury exposure results in neurotoxic and/or toxicity to other organ systems. This means that exposure information in this study probably reflects the wrong time period. Exposure misclassification would weaken any relation between B-Hg concentration and cognitive function or arterial BP. Comparing B-Hg and BP is also complicated by gender-, as well as individual differences in antihypertensive drug treatment.

*Table 1.* Demographic and clinical data of 106 subjects (sub-sample from the Kungsholmen project) participating in blood mercury analyses.

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | MMSE ≤ 23 | MMSE = 24 | MMSE > 24 | MMSE ≤ 23 | MMSE = 24 | MMSE > 24 |
| Subjects (*n*) | 6 | 1 | 41 | 7 | 4 | 47 |
| Age (year) [a] | 84 | 87 | 86 | 87 | 89 | 87 |
| Weight (kg) [a] | 70.5 | 69.0 | 70.0 | 53.0 | 57.0 | 58.0 |
| Height (m) [a] | 1.73 | 1.64 | 1.71 | 1.55 | 1.61 | 1.61 |
| BMI [b] | 24 | 26 | 24 | 22 | 22 | 23 |
| BPs [c] | 170 | 170 | 160 | 165 | 135 | 160 |
| BPd [d] | 90 | 65 | 75 | 70 | 70 | 80 |
| SS/SM/NS [e] | 1/2/3 | 0/0/1 | 5/5/31 | 0/0/7 | 3/0/1 | 5/5/36 |
| Antihypertensive drug-treatment [f] | 1 | 0 | 13 | 3 | 2 | 26 |

[a]Mean value in phase IV
[b]Body mass index, mean value in phase IV
[c]Blood pressure systolic, mean value in phase IV
[d]Blood pressure diatolic mean value in phase IV
[e]Smoker/stopped snoking/nonsmoker
[f]Antihypertensive drugs (Anatomical Therapeutic Chemical (ATC) classification system, No. CO2, CO3, CO7, CO8).

Neither age nor MMSE score were related to B-Hg in this study. Nor was age and MMSE-score related which might be expected as ageing have been a risk-factor for dementia in other population based studies, as in the Kungsholmen cohort (Fratiglioni *et al.* 1991). In this study there were relatively few subjects in the upper range of the age interval that might, at least in part, explain the absence of relation between age and MMSE.

The mean age of this population was 87 years, which exceeds the average life expectancy for females and males in Sweden with 5 and 10 years, respectively. It is thus a long-lived population and, might be considered a comparatively healthy sub-population from the initial cohort.

Genetic and environmental conditions can effect neurobehavioral function making riskassessment of Hg, especially in the lower range of the dose-response curve difficult. This is illustrated by the fact that this study-population, recruited from the same cohort as the 12 AD patients in Basun *et al.* (1994) study, demonstrates B-Hg in the same range as the AD patients did. Using concentrations of Hg in blood is an indirect method of predicting concentrations in those organs that might be effected. The concentration of Hg in blood illustrates a recent exposure, and to be useful in correlating to symptoms due to mercury toxicity, a constant exposure and/or a time-series of exposures would be required. This study has its merits in being a study performed on elderly people, recruited from a large-scale cohort- study on well defined elderly urban people. Information on this age group is scarce and needs to increase. It is important to identify environmental factors influencing an ageing population in order to prevent loss of life-quality. Exposure for neurotoxic agents such as mercury during development and / or a significant portion of the lifespan may result in an acceleration of age-related neurodegenerative diseases. This issue is of great concern considering the changing demographics of industrialised countries with an increasing mean age in the populations. Even small changes of functional abilities could have potentially serious consequences for society, as well as for affected individuals, if a significant portion of the population would to be affected.

The mechanisms of mercury toxicity are not fully understood which makes an epidemiological approach investigating any connection between low dose exposure of mercury and any cognitive impairments difficult. In our study we use a simple but common tool to screen cognitive ability, to correlate to a biological marker that may or, most likely, may not reflect the actual CNS-Hg level at time of a possible injury. It is obviously a very blunt instrument to capture subtle changes that may be in the range of normal function.

## Conclusions

In this elderly urban population no relations were found between B-Hg concentration and cognitive function, arterial BP, age, gender or BMI.

## Acknowledgements

Professor Laura Fratiglioni is gratefully acknowledged for her support of the project. We thank all the members in the Kungsholmen Study Group for their collaboration and for financial support from Karolinska Institutet and Alzheimer foundation, Sweden.

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