Renal function and historical environmental cadmium pollution from zinc smelters

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Summary

We investigated whether there was an association between renal function and cadmium pollution in areas with different exposures. Cadmium was measured in the soil and in vegetables in 10 districts, 6 of which were close to zinc smelters; and renal function and the concentrations of metals in blood and urine were measured in 703 randomly selected residents.

6 polluted areas, compared with 4 others showed higher cadmium concentrations in the soil (4·86 *vs* 0·81 ppm) and in locally grown vegetables, such as celery (2·43 *vs* 0·68 ppm) and beans (0·42 *vs* 0·15 ppm). Residents in polluted areas had higher urinary cadmium (10·5 *vs* 7·9 nmol/24 hours) and copper (0·16 *vs* 0·14 μmol/24 hours); higher serum creatinine (100 *vs* 97 μmol/L) urinary excretions of β_2-microglobulin (109 *vs* 95 μg/24 hours), retinol-binding-protein (136 *vs* 118 μg/24 hours), and N-acetyl-β-glucosaminidase (1·78 *vs* 1·38 U/24 hours). Serum zinc (12·2 *vs* 12·6 μmol/L) and creatinine clearance (87 *vs* 92 mL/min) were reduced in the 6 polluted areas. In all 10 districts, cadmium in the soil was positively correlated with cadmium in celery ($r=0·77$), in beans ($r=0·67$), and in residents' urine ($r=0·76$). The creatinine clearance was inversely correlated with cadmium in soil ($r=-0·78$), in celery ($r=-0·90$), and in beans ($r=-0·70$).

Past emissions from zinc smelters gave rise to contamination of the environment with cadmium, which gets into the food chain and has the potential to cause renal dysfunction and alterations in zinc and copper homeostatis.

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Introduction

After inhalation or gastrointestinal absorption, cadmium is concentrated in the kidney, where its half-life exceeds 10 to 20 years, and where toxicity is usually first expressed.[1] The surroundings of the earliest zinc smelters provide an opportunity to investigate how pollution with cadmium may interfere with renal function, as the smelters operated under less-stringent regulations and cadmium emissions persist in soil.[2]

The Cadmibel Study,[3-6] a cross-sectional population survey in Belgium, showed that environmental cadmium pollution was associated with a 30% higher urinary cadmium excretion and with alterations in biomarkers for renal tubular dysfunction such as mild microproteinuria[4] and possibly hypercalciuria.[4,5] Measurements of cadmium in cultivated soil suggest that the metal enters the food chain through locally grown vegetables.[7] We investigated glomerular and tubular renal function in populations exposed to different amounts of cadmium pollution and whether locally grown vegetables could be identified as an intermediary.

Methods

The study was in a rural area in the north-east of Belgium. Six land areas with an estimated population of 9840 inhabitants: Balen-Wezel, Mol-Wezel, Lommel-Werkplaatsen, Lommel-Barrier, Overpelt-Fabriek, and Neerpelt-Heide, were close to 3 smelters, of which 2 were in operation. As a contrast, we studied four districts with 9390 inhabitants: Eksel-Kern, Eksel-Locht, Hechtel-Kern, and Hechtel-Rest more than 10 km away from smelters.

Of 2327 participants in the Cadmibel Study,[3-6] 1107 had been randomly selected from the 10 districts. The sample had been stratified by sex and age (20–39, 40–59, ⩾60 years),[3] in an attempt to recruit the same number of subjects in each stratum. Households were identified from population registers as persons who shared the same address; a random sample of households was then drawn from each district. All household members aged 20 years old or more were eligible, but were not included if they had resided in the region for less than 8 years, if they were foreign nationals, and if the quota of their age-sex stratum had been fulfilled.[3]

Of 1107 subjects investigated from 1985 to 1989, 176 were excluded because not all relevant measurements were available, 15 because by previously published criteria[8] their 24-hour-urine sample was judged to be under-collected or over-collected, and 6 because their smoking habits could not be ascertained from the questionnaire. Of the remaining 910 participants, 207 were excluded as they may have been exposed to heavy metals at work; leaving 703. Compared with the whole sample or 1107, the 312 non-respondents had the same sex distribution (165 men and 147 women), but were slightly older (54 [18] *vs* 48 [17] years; $p<0·001$). The participation rate was higher in the 6 polluted than in the 4 control districts (74 *vs* 82%; $\chi^2=11·3$; $p<0·001$).

All subjects completed a self-administered questionnaire inquiring into their medical history, current and past occupations, smoking habits, consumption of alcohol, and medication. Social class and socio-economic position were coded according to the guidelines of the Office of Population Censuses and Surveys in

	Low exposure	High exposure	Contrast
Number	372	331	703
Men (%)	29·6	44·1	14·5 (7·4–21·5)‡
Clinical measurements			
Age (years)	49·3 (16·0)	45·5 (16·5)	−3·8 (−6·2 to −1·4)‡
Body mass index (kg/m²)	25·9 (4·3)	26·0 (4·9)	+0·1 (−0·5 to +0·8)
Systolic pressure (mm Hg)	132 (19)	129 (16)	−3 (−6 to −1)*
Diastolic pressure (mm Hg)	76 (9)	76 (8)	0 (−2 to +1)
Measurements on blood			
Blood cadmium (nmol/L)	10·8 (0·9–45·4)	10·2 (1·8–64·9)	0·94 (0·85–1·05)
Blood lead (μmol/L)	0·39 (0·11–1·66)	0·36 (0·08–2·91)	0·94 (0·88–1·00)
Zinc protoporphyrin (μg/g haemoglobin)	1·1 (0·3–5·2)	1·0 (0·3–8·2)	0·92 (0·87–0·97)†
Serum zinc (μmol/L)	12·7 (6·3–32·4)	12·1 (7·0–17·1)	0·95 (0·93–0·98)‡
Serum creatinine (μmol/L)	98 (25)	98 (20)	0 (−3 to +3)
Serum β_2-microglobulin (μg/L)	1·84 (0·17–8·10)	1·85 (0·90–8·00)	1·00 (0·96–1·05)
Serum ferritin (nmol/L)	0·23 (0·02–5·03)	0·23 (0·02–3·64)	1·01 (0·87–1·16)
Serum γ-glutamyl-transferase (U/L)	10·5 (2·0–151·0)	9·3 (2–117)	0·88 (0·81–0·97)†
Measurements on urine			
Volume (L/24 hours)	1·66 (0·68)	1·59 (0·56)	−0·07 (−0·17 to +0·02)
Creatinine (mmol/24 hours)	12·8 (3·9)	12·1 (4·2)	−0·7 (−1·2 to −0·1)*
Cadmium (nmol/24 hours)	8·4 (0·7–35·9)	9·8 (1·5–47·1)	1·17 (1·06–1·29)†
Copper (μmol/24 hours)	0·14 (0·04–0·71)	0·16 (0·03–0·46)	1·10 (1·04–1·17)†
β_2-microglobulin (μg/24 hours)	97 (21–3985)	106 (9–5004)	1·08 (0·98–1·21)
Retinol binding protein (μg/24 hours)	122 (21–5440)	130 (22–2182)	1·06 (0·96–1·17)
N-acetyl-β-glucosaminidase (U/24 hours)	1·4 (0·1–11·4)	1·7 (0·2–8·9)	1·23 (1·13–1·34)‡
Creatinine clearance			
Measured (mL/min)	93 (28)	87 (29)	−6 (−9, −1)†
Calculated (mL/min)	76 (23)	76 (23)	0 (−4, +3)

Arithmetic or geometric means with standard deviation or range in parentheses. Contrasts between low and high exposure areas (95% CI between parentheses) are expressed either as differences between arithmetic means or proportions, or as ratios of geometric means; *p<0·05; †p<0·01; ‡p<0·001. Creatinine clearance was either measured or calculated from serum creatinine according to the formula of Cockcroft and Gault.[15]

Table 1: **Characteristics of 703 participants before adjustments for confounding factors**

London.[9] The location of participants' homes and of the smelters, was determined from 1/10 000 scale maps.

All participants collected a 24-hour urine sample in wide-neck polyethylene containers. A venous blood sample was obtained within 2 weeks. Techniques and procedures have been described elsewhere.[3] Lifetime exposure to cadmium was assessed from the metal's 24-hour urinary output,[1] and alcohol intake from γ-glutamyltransferase activity in serum.[10] Concentrations of cadmium, copper, and lead in blood or urine were measured by electro-thermal atomic-absorption spectrometry,[3] and concentrations of serum zinc by flame atomic absorption spectrometry after serum deproteinisation.[11] 24-hour urinary excretion of β_2-microglobulin, retinol-binding-protein, and N-acetyl-β-glucosaminidase were assumed to reflect renal tubular toxicity.[4] Glomerular function was estimated from the concentrations of creatinine[12] and β_2-microglobulin[13] in serum, and from creatinine clearance.[14] The latter was also calculated by the Cockcroft and Gault formula.[15] Retinol-binding-protein and β_2-microglobulin in urine and β_2-microglobulin and ferritin in serum were determined by a non-isotopic immunoassay based on latex particle agglutination,[16] and the activity of N-acetyl-β-glucosaminidase in urine by a fluorimetric method.[17]

	Low exposure		High exposure		Contrast
Soil	n	ppm	n	ppm	ppm
Cadmium	56	0·81 (0·20–5·50)	612	4·86 (0·40–70·50)	6·02 (5·49–6·61)
pH	56	5·93 (4·60–7·40)	577	6·34 (4·40–7·70)	1·07 (1·05–1·08)
Vege					
Carrots	55	0·45 (0·10–1·50)	36	0·98 (0·28–2·65)	2·18 (1·97–2·38)
Leek	57	0·67 (0·20–1·79)	37	1·58 (0·12–5·38)	2·36 (2·14–2·56)
Beans	48	0·15 (0·02–1·93)	41	0·42 (0·11–1·20)	2·80 (2·59–3·18)
Celery	49	0·68 (0·12–3·09)	36	2·43 (0·59–11·79)	3·57 (3·17–3·99)

Geometric means with range between parentheses. n indicates the number of specimens available. All contrasts, expressed as ratios of geometric means, were significant at p<0·001. Vege = vegetables.

Table 2: **Cadmium in soil and in vegetables**

668 kitchen gardens were investigated from 1985 to 1989. Ten soil samples were taken from the top layer at depths from 0 to 25 cm. Samples were dried for 24 hours at 60°C, passed through a 2 mm sieve, blended, digested with aqua regia, and analysed for cadmium by atomic absorption spectrometry.

From 1991 to 1993, Cadmibel participants were invited to take part in a longitudinal survey. After excluding subjects who had died (67) and those who had still to be contacted in 1994 (119), 92 were left. Of these, 783 (85%) took part and all who owned a kitchen garden made vegetables available for the determination of cadmium—celery and leek, which readily concentrate cadmium, and/or carrots and beans, which concentrate less.[18] Vegetables were dried for 24 hours at 60°C, incinerated at low temperature, digested with 3 molar HCl and cadmium measured as in soil samples.

Non-normally distributed data were logarithmically transformed and expressed as geometric means. Between-group comparisons in a univariate approach involved Student's *t*-test and for proportions χ^2. Covariates of the metal and renal-function measurements were traced in individuals by stepwise linear regression,[4-7] and the probability of renal insufficiency was modelled by logistic regression. After standardising for known confounders, the 6 districts located near smelters and the 4 others were compared by analysis of covariance. Contrasts between polluted and control areas were expressed as differences of arithmetic means, or as ratios of geometric means if the variables had been logarithmically transformed. Spearman rank correlations were used to test the relationship between the exposure and renal function measurements in the 10 districts.

Results

The 703 subjects were 48 (16) years old (range 20–87 years). The 331 recruited from the 6 areas close to smelters were on average 3·8 years younger and comprised 14·5% fewer men than the 372 inhabitants from the 4 other districts (table 1)—in polluted areas, middle-aged men were often employed at the zinc smelters and were therefore excluded.

The sample included 262 men and 441 women. In the men, the 10th to 90th percentile (P_{10-90}) interval of serum creatinine ranged from 87 to 129 μmol/L. P_{10-90} intervals of the mens' measured and calculated creatinine clearance were 68 to 143 mL/min, and 52 to 117 mL/min, respectively. In women, equivalent P_{10-90} intervals were 73 and 112 μmol/L, 50 and 111 mL/min, and 47 and 97 mL/min. Numbers of current smokers, subjects reporting daily alcohol consumption, diabetics, and participants taking diuretics or analgesics were the same in the low-exposure and high-exposure areas. Most subjects were middle-class (92%) and in the middlemost of 3 socio-economic groups (77%).

In the 4 less-polluted areas (56 gardens) cadmium in soil averaged 0·81 ppm and the soil pH 5·93. This was significantly less than in the 6 polluted districts (612 gardens), where these values were cadmium 4·86 ppm and

Measurements	Covariates*
Blood cadmium and lead, urinary cadmium and copper	Serum fernitin and γ-glutamyltransferase
Serum zinc	Serum ferritin, γ-glutamyltransferase, and cholesterol, hour of blood sampling
Serum creatinine and β_2-microglobulin, creatinine clearance	Serum γ-glutamyltransferase, blood lead or zinc protoporphyrin, diabetes, intake of diuretics and analgesics
Excretion of β_2-microglobulin, retinol binding protein and N-acetyl-β-glucosaminidase	Diabetes, urinary tract disease, intake of diuretics and analgesics

*Covariates cumulated with gender, age, age², body mass index, socio-economic status, and current and past smoking (coded 0 vs 1, for condition absent vs present).

Table 3: **Covariates of the metal and renal function measurements**

soil pH 6·34. The vegetables contained significantly ($p < 0·001$) more cadmium in polluted areas (table 2). The determinants of metal concentrations and renal function measurements were identified in individual subjects by step-wise regression (table 3). The least square means of the metal and renal function measurements are shown for the 6 polluted *vs* the 4 other districts in table 4. Urinary cadmium was significantly higher in the 6 polluted areas, but blood cadmium and blood lead were similar. Serum zinc was slightly lower in polluted districts, whilst the opposite was seen for urinary copper. Serum creatinine and β_2-microglobulin, and urinary excretion of microproteins and N-acetyl-β-glucosaminidase were higher in polluted districts, whereas creatinine clearance was lower. Differences between areas with low and high exposure remained significant when the metal and renal function measurements were studied in women separately. In men, all differences between polluted and other districts were in the same direction as in the women, but due to the smaller number statistical significance was not always reached.

The correlation coefficients between cadmium in soil and in vegetables were: +0·52 (95% CI −0·16 to +0·87; $p = 0·15$) for carrots, +0·63 (−0·01 to +0·90; $p = 0·07$) for leek, +0·67 (+0·07 to +0·91; $p = 0·05$) for beans, and +0·77 (+0·27 to +0·94; $p = 0·02$) for celery. Cadmium in the soil and in the vegetables was also positively correlated with urinary cadmium (table 4).

After standardisation of metal and renal function measurements for the covariates in table 3, Spearman rank correlations were calculated (table 5). In general, glomerular function, as reflected by the measured or calculated creatinine clearances, decreased with higher urine, soil, and vegetables concentrations of cadmium. Higher cadmium doses were also associated with increased microproteinuria and greater N-acetyl-β-glucosaminidase activity output. These results were not materially altered when only the soil samples obtained from the gardens of the Cadmibel participants were considered to rank the areas.

Median distance from the participants' homes to the nearest smelter was 8·1 km, (0·3 to 21·1). After adjustment for possible confounders, urinary cadmium increased by 2·7% (CI 2·0–3·5%) for each km that people lived closer to the nearest smelter.

To investigate to what extent changes in renal function reflected the proximity to pollution sources rather than cadmium dose, multiple regression analysis was done in individual subjects. Urinary cadmium, distance from the nearest smelter, and possible confounders were entered into models as explanatory variables. Serum creatinine and calculated creatinine clearance were chosen as the dependent variables in order to avoid bias from inaccuracies in urine collections. In these analyses, neither serum creatinine nor the calculated clearance were significantly related to urinary cadmium, but serum creatinine was higher by 0·40 mmol/L (0·09–0·70; $p = 0·01$) and the calculated clearance decreased by 0·31 mL/min (0·11–0·49; $p = 0·002$) for each km that subjects lived closer to smelters.

For tubular function, partial regression coefficients were compatible, with a 7·0% (1·0–13·3%; $p = 0·02$) increase in the urinary excretion of β_2-microglobulin for a doubling of urinary cadmium. The latter was also associated with a significantly greater N-acetyl-β-glucosaminidase activity in the urine (+9·3%; CI: +4·7 to +14·2%; $p < 0·001$), but not with a significant increase in the urinary output of retinol binding protein (+4·1%; −1·7 to +10·2%; $p = 0·17$). For each km that people resided closer to the smelters, independent of urinary cadmium, urinary excretion of retinol-binding protein was higher by 1·5% (0·6 to 2·5%; $p = 0·001$), and the excretion of N-acetyl-β-glucosaminidase by 2·0% (1·1 to 2·8%; $p < 0·001$); the corresponding association with the urinary excretion of β_2-microglobulin was weaker (+0·9%; −0·1 to +2·0%; $p = 0·09$).

For the purpose of analysis, renal impairment was defined as measured creatinine clearance less than the sex-specific 10th percentile. There were more individuals with renal impairment defined in this way in the 6 polluted

	Low exposure	High exposure	Contrast	p
Number	372	331	703	
Metal concentrations				
Blood cadmium (nmol/L)	10·6 (7·2–15·5)	10·4 (7·1–15·3)	0·98 (0·90–1·07)	0·70
Cadmium excretion (nmol/24 h)	7·9 (5·6–11·1)	10·5 (7·4–14·9)	1·33 (1·24–1·45)	<0·001
Blood lead (μmol/L)	0·37 (0·28–0·49)	0·38 (0·29–0·50)	1·03 (0·96–1·09)	0·42
Serum zinc (μmol/L)	12·6 (11·2–14·2)	12·2 (10·8–13·8)	0·97 (0·94–0·99)	0·02
Copper excretion (μmol/24 h)	0·14 (0·11–0·19)	0·16 (0·12–0·21)	1·14 (1·03–1·27)	<0·001
Glomerular function				
Serum creatinine (mmol/L)	97 (83–110)	100 (87–114)	+3 (+1 to +6)	0·03
Serum β_2-microglobulin (μg/L)	1·82 (1·53–2·17)	1·88 (1·58–2·24)	1·03 (0·99–1·07)	0·10
Measured clearance (mL/min)	92 (77–108)	87 (72–103)	−5 (−2 to −8)	0·003
Calculated clearance (mL/min)	78 (69–86)	74 (66–83)	−4 (−2 to −6)	0·001
Tubular function				
Urinary β_2-microglobulin (μg/24 h)	95 (59–155)	109 (67–177)	1·15 (1·03–1·27)	0·02
Retinol binding protein (μg/24 h)	118 (77–180)	136 (88–209)	1·15 (1·05–1·27)	0·003
N-acetyl-β-glucosaminidase (U/24 h)	1·38 (0·95–2·00)	1·78 (1·22–2·57)	1·29 (1·18–1·39)	<0·001

Values are arithmetic or geometric means with interquartile range between parentheses. Measurements were standardized for confounding factors (see table 3). Creatinine clearance was either measured or calculated from serum creatinine according to the formula of Cockcroft and Gault.[18] Contrasts between low and high exposure areas (95% CI between parentheses) are expressed as differences or as ratios of the adjustment means.

Table 4: **Metal concentrations and renal function in 4 low exposure *vs* 6 high exposure areas**

	Cadmium in:					
	Soil	Carrots	Leek	Beans	Celery	24-hour urine
Metal concentrations						
Blood cadmium	+0·07 (0·85)	−0·15 (0·70)	−0·07 (0·86)	−0·35 (0·36)	−0·20 (0·60)	−0·15 (0·68)
Cadmium excretion	+0·76 (0·01)	+0·57 (0·11)	+0·70 (0·03)	+0·92 (0·001)	+0·63 (0·07)	..
Blood lead	+0·07 (0·85)	−0·15 (0·70)	−0·07 (0·86)	−0·35 (0·36)	−0·20 (0·61)	+0·14 (0·70)
Serum zinc	−0·50 (0·14)	−0·43 (0·24)	−0·52 (0·15)	−0·83 (0·005)	−0·48 (0·19)	−0·89 (0·001)
Copper excretion	+0·43 (0·21)	−0·03 (0·93)	+0·42 (0·26)	+0·50 (0·17)	+0·10 (0·80)	+0·67 (0·03)
Glomerular function						
Serum creatinine	+0·38 (0·28)	+0·45 (0·22)	+0·53 (0·14)	+0·47 (0·21)	+0·52 (0·15)	+0·47 (0·17)
Serum β_2-microglobulin	+0·03 (0·93)	+0·03 (0·93)	+0·25 (0·52)	+0·27 (0·49)	+0·18 (0·64)	+0·28 (0·43)
Measured creatinine clearance	−0·78 (0·007)	−0·63 (0·07)	−0·53 (0·14)	−0·70 (0·04)	−0·90 (0·001)	−0·63 (0·05)
Calculated creatinine clearance	−0·61 (0·06)	−0·58 (0·10)	−0·85 (0·004)	−0·70 (0·04)	−0·55 (0·12)	−0·72 (0·02)
Tubular function						
β_2-microglobulin excretion	+0·44 (0·20)	+0·40 (0·29)	+0·73 (0·02)	+0·70 (0·04)	+0·42 (0·26)	+0·65 (0·04)
Retinol-binding protein excretion	+0·31 (0·38)	+0·45 (0·22)	+0·70 (0·04)	+0·66 (0·05)	+0·27 (0·49)	+0·67 (0·03)
N-acetyl-β-glucosaminidase excretion	+0·43 (0·21)	+0·45 (0·22)	−0·03 (0·93)	+0·56 (0·11)	+0·72 (0·03)	+0·44 (0·20)

Spearman rank correlation coefficients with 2-tailed probability between parentheses. The correlations involving the cadmium content in vegetables included only 9 areas, because the participants living in Neerpelt-Heide did not grow vegetables. The other correlations comprised all 10 areas. Creatinine clearance was either measured or calculated from serum creatinine according to the formula of Cockcroft and Gault.[16]

Table 5: **Spearman rank correlations across 10 land areas**

districts (12·7% *vs* 8·3%; p=0·06). After adjustment for confounders, the probability of having impaired renal function increased with shorter distance to the smelters (odds ratio for living 1 km closer: 1·13; 1·06 to 1·21; p<0·001). Independent of proximity to smelters, the multiple logistic regression model also showed that the odds of having renal impairment were 1·50 (0·96–2·33; p=0·06) for a doubling of blood lead and 2·60 (CI: 2·09–3·22; p<0·001) for being 10 years older.

Discussion

This study focused upon cadmium in view of the situation in Belgium, where zinc smelters releasing cadmium into the atmosphere have been in operation since 1888. Thermal processes were replaced by electrolytic refining in the early 1970s such that airborne cadmium emissions dropped from 125 000 kg in 1950 to less than 130 kg in 1989.[19] However, cadmium emitted in the past continues to contaminate the environment.

Renal tubular dysfunction, characterised by microproteinuria and preceeded or followed by tubular and interstitial renal lesions, is known to occur in subjects exposed to cadmium at work[1,20] or environmentally.[4,21] A cross-sectional analysis of the Cadmibel database[4] has shown that, in individuals, urinary excretion of various markers of tubular dysfunction increased with cadmium dose. The present study, in which 10 areas were the principal units of analysis, confirms that finding,[4] and also agrees with histopathological studies in which alterations in proximal tubules were an early sign of cadmium toxicity.[22] A causal link between cadmium dose and renal tubular dysfunction is likely.

In the present study, glomerular function was also measured. An inverse correlation between creatinine clearance and cadmium was consistent, regardless of whether measured or calculated clearances, or body or environmental cadmium concentrations were considered. Calculated creatinine clearance,[15] and cadmium doses in the environment did not involve urinary volume, so exclude bias arising from inaccuracies in urine collections. Creatinine and β_2-microglobulin in serum were also slightly but significantly higher in polluted areas. Although these observations suggest a mild impairment of glomerular function with cadmium exposure, they may also be due, to some extent, to diminished tubular secretion of creatinine, of which 10 to 40% is normally secreted by renal tubules.[14] An inverse association between creatinine clearance and concentration of lead or zinc protoporphyrin in the blood has also been shown.[23] However, the present results were not altered by adjustments for lead exposure or other covariates.

The present survey had the limitations of an observational study and cannot establish that cadmium causes alterations in glomerular function. In the Shipham area of the UK,[24] the concentration of cadmium in soil, house dust, and crops was not correlated with cadmium and β_2-microglobulin in urine. In contrast, increased β_2-microglobulin and/or creatinine in serum, associated with a diminished creatinine clearance, have been reported in individuals occupationally exposed to cadmium,[25-27] as well as in Japanese people suffering from proximal tubular dysfunction attributable to more intensive environmental exposure than in the present study.[28] Renal tubular reabsorption defects and microproteinuria are generally regarded as early signs of cadmium toxicity, and glomerular dysfunction as a late sign of more severe toxicity. It is therefore of interest that in the present within-person analysis, serum creatinine and calculated creatinine clearance were not related to urinary cadmium, whereas glomerular function diminished as people lived closer to the smelters. Thus, the inverse relationship across the 10 areas between creatinine clearance and cadmium dose need not be causally related, but could be due to an as-yet-unidentified substance released with cadmium during smelting. Previous studies have suggested that lead could be such a factor,[23] but lead was not measured in soil samples. However, concentrations of lead and zinc protoporphyrin in the blood, although such concentrations are imperfectly related to body burden,[29] were not higher in contaminated areas. Alternatively, the association between the geographic proximity to smelters and glomerular dysfunction may reflect social confounders not detected by our coding system, although this is unlikely.

In Stolberg, Germany, cadmium in soil and in vegetables was as high as in the present study.[30] The residents, however, did not have higher blood or urinary cadmium. This finding may reflect the relatively limited contributions of home-grown vegetables to the diet and so a lower uptake of cadmium in Stolberg, and may have even been further reduced by the high zinc content of their diet.[30] Increased urinary copper excretion has been observed among the inhabitants of a cadmium-exposed area in Japan,[21] and has

been attributed to renal tubular dysfunction.[31] Blood-borne cadmium is a strong stimulant of metallothionein synthesis in the liver, kidney, and various other tissues[32] and may activate the sequestration of cadmium, zinc, and copper. Under these circumstances, serum concentration of these metals may fall, whereas their urinary excretion may rise as observed in this study. It is likely that a similar mechanism also applies to blood and urinary cadmium and explains why the concentration of blood cadmium was the same in all areas.

Alternatively, similar blood cadmium in the areas may have been due to the fact that from the 1980's, inhabitants of the polluted districts have been advised to lime their kitchen gardens and cultivate only vegetables which do not readily concentrate cadmium. Blood cadmium is more influenced by recent exposure, whereas urinary cadmium reflects life-time exposure.[1] Thus, recent preventive measures may explain why blood cadmium was the same in all areas, why renal function was not correlated with blood cadmium, and why the pH of the soils was slightly higher in the 6 polluted districts.

The present survey showed that in districts with differing cadmium contamination, renal glomerular and tubular function were inversely associated with bodily and environmental cadmium. Locally grown vegetables probably play a part in transferring this contaminant from the environment to man. The findings are compatible with previous suggestions that environmental cadmium exposure causes renal tubular dysfunction in the population at large; however, further investigations are required to identify the factors responsible for alterations in the creatinine clearance. The prognostic implications of the present findings also need to be determined, in particular for subjects, who carry other risk factors for renal dysfunction and who might therefore be more susceptible to developing overt kidney disease as a consequence of life-long exposure to environmental cadmium.

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