BioMetals **13:** 311–317, 2000.

Cadmium concentration in blood in an elderly urban population*

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Received 20 October 2000; accepted 25 October 2000

Key words: cadmium, blood pressure, BMI, cognitive function, elderly

Abstract

Concentration of cadmium in blood in an elderly population with a mean age of 87 years was studied in relation to age, blood pressure, BMI, cognitive function, gender and smoking. This population-based study consisted of 804 subjects both men and women. Clinical examination included medical and social history, physical and neurologic examination, and assessment of cognitive functions with Mini-Mental State Examination (MMSE). Information on prescription and non-prescription drug use was collected. Anti-hypertensive drugs included all medicines potentially used for treating high blood pressure. Blood pressure was measured. Whole blood from 763 subjects was analysed for cadmium by atomic absorption spectrophotometry (GFAAS) with Zeeman background correction and with a graphite furnace using the L'vov platform technique including quality control. Differences in cadmium concentrations were related to non- smokers (3.9 nmol/l), previous smokers (4.4 nmol/l) and current smokers (7.5 nmol/l). There were no relations between cadmium and age, blood pressure or cognitive functions. In conclusion, increased cadmium levels were found in smokers. A possible contribution from previous occupational exposure needs to be further evaluated.

Introduction

Cadmium (Cd) exposure in humans may lead to adverse health effects (WHO, 1992). Renal failure occurs after exposure and the kidney is the critical organ (Nordberg *et al.* 1985) independent of exposure route. IARC classified cadmium as a human carcinogen belonging to group 1 (IARC 1993). This decision was based upon data indicating that Cd is a risk factor for lung cancer in industrial workers. This is so far only reported to occur after inhalation of Cd. There are no reports supporting a relationship between oral Cd exposure and lungcancer. Metabolism and kinetics of Cd is influenced by a number of external factors, such as species of metal, intake of protein and calcium, iron status, interaction with other metals and strongly related to metallothionein (MT). The role of MT in metal metabolism and modulation of toxicity are explained particularly in relation to cadmium, based on experimental data. The extremely long biological half-life of Cd in the human kidney of 15-20 years is to be regarded as a result of continuos Cd rebinding to de-novo synthesized MT (Nordberg *et al.* 1985).

Neurotoxicity has been reported in lactating pups of dams exposed to Cd (Andersson *et al.* 1997) but remains controversial since Cd does not pass the blood-brain barrier. The mechanism for this is at present not known. Whether there is a direct effect e.g. such toxicity may be due to interference of Cd with Zn-metabolism and MT-III in brain (Jin *et al.* 1998) is at present not quite clear. Another explanation could be that there is an uptake of cadmium via olfactory bulb similar as described for Ni (Tjälve *et al.* 1996). Cd might also serve as an endocrine disrupter.

The newborn is almost Cd free and Cd is accumulated with age in both liver and kidney. The occurrence of toxicity is considered to be dependent on the balance

*Partly presented at [26]ICOH congress Singapore, 2000

between de-novo-synthesis of MT in renal tubular cells and the release of Cd-ions from lysosomal degradation of CdMT taken up from tubular fluid (Nordberg *et al.* 1992).

Under special conditions some studies have reported increased blood-pressure in animals. Performed studies on environmentally exposed humans and occupational exposed subjects are in accordance with observations seen in animal studies. Increased effects on blood pressure have been reported in humans but the studies have not been adjusted for smoking habits (WHO 1992).

Blood pressure and metal exposure has been debated for decades. In some studies it was shown a relationship between blood pressure and cadmium as had been reported in animal studies (Schroeder 1964). However studies reported for humans (Schroeder 1965) did not give information of smoking habits. In a previously reported study (Basun *et al.* 1994) on cadmium in blood in a an aged population it was found that Cd concentration in blood was related to diastolic blood pressure in non-smoking and non-demented individuals. There were also no correlation between blood Cd concentration, age and cognitive function. There were no differences between cadmium in blood for Alzheimer disease (AD) suffers and for non-demented persons. The observed differences in Cd concentration in blood were related to smoking habits (Basun *et al.* 1994).

Since cadmium in humans has a biological half life of 20–30 years it is of interest to study humans of age 77+ as the turn over rate of Cd might be seen in the blood. It could also be interesting to study effects and exposure levels in aged people, as there is a need for gaining more knowledge for this age group. There is a demand for further knowledge of turnover of chemicals and biological parameters in aged humans (WHO 1993).

The aim of the present study was to in a large population based sample evaluate possible relation between Cd concentrations in blood and blood pressure (BP) to age, body mass index (BMI), cognitive function, gender and smoking habits.

Subjects, material and methods

Study subjects

The Kungsholmen Project is a longitudinal study on ageing and dementia. Details of the study design have been reported previously (Fratiglioni *et al.* 1991, 1992). Briefly, the study sample consisted of all inhabitants born 1912 and before and living in the Kungsholmen district of Stockholm1987. 1810 persons took part in the first phase of the study 1987–1989. In the follow-up 1994–96, 804 subjects participated and 763 subjects with mean age of 88.4 years had their blood samples analysed for cadmium. Lead was as well analysed in the same group (Nordberg *et al.* 2000).
Clinical examination included medical and social history, physical and neurologic examination, and assessment of cognitive function Mini-Mental State Examination (MMSE). Family interview including diet assessment and laboratory tests gave a final diagnosis of dementia and different types of dementia. Dementia diagnosis was based on DSM-III-R criteria. Arterial blood pressure (systolic Korotkoff phase 1 and diastolic phase 5) was measured with a mercury sphygmanometer with the subject in a sitting upright position after a 5-min rest Information on prescription and non-prescription drug use was collected for the two weeks preceding the baseline interview. Antihypertensive drugs included all medicines potentially used for treating high blood pressure (Codes C02, C03 and C07 of the Anatomical Therapeutic Chemical (ATC) classification system). Smoking habits such as current smokers, previous smokers and nonsmokers were recorded. No information for the analyses of cadmium was given. There was an informed consent and approval by the local Ethical committee KI: 90:251.

Material and methods

Cadmium analysis

10 ml of whole blood was collected following an instruction for blood sampling under controlled conditions and stored at −80 °C until analyzed for cadmium. Also lead, mercury, selenium and glutathione peroxidase activity was analyzed and reported elsewhere. The blood samples were split into three tubes before freezing to avoid contamination in the future handling of samples. Sampling started in spring 1994 and ended 2 years later. Analyses started almost immediately on a random basis and were done blinded.
Metal analyses including a quality control program was performed. Equipment used for the metal determination in blood was either Varian Spectra AA-800 GTA 100 and a PU 9200 GFAAS unit or graphite furnace atomic absorption spectrophotometry (GFAAS)

Perkin Elmer 5000 with Zeeman background correction and with a graphite furnace HGA-500 using the L'vov platform technique (Nordberg *et al.* 2000).

Two different laboratories were involved in the cadmium analyses in blood. The first 215 samples were analyzed at Institute of Environmental Medicine (IEM), Karolinska Institutet, The remaining samples were analyzed at Analytica AB, Stockholm, Sweden, a commercial accredited laboratory with an accredited method. The company participated successfully in the quality control program of IEM, KI for lead and cadmium analyses in blood and used daily reference material from European Commission Joint Research Centre, Institute for Reference Materials and Measurements, Geel, Belgium. Some samples were analyzed at both laboratories for an inter-laboratory comparison. Apart from different equipment in the two laboratories, different methods for sample preparation were used. At Analytica AB, the samples were treated with Triton X-100 and diammoniumhydrogenphosphate as matrix modifier according to a method AAS 17 (ver 5). Standards were made by spiking blood low in Cd with known amounts of cadmium via a Microlab 1000 dilution equipment. Equipment used for the metal determination in blood was Varian Spectra AA-800 GTA 100 and a PU 9200 GFAAS unit. Limits of accreditation for whole blood, quantification limit and detection limit for blank as well as reproducibility, (RSD) fulfilled the criteria for cadmium analyses. As earlier analyses were performed at IEM and later taken over by Analytica AB, a comparison of samples analyzed at the two laboratories was performed. Results from the inter- laboratory comparison of samples showed good and acceptable results. This meant that the obtained analyses could be evaluated on one group basis (Nordberg *et al.* 2000). Samples for comparison covered low, medium and high concentration and covered the full collection time.

Statistical analysis

Various statistical methods were used. Comparison between groups was done with Student's t-test and with a χ^2 test. Multiple regression was used to study the relationship between cadmium and other variables. Statistica for the Windows operating system was used. Statistical significance was set at $P < 0.05$.
The program was chosen that the subjects were grouped by age on 5 years interval.

Results

The results of the variables that were studied were as follows. The age of the subjects was 87.3 ± 4.9 years and the ratio of gender of M:F 178/585 with a BMI expressed as m^2/kg of 23.0 ± 11.5. The blood pressure was 153.0 ± 25.4 mm Hg (Systolic BP) and 76.6 ± 11.5 mm Hg (Diastolic BP). The MMSE was 24.9 ± 12.6.

Cd concentration in blood was analyzed in 763 subjects. Mean level was 4.4 nmol/L whole blood with a standard deviation of 3.54 and a range between 0.53 and 38.00. The study group was further divided into present smokers, non-smokers and previous smokers. The last group was defined as stopped smoking 10 years before blood sampling in this study.

Figure 1 displays the concentration of cadmium in blood expressed as nmol/L in relation to different age groups based on 5-year interval. In Figures 2 and 3 the cadmium concentration in blood expressed as nmol/L in non-smokers and smokers are displayed for the different age groups. Figure 4 displays the diastolic blood pressure as a function of cadmium concentration in blood expressed as nmol/L.

There were 750 subjects with known smoking habits and Cd concentrations. Current smokers compared to non-smokers or previous smokers had higher cadmium concentrations 7.5 *vs.* 4 nmol/L whole blood; $P < 0.000001$), were younger (85 versus 87 years; $P = 0.006$), more often men (30/145 (21%) versus 44/531 (8%); $P = 0.0002$), had lower BMI (21.2 *vs.* 23.2; $P = 0.0003$). Previous smokers had a Cd concentration of 4.4 nmol/L.
There was no significant gender difference in Cd concentrations (4.2 nmol/L in men compared to 4.4 nmol/L in women; $P = 0.52$). Furthermore, both men and women smokers had high Cd levels, 7 and 7.8 nmol/L, respectively with a higher concentration seen in women.

When different multiple regression models were tested with Cd as dependent variable, no relation was found between Cd concentrations and age, BMI, MMSE, systolic BP or diastolic BP. Regression analyses were also performed with and without subjects treated with anti-hypertensive drugs but no association between Cd concentrations and BP (systolic or diastolic) was seen.

There were 41 subjects (5%) with missing Cd values. They were two years younger (85 years) than the subjects with a cadmium value. Otherwise there were no statistical significant changes between the groups

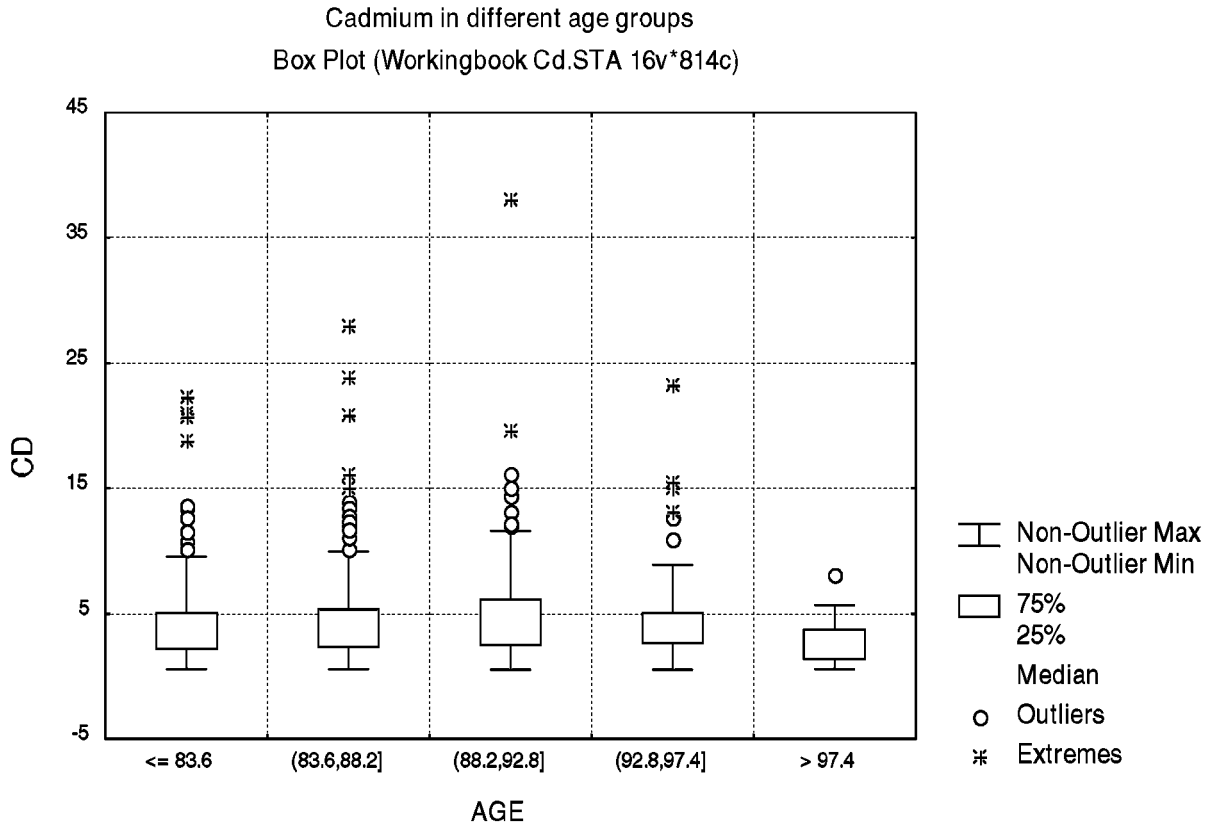

Figure 1. The concentration of cadmium in blood expressed as nmol/L in relation to different age groups based on 5-year interval.

concerning gender difference, BMI, systolic BP, diastolic BP, smoking habits or percentage taking blood pressure medicine.

Discussion

This is a population-based sample of urban population not occupational exposed to Cd. The merits are the high number of participants (804) and a low percentage with a missing Cd value (5%). The subjects with a missing Cd value did not differ from the subjects with Cd value in any essential aspect. The present results of the Cd concentration in blood do not indicate an industrial or occupational exposure in this population, which is further, emphasized by the lack of gender difference. A potential contribution from previous exposure seems likely to be excluded taking into account the long biological half-life for Cd in human tissue. Factors that might influence the concentration of Cd in blood could be genetic differences and possible genetic polymorphisms in key enzymes and transport proteins involved in Cd metabolism.

No relation between age and Cd concentration in blood (Figure 1) was seen in the current study. This is worth emphasizing, as Cd is known to increase by age in the body. The lack of relation between indicates that at higher age Cd is not further accumulated in the body, which might depend on an aging mechanism for synthesis of the metallothionein.

In this elderly the not industrial exposed population no relation was found with cognitive function BMI and BP. As reported earlier, high Cd concentrations were found in current smokers. Life-style factors e.g. physical activity and intake of alcohol could have influenced this result.

In the present study with a well-defined cohort of 804 subjects by age 77+, no relation was found between Cd and systolic BP or diastolic BP. Regression analyses were also performed with and without subjects treated with anti-hypertensive drugs but no association between cadmium concentrations and BP

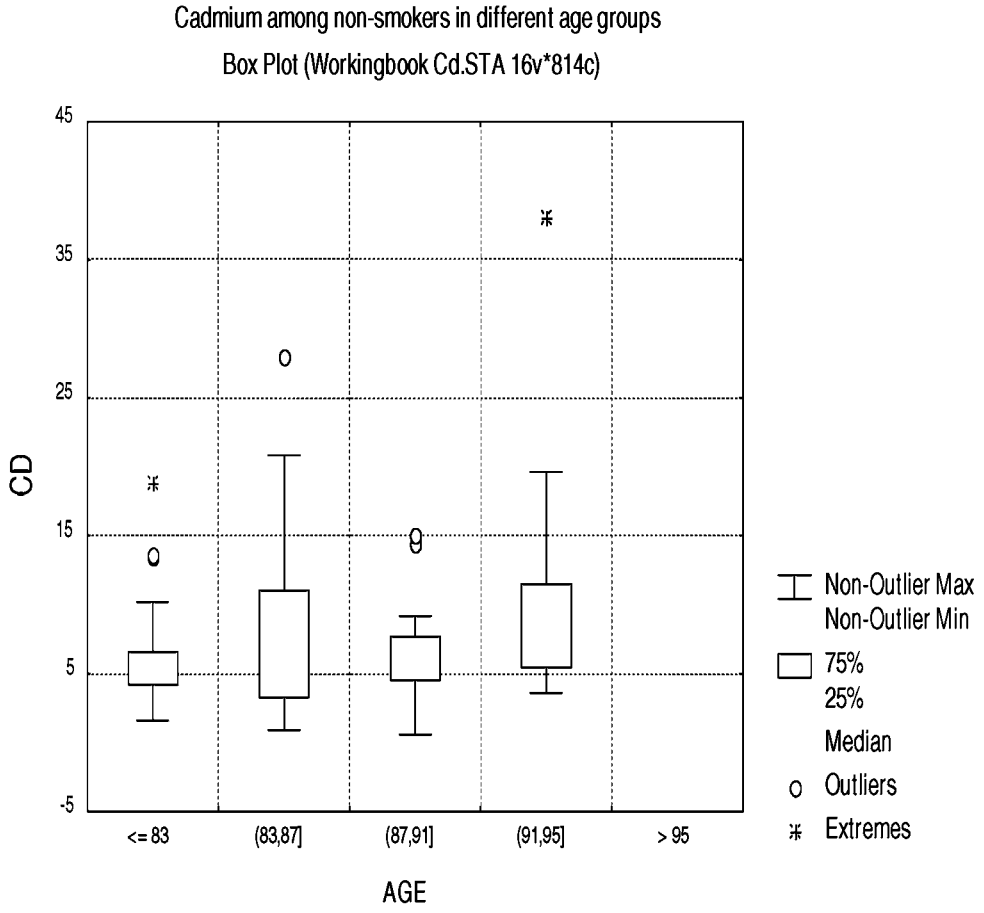

Figure 2. Cadmium concentration in blood expressed as nmol/L in non-smokers.

(systolic or diastolic) was seen. Results were also corrected for smoking habits.

The PheeCad (Public Health and Environmental Exposure to cadmium) study group investigated a random sample consisting of 692 subjects in large age span, 20–83 years of age how environmental exposure to Cd by time influenced the incidence of hypertension and blood pressure. Blood pressure was measured by conventional sphygmomanometry with 15 readings in total and also 24-h ambulatory blood pressure (ABP) monitoring. Systolic/diastolic blood pressure was on average 128.4/77.3 mm Hg. The base line blood cadmium concentration was of 11.1nmol/l and urinary cadmium excretion of 10.2 nmol/24 h (both geometric means). Cd in blood and in urine declined by 29.6% and 15.2% respectively over a 5-year follow up. The systolic BP decreased 2.2 mm Hg in men and remained unchanged in women. The diastolic BP increased by 1.8 mm Hg in both genders. It was concluded (Staessen *et al.* 2000) that environmental exposure to Cd was not associated with higher CBP or 24 h ABP or with increased risk of hypertension. The importance of prevention to exposure to cadmium is emphasized by the slower decrease of Cd in blood in premenopausal women.

The mechanism behind a possible influence of cadmium on the BP is less discussed. A speculative explanation could be that the toxic insult of cadmium on blood pressure might only be possible to see and to catch during ongoing exposure e.g. momentanously when influence on nitrogen oxide signaling in the blood stream. If that is the case it will on population basis be most difficult to individually relate changes in BP to Cd exposure. During ongoing exposure to Cd equilibrium is likely to occur.

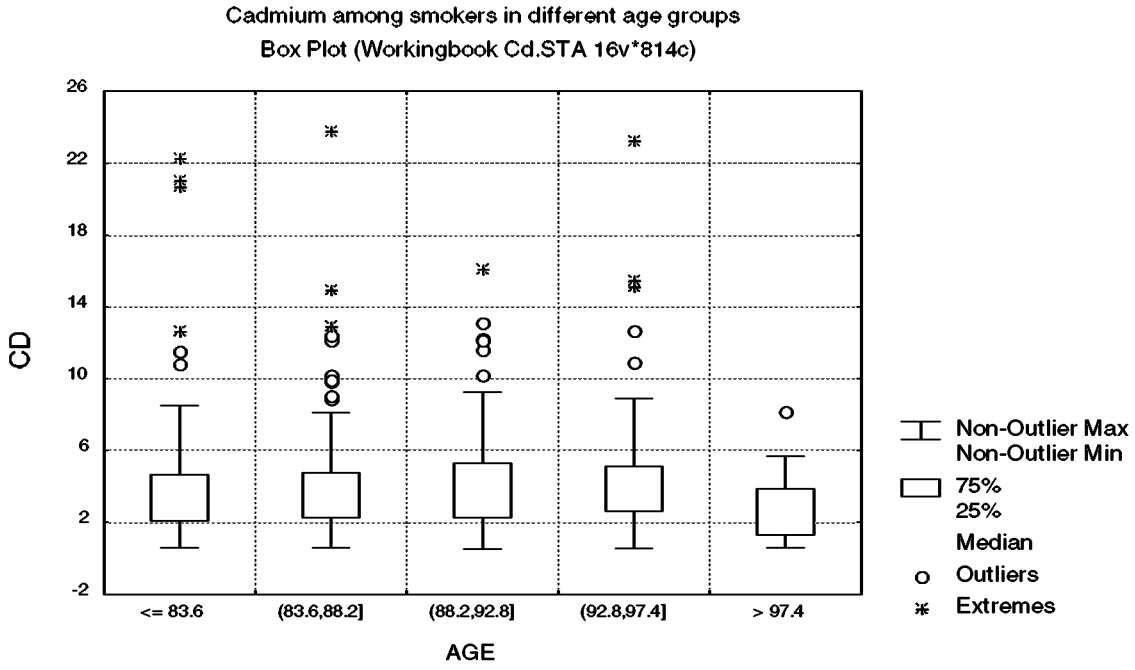

Figure 3. Cadmium concentration in blood expressed as nmol/L in smokers.

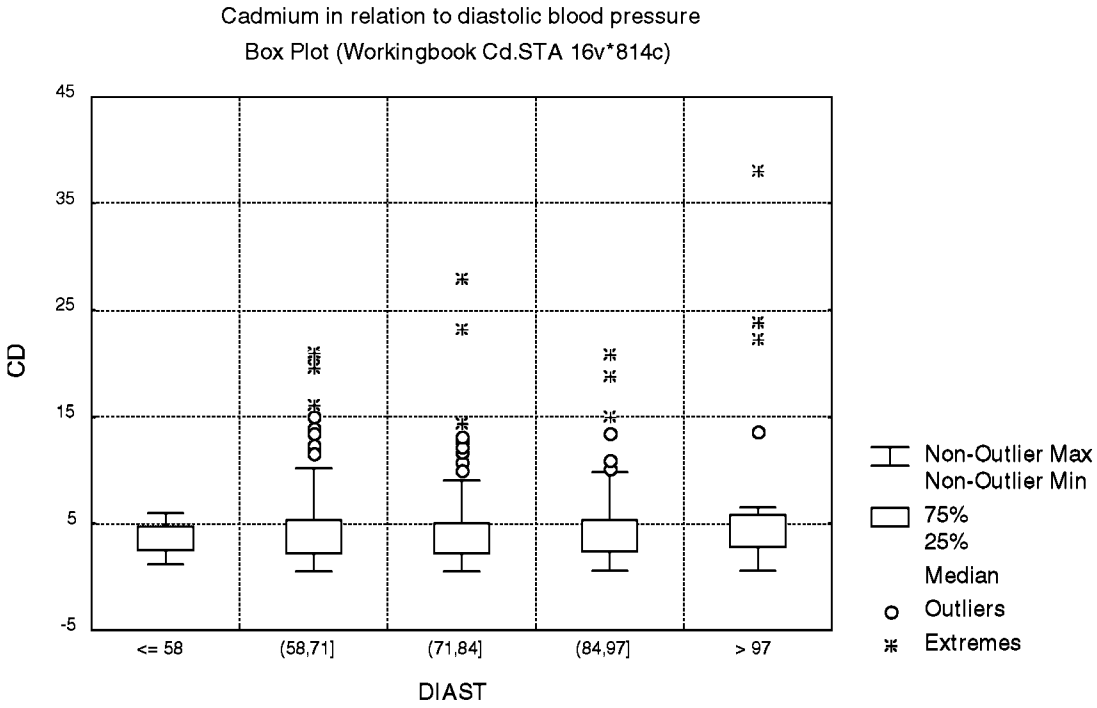

Figure 4. Diastolic blood pressure as a function of cadmium concentration in blood expressed as nmol/L.

Conclusion

Increased Cd levels were found in smokers and previous smokers compared to non- smokers. No associations were found between Cd in blood and BMI, systolic BP and diastolic BP. No relation was seen between MMSE and Cd concentration in blood. This is a strong indication that Cd does not influence cognitive processes or blood pressure. This emphasizes the importance of Cd prevention might be related to other factors such as bone effects caused by exposure to Cd.

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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