Cadmium, Mercury, and Lead in Kidney Cortex of the General Swedish Population: A Study of Biopsies from Living Kidney Donors

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Cadmium, mercury, and lead concentrations were determined in deep-frozen kidney cortex biopsies taken from 36 living, healthy Swedish kidney donors (18 males and 18 females), who were 30–71 (mean 53) years of age. Information about occupation, smoking, the presence of dental amalgam, and fish consumption could be obtained for 27 of the donors. The samples (median dry weight 0.74 mg) were analyzed using inductively coupled plasma mass spectrometry, and the results were transformed to wet-weight concentrations. The median kidney Cd was 17 µg/g (95% confidence interval, 14–23 µg/g), which was similar in males and females. In 10 active smokers, the median kidney Cd was 24 µg/g, and in 12 who never smoked, it was 17 µg/g. The median kidney Hg was 0.29 µg/g, with higher levels in females (median 0.54 µg/g) than in males (median 0.16 µg/g). Subjects with amalgam fillings had higher kidney Hg (median 0.47 µg/g, $n = 20$) than those without dental amalgam (median 0.15 µg/g, $n = 6$), but kidney Hg was below the detection limit in some samples. Nearly half of the samples had kidney Pb below the detection limit. The median kidney Pb was estimated as 0.14 µg/g. This is the first study of heavy metals in kidney cortex of living, healthy subjects, and the results are relatively similar to those of a few previous autopsy studies, indicating that results from autopsy cases are not seriously biased in relation to kidney metal concentrations in the general population. Cd concentrations in those who never smoked were relatively high, indicating considerable Cd intake from the diet in Sweden. The effect of dental amalgam on kidney Hg was as expected, although the reason for the difference in Hg levels between males and females is unclear. *Key words*: **biopsy, cadmium, heavy metals, kidney, kidney donors, lead, mercury, renal cortex.** *Environ Health Perspect* **107:867–871 (1999). [Online 1 October 1999]**
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Cadmium is accumulated in the human kidneys, with the highest concentration in the cortex. The kidney is also the critical organ at long-term Cd exposure. Tubular and glomerular damage are well-known effects of occupational exposure to Cd (*1,2*). The general population is exposed through the diet and smoking. Studies in recent years have challenged previous risk assessments and have indicated that slight renal effects from Cd exposure may also occur in the general population (*2–6*).

Most of the present knowledge on kidney Cd concentrations in the general population has been obtained from analyses of autopsy samples (*7–12*). In addition, donor kidneys rejected after transplantation (*13*) and kidney biopsies from living subjects with tubulointerstitial disease (*10*) or renal cancer (*11*) have been studied. Kidney Cd can also be estimated using *in vivo* x-ray fluorescence (XRF) (*14,15*) or *in vivo* neutron activation analysis (*16–18*), but relatively high detection limits and limited precision make it difficult to use these techniques in the general population.

Inorganic mercury is also accumulated in the kidneys, and occupational exposure can cause renal damage (*19*). In the general population, the main sources of exposure are amalgam fillings and the diet. The presence of kidney Hg in autopsy samples from the general population has recently been reported in studies from Sweden and Germany (*20–22*). Kidney Hg can be measured by *in vivo* XRF in occupationally exposed subjects, but not yet in the general population (*23*).

Lead can also cause renal disease (*24*). Although most of the body burden of Pb is located in the skeleton, the kidneys and the liver have the highest concentrations among the soft tissues (*25*). There are a few reports on Pb in autopsy kidneys (*25–27*) or in kidneys removed because of cancer or other diseases (*28*).

In contrast to the autopsy sample studies, assessment of heavy metal concentrations in kidney biopsies from living subjects can be combined with information about smoking, diet, and occupation supplied by the biopsied subjects themselves. The aim of the present study was to determine Cd, Hg, and Pb concentrations in kidney cortex biopsies from living kidney donors and to compare the results with information on possible sources of exposure and with results from autopsy studies. The kidney donors can be considered representative of the general healthy Swedish population.

Subjects and Methods

Selection of kidney biopsies. At Sahlgrenska University Hospital (Göteborg, Sweden), surgical wedge biopsies are obtained from donor kidneys during transplantation, after revascularization, to determine the status of the transplanted renal tissue and to have a reference in case of later graft biopsies. In the Department of Clinical Pathology, 102 such biopsies from living kidney donors were processed between 1986 and 1991. Part of the wedge biopsy was embedded in Tissue-Tek OCT medium (Sakura, Tokyo, Japan), frozen, and prepared for immunohistologic study. The tissue samples were kept frozen at -70°C until the present study.

In most of the biopsy cases, the remaining material was of poor quality, was too limited to allow further analysis, or had positive findings at immunofluorescence. The remaining kidney cortex samples were analyzed for Cd, Hg, and Pb content.

Kidney donors. In total, the heavy metal content could be determined in kidney cortex samples from 36 donors from all over Sweden. These were 30–71 (mean 53) years of age and included 18 males and 18 females. As of 1997, five of the recipients had died, and in another four the donated kidney had been lost because of allograft rejection (none of these donors were approached). The remaining 27 subjects, 14 males and 13 females aged 30–71 (mean 54) years, answered a questionnaire on lifelong smoking habits and occupations. The questionnaires were mailed to the subjects. For two additional donors, smoking habits were ascertained from their medical files. In the questionnaires, we also asked about diet (number of fish meals per week, vegetarian yes/no) and the presence of amalgam fillings (yes/no) during

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the last years before removal of the kidney. The occupational histories were checked and, if necessary, completed via a telephone interview performed by an occupational hygienist who was unaware of the metal concentrations in the respondent's kidney.

Because exposure sources are expected to affect the total metal content in the kidney cortex, the total amounts of the respective metals were calculated by multiplying the metal concentration by the estimated weight of the kidneys for each donor. The kidney weights were estimated from body surface area according to Kasiske et al. (*29*).

Age, smoking history, diet, and occupational history for each of the 27 kidney donors who answered the questionnaire are shown in Table 1. None of the donors were vegetarians.

The study was approved by the Ethics Committee of the Sahlgrenska University Hospital.

Determination of heavy metal concentrations. The samples had become nearly freeze-dried during storage, which made determination of fresh weight impossible. The first 18 samples were brought to the analytical laboratory embedded in the backup material (OCT gel), whereas the other 18 samples had been removed from the backup material by dissection under the microscope by a pathologist. The embedded samples were removed from the backup material as completely as possible while still frozen, transferred into preweighed acid-washed glass tubes, and rinsed with 2 × 2.0 mL deionized water to remove any remaining OCT gel. The rinse water was poured off into another acid-washed tube and analyzed separately. The dry weights of all samples were determined after 1.5 hr drying at 80°C in a thermostat-controlled cupboard. The dry weights of the samples varied between 0.24 and 7.12 mg (median 0.74 mg). Repeated weighing of 20 empty glass tubes showed a standard deviation (SD) of 0.03 mg. The maximum difference between two weighings was 0.06 mg.

After the samples were dried, 0.10 mL concentrated nitric acid (Aristar, BDH Laboratory Supplies, Poole, Dorset, UK) was added, and the sample was digested for 3 hr at 70°C in a thermostat-controlled heating block. The samples were diluted with 2.0 mL deionized water containing 10 mL concentrated ammonia, 0.5 g sodium ethylenediaminetetraacetic acid, and 0.5 g Triton X-100 per liter. After the addition of an internal standard (100 µL) containing 0.10 µg indium and 0.10 µg thallium, the sample digests and rinse water from the embedded samples (n = 18) were analyzed using inductively coupled plasma mass spectrometry (VG PQ2+; Fisons Elemental, Winsford, Cheshire, UK). The amount of each element in the embedded biopsy samples was calculated as the sum of the amounts found in the sample digest and in the rinse water. The dry weight metal concentrations were transformed to wet weight concentrations by multiplication by 0.18 (*13*).

The detection limits per sample, calculated from reagent blanks (3 × SD), were 0.07 ng for Cd, 0.37 ng for Hg, and 0.06 ng for Pb. The accuracy of the method was checked by including samples (n = 6; sample weights 5–16 mg) of a certified reference material of freeze-dried kidney tissue from the Community Bureau of Reference, Brussels (BCR 186), in the analytical series. Our results (mean ± SD) were 2.63 ± 0.077 µg/g for Cd, 1.94 ± 0.244 µg/g for Hg, and 0.27 ± 0.040 µg/g for Pb. The certified values were 2.71 ± 0.15, 1.97 ± 0.04, and 0.306 ± 0.011 µg/g, respectively.

Statistics. The kidney cortex concentrations of Cd, Hg, and Pb were approximately log-normal, although there was a tendency toward bimodal distribution of the log-transformed kidney Hg concentrations. We present arithmetic means (AMs) and geometric means (GMs) as well as medians.

Differences between groups were compared using the Wilcoxon rank sum test. Associations between single variables were assessed with the Spearman rank correlation coefficient. Associations between log-transformed metal concentrations on the one hand and combinations of several potential explanatory variables on the other were assessed using multiple linear regression analyses. Some samples had Hg concentrations below the defined detection limit; nevertheless, the point estimates for these determinations were used in some calculations.

Table 1. Background factors and kidney cortex concentrations[a] of Cd, Hg, and Pb in 27 Swedish kidney donors, based on their questionnaire responses.

	Females			Males		
	No.	Mean (range)	Median	No.	Mean (range)	Median
Age (years)	13	52 (31–71)	53	14	53 (30–67)	57
Occupational exposure						
To Cd	0	–	–	1	–	–
To Hg	1	–	–	0	–	–
To Pb	0	–	–	3	–	–
Smoking history (pack-years)						
Never smoked	7	0	–	5	0	–
Former smokers	1	3.6	3.6	4	6.3 (3.6–9)	6.3
Active smokers	5	9.4 (7–11.7)	8.7	5	28 (14-64)	15.1
Fish meals per week						
< 1	6	–	–	3	–	–
1	6	–	–	10	–	–
> 1	1	–	–	1	–	–
Amalgam fillings						
Yes	11	–	–	10	–	–
No	2	–	–	4	–	–
Kidney Cd (µg/g)[b]	–	22 (7–46)	16	–	17 (5–42)	14
Kidney Hg (µg/g)[c]	–	0.71 (BD–2.1)	0.65	–	0.40 (BD–1.5)	0.16
Kidney Pb (µg/g)[d]	–	0.18 (BD–0.56)	0.16	–	0.18 (BD–0.44)	0.14

BD, below detection limit.
[a]The metal concentrations on dry weight basis can be obtained by dividing all values by 0.18. [b]One Cd-exposed male excluded. [c]One Hg-exposed female excluded. [d]Three Pb-exposed males excluded.

Results

Cadmium. In the total group of 36 donors the range of kidney cortex Cd concentrations was 5.5–46 µg/g. All samples had concentrations above the detection limit. The AM, GM, and median were 19, 17, and 17 µg/g [95% confidence interval (CI), 14–23 µg/g], respectively, and the geometric standard deviation (GSD) was 1.7. The kidney Cd concentrations were similar in females (n = 18, median 17 µg/g, range 5.5–46) and males (n = 18, median 16 µg/g, range 5.2–42). In females, the maximum Cd level was found in the 50–59-year-old age group. The kidney weight could be estimated in 33 subjects. Median kidney weight was 347 g (range 308–377, n = 18) for the males and 293 g (range 237–329, n =15) for the females. When accounting for kidney weight, males had slightly higher kidney Cd than females. Total kidney Cd amounts were 5,300 µg in males and 4,600 µg in females (medians).

In the 27 subjects who completed the questionnaire, the Cd levels were similar to those of the total group (Table 1). One man had been occupationally exposed to Cd for 5 years as an electrician at a Ni-Cd battery plant (kidney Cd 12 µg/g). In 10 active smokers, the median kidney Cd was 24 (CI, 14–35) µg/g, as compared to 17 (CI, 13–34) µg/g in 12 subjects who had never smoked. Only 5 males and 1 female were ex-smokers. Their median kidney Cd was 9 µg/g.

Mercury. In the total group of 36 subjects, kidney Hg was below the detection limit in six samples, and the range in the

others was 0.04–2.1 µg/g. The point estimates for these six samples were used in our calculations. The median (n = 36) was 0.29 (CI, 0.17–0.40) µg/g, and the AM was 0.50 µg/g. The females had higher kidney Hg than the males. In the 18 females, the median was 0.54 µg/g, whereas it was 0.16 µg/g for the 18 males. When estimating the total amounts of kidney Hg, similar results were obtained: medians were 207 µg in 15 females and 55 µg in 18 males. Kidney Hg decreased with age (r_s = -0.46, p = 0.005). In a model in which sex and age were both taken into account (n = 36), the difference in log-transformed kidney Hg between males and females and the decrease with age were both statistically significant (p = 0.03 and 0.004, respectively).

For the 27 subjects who completed the questionnaire, the difference between females and males was even more clear—medians were 0.65 and 0.16 µg/g, respectively (Table 1 and Figure 1). One female had low-level occupational exposure as a dental nurse for 28 years. Kidney Hg was higher in 20 subjects (the dental nurse excluded) with amalgam fillings (median 0.47 µg/g) than in 6 who had no dental amalgam (median 0.15 µg/g), but the difference was not statistically significant. The total amounts of kidney Hg were estimated as 107 µg in 20 subjects with amalgam fillings and 42 µg in 6 subjects without amalgams. In the subgroup with amalgam fillings, kidney Hg was higher (p = 0.01) in females (n = 10, median 0.68) than in males (n = 10, median 0.16), even when age was taken into account. Kidney Hg increased with fish consumption: 8 subjects who reported eating less than one fish meal per week had a median concentration of 0.24 µg/g. In 16 subjects that ate one fish meal per week, it was 0.27 µg/g, and in 2 subjects that ate fish more than once a week, it was 1.2 µg/g.

It was difficult to separate the specific influences of fish consumption and amalgam fillings because the subjects with no amalgams tended to eat little fish. In a model in which sex, age, fish consumption, and amalgam fillings were included (n = 26), only the first three variables had statistically significant influences on log-transformed kidney Hg. On the other hand, in the subgroup with amalgam fillings (n = 20), the effect of fish consumption on kidney Hg was not statistically significant. Based on 36 subjects, the influence of sex and age on kidney Hg seems clear. Mercury from dental amalgam and/or fish consumption increased kidney Hg, but the relative effect of the two sources was difficult to assess.

Lead. Kidney Pb was below the detection limit in 17 samples, and the range in the other 19 was 0.02–0.56 µg/g. The median was estimated as 0.14 µg/g. The levels in males and females were similar. There was a trend toward increasing Pb levels with age.

In the 27 subjects who completed the questionnaire, Pb levels were similar to those of the total group (Table 1). One man was occupationally exposed during a 30-year career at a Pb-storage battery plant (kidney Pb 0.42 µg/g). In the year of his kidney biopsy, his blood Pb was 1.6–1.7 µmol/L. Two other subjects had been exposed for 9 and 5 years, but had relatively low kidney Pb levels. No association between kidney Pb and smoking history could be shown.

Discussion

To our knowledge, this is the first report on chemical analysis of concentrations of heavy metals in the kidneys of living healthy subjects. The overall impression is that there are no large differences between our results and those obtained from autopsies of people dying from accidents or various diseases, although there are few previous data on Hg and Pb levels in kidney cortex. The most interesting finding with respect to kidney Cd was the fact that Cd concentrations in those who never smoked were relatively high. Unexpectedly, females had markedly higher kidney Hg than males. We will first discuss some general aspects of validity and then try to separately interpret our results for Cd, Hg, and Pb.

Validity. Kidney donors are often recruited from relatives or spouses of the recipients. For diseases with a certain degree of heredity, one would expect those diseases to be overrepresented in the donors. Potential donors are checked for diseases such as diabetes mellitus and hypertension, as well as for signs of kidney disease, before they are accepted as donors, and heredity plays no role for spouses. Therefore, we believe that the donors are representative of the healthy part of the general population. The number of smokers or ex-smokers was comparable to that of the general population in this age group. In autopsy studies, cardiovascular diseases and cancer are common causes of death, and, if only cases of sudden death are included, alcoholism and psychiatric diseases should be overrepresented (*30*).

The small biopsy samples (dry weight approximately 1 mg) could lead to a larger variability than in samples from autopsy studies if metals are not homogeneously distributed in the kidney cortex. For Cd, Livingston (*31*) showed that the concentration decreases from the outer to the inner layers; however, the wedge biopsies in the present study were taken from the outer part of the kidney cortex in the lower kidney pole. The GSD for kidney cortex Cd in our study group was 1.7. This is lower than the GSD of 1.9 found in the Elinder et al. (*7*) study on Cd in autopsy kidneys, and is similar to the GSD of 1.5–2.2 found in the Friis et al. (*12*) study of various age groups. These levels give no support for increased variability when biopsies are used.

Quality control of the analytical step included external reference material, indicating that the accuracy was satisfactory. The sample preparation, particularly the removal of the OCT gel, was complicated, however. This step, as well as errors in weighing the smallest samples, may have introduced imprecision in the metal determinations. The transformation from dry-weight (dw) to wet-weight (ww) concentrations also introduces some imprecision because the ratio of dw/ww is not necessarily the same in all kidneys. Moreover, our choice of a ratio of 0.18 deserves a comment. In the literature the ratio 0.20 is more commonly used, but it is based on studies of autopsy kidneys. We chose to use the ratio 0.18 based on a study of donor kidneys (*13*), although only seven kidneys were used in that study. If the true ratio of dw/ww in our study is 0.20, we underestimated the ww metal concentrations by 10%.

Most data on heavy metal concentrations in kidneys are presented as concentrations. This is logical as long as metals in the kidneys are compared with renal function or with determinants that are correlated to body weight, such as intake of contaminated food. Sometimes, however, it would be theoretically preferable to use the total amount of metal in the kidneys, accounting for kidney weight. This would be the case when comparing kidney Cd with the number of cigarettes smoked or when comparing kidney Hg with the number of amalgam surfaces. In the present study, kidney weights were estimated from body surface area, a method that introduces some additional variability.

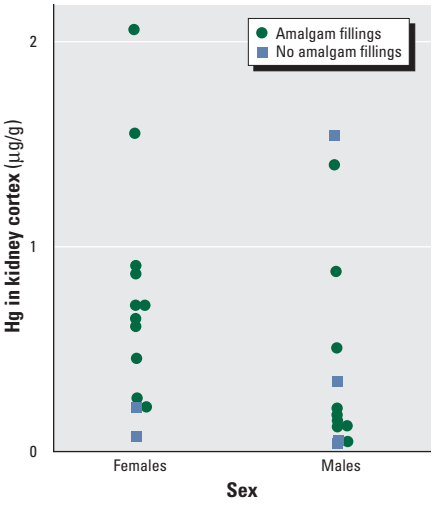

Figure 1. Mercury in kidney cortex of living kidney donors stratified for sex and dental amalgam fillings.

Nevertheless, the difference between the results using the two measures of kidney metal burden was small.

Cadmium. The kidney cortex Cd concentrations in the present study were somewhat lower than those reported by Elinder et al. (*7*) but higher than those reported by Friis et al. (*12*) in autopsy samples from individuals of similar ages (30–69 years) (Table 2). In the study by Elinder et al. (*7*), no external quality control procedures were performed, which makes their data somewhat difficult to evaluate.

Increasing kidney Cd levels were found in subjects up to approximately 50 years of age by Elinder et al. (*7*) and Friis et al. (*12*). This increase was not obvious in the present study, probably because there were only a few subjects in each age group. Assuming that smoking corresponding to 25 pack-years (1 pack-year = smoking 20 cigarettes/day for 1 year) increases kidney cortex Cd by 15 µg/g (*7*), the active smokers in the present study were expected to have levels approximately 8 µg/g higher than those who never smoked, which is in agreement with our findings. The low kidney Cd in ex-smokers could be the result of chance, given the small number of subjects in that group. Apart from age, diet and iron stores also affect kidney Cd (*2,32,33*), and these factors could differ between our subgroups based on smoking habits. The kidney Cd level in the active smokers was similar to that found by Elinder et al. (*7*) in smokers in the same age groups and slightly higher than those found by Friis et al. (*12*). The 12 subjects in the present study who never smoked had slightly higher kidney cortex Cd than did those in the study by Elinder et al. (*7*), and much higher than in the study by Friis et al. (*12*), even when the children and old subjects in those studies are excluded. If this is not caused by chance, it contradicts the assumption that dietary Cd intake in Sweden has decreased during the last couple of decades (*12*). Kidney Cd decreases slowly after ceased or decreased exposure; the half-life is on the order of decades (*1*).

If the distribution of kidney Cd in the general Swedish population is log-normal and the GM and GSD in the present group is representative of this population, 2% would have kidney Cd above 50 µg/g and 0.05% would have kidney Cd above 100 µg/g. In groups with the latter kidney cortex Cd concentration, the prevalence of renal tubular damage has been estimated as approximately 5% (*34*).

Mercury. The kidney Hg levels in this study were higher than those recently reported for German autopsy kidneys: The median in the present study is 0.25 µg/g, as compared to 0.1 µg/g or less in the German studies (*21,22*). In a Swedish study (*20*), the median for 12 autopsy kidneys was 0.18 µg/g. The general Swedish population has, on average, more amalgam fillings and possibly also a higher dietary intake of Hg from fish than the German population. Urinary Hg levels in the general population of Sweden seem to be somewhat higher than those in the general population of Germany (*35–37*).

The markedly higher kidney Hg in females than in males (Figure 1) was unexpected, and we found no obvious explanation for it. The CIs indicated that it was probably not a random finding. There is no difference between the average number of amalgam surfaces in females and males, as estimated from published studies of general population samples (*38*). Urinary Hg excretion is often higher in females if corrected for creatinine (*37*), but this could be caused by the lower levels of urinary creatinine found in females. Drasch et al. (*21*) found no effect of sex on kidney Hg. Future studies will be necessary to shed light on this issue.

The present data did not allow an assessment of the relative importance of the two main sources of Hg: the presence of amalgam fillings and fish consumption. A more detailed examination of dental status and dietary habits would have been advantageous, but for ethical reasons this was not possible. German studies (*21*) have shown that nearly all kidney Hg is inorganic. Methylmercury, which is the predominant form of Hg in fish, can be demethylated *in vivo*, and thereby accumulate in the kidneys, but in studies of urinary Hg excretion in the general population, the number of amalgam surfaces is in general better correlated to urinary Hg than is fish consumption (*36*). We therefore believe that the amount of dental amalgam is more important than diet for the kidney Hg burden. The major part of kidney Hg is assumed to have a half-life of approximately 2 months. Therefore, the last year is the relevant period with respect to the impact of Hg exposure on the kidney Hg level.

The present kidney Hg concentrations are lower than those reported after occupational Hg exposure in industry (*23,39*). The variability in the present small group seems to be at least as high as that of the distribution of urinary Hg in the general Swedish population (*40*), for which there is a much larger database. Therefore, it is likely that some individuals in the general population, such as those with amalgam fillings who are long-term nicotine gum chewers (*41*), indeed have kidney Hg levels similar to occupationally exposed workers, as has been shown for blood and urinary Hg levels (*38,41*).

Lead. Some reports on kidney Pb in the general population (*26–28,42*) have shown slightly higher concentrations than in the present study; for example, a median of 0.23 µg/g was found in 24 Swedish autopsy kidneys (*26,27*). Blood Pb concentrations have, however, declined considerably over the last decades (*43*), and it is probable that kidney Pb levels have also decreased.

A flaw in the present data is the fact that in nearly half of the samples, kidney Pb was below the formal detection limit. The results do not add much to the knowledge of determinants of kidney Pb concentrations. Smoking slightly increases kidney Pb concentrations (*28*). The worker with long-term exposure had a normal kidney Pb concentration. This indicates that the fraction of absorbed Pb deposited in the kidney cortex is small and/or that the half-life for kidney Pb is short. In a few autopsy studies of kidney Pb in former Pb workers, the levels were also low (*26,27,42*).

In summary, this study on living healthy Swedish subjects showed heavy metal concentrations in kidney cortex that were of the same order as those reported from autopsy studies. This indicates that bias in autopsy studies, owing to possible overrepresentation of certain causes of death and lifestyle factors, is not a serious problem. The kidney Cd levels in those who never smoked were unexpectedly high, indicating that dietary Cd is at least as high as it was previously. Interestingly, kidney Hg was higher in females than in males, a finding that requires confirmation in other studies.

Table 2. Cadmium in kidney cortex (microgram per gram, wet weight) in 35 living Swedish kidney donors 30–69 years of age.[a]

	Present study		Elinder 1976		Friis 1998	
Age (years)	Females GM (*n*)	Males GM (*n*)	Females GM	Males GM	Females GM	Males GM
30–39	16 (2)	26 (3)	19	17	8	7
40–49	19 (3)	19 (6)	26	19	17	12
50–59	23 (6)	9 (4)	21	16	16	13
60–69	15 (6)	13 (5)	19	17	14[b]	9
30–69[c]	18 (17)	15 (18)	21	18	14	11

Kidney Cd is compared to two studies of Swedish autopsy kidneys [Elinder et al. (*7*) and Friis et al. (*12*)].
[a]There were 36 subjects in the group, but there was only one donor > 69 years of age. [b]Because there was only one female in this stratum in the Friis et al. study (*12*), we used the average for females 50–79 years of age ($n = 25$) to estimate kidney Cd in this stratum. [c]The results from the two autopsy studies were used to calculate average Cd concentrations for males and females weighted with respect to the age distribution in the present study.

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