Environmental exposure to cadmium, forearm bone density, and risk of fractures: prospective population study

*Jan A Staessen, Harry A Roels, Dmitri Emelianov, Tatyana Kuznetsova, Lutgarde Thijs, Jaco Vangronsveld, Robert Fagard, for the Public Health and Environmental Exposure to Cadmium (PheeCad) Study Group**

Summary

Background Chronic low-level exposure to cadmium may promote calcium loss via urinary excretion. We undertook a prospective population study to investigate whether environmental exposure to cadmium lowers bone density and increases risk of fractures.

Methods We measured urinary cadmium excretion, a biomarker of lifetime exposure, in people from ten districts of Belgium, of which six districts bordered on three zinc smelters. We also measured cadmium in soil and in vegetables from the districts, and collected data on incidence of fractures and height loss. Bone density was measured at the forearm just above the wrist by single photon absorptiometry, and calculated as the mean of six proximal and four distal scans.

Findings Mean cadmium excretion at baseline was 8·7 nmol daily. Across the ten districts, mean cadmium concentration in soil ranged from 0·8 to 14·7 mg/kg, and from 0·1 to 4·0 mg/kg dry weight in vegetables. Median follow-up was 6·6 years. Mean forearm bone density in proximal and distal scans was 0·54 g/cm^2 and 0·43 g/cm^2 in men, and 0·44 g/cm^2 and 0·34 g/cm^2 in women. In postmenopausal women, a two-fold increase in urinary cadmium correlated with 0·01 g/cm^2 decrease in bone density ($p<0·02$). The relative risks associated with doubled urinary cadmium were 1·73 (95% CI 1·16–2·57; p=0·007) for fractures in women and 1·60 (0·94–2·72, p=0·08) for height loss in men. Cadmium excretion in districts near smelters was 22·8% higher (p=0·001) than in other districts, with fracture rates of 16·0 and 10·3 cases per 1000 person-years, respectively, and a population-attributable risk of 35·0%.

Interpretation Even at a low degree of environmental exposure, cadmium may promote skeletal demineralisation, which may lead to increased bone fragility and raised risk of fractures.

Lancet 1999; **353:** 1140–44

*Other investigators listed at the end of the paper

The Hypertensie en Cardiovasculaire Revalidatie Eenheid, Departement Moleculair en Cardiovasculair Onderzoek, Katholieke Univeriteit Leuven, Belgium (J A Staessen MD, D Emelianov MD, T Kuznetsova MD, L Thijs BSc, Prof R Fagard MD)**; Unité de Toxicologie Industrielle et Médecine du Travail, Université catholique de Louvain, Bruxelles** (H A Roels PhD)**; Limburgs Universitair Centrum, Diepenbeek** (J Vangronsveld PhD)**, Belgium**

Correspondence to: Dr Jan A Staessen, Hypertension and Cardiovascular Rehabilitation Unit, Department of Molecular and Cardiovascular Research, Campus Gasthuisberg, University of Leuven, Herestraat 49, B-3000 Leuven, Belgium (e-mail: jan.staessen@med.kuleuven.ac.be)

Introduction

Cadmium is a heavy metal with high toxicity, and has an elimination half-life of 10–30 years.[1] Cadmium accumulates in the body, in particular in the kidney, and its 24-h urinary excretion is a biomarker of lifetime exposure.[1] People are exposed to cadmium by intake of contaminated food or inhalation of cadmium particles in tobacco smoke or polluted air.[1] Cadmium may interfere with the metabolism of calcium, vitamin D, and collagen,[1,2] and bone disorders such as osteomalacia or osteoporosis are late manifestations of severe cadmium poisoning. In the general population, bone lesions have occurred only in Japan.[3] Itai-Itai disease was endemic in the heavily polluted mining area around Fuchu town, Toyama Prefecture, Japan, and occurred mainly in malnourished people and in postmenopausal women.[3]

In 1991, the cross-sectional Cadmium in Belgium (CadmiBel) study[4] recruited a representative population sample whose environmental exposure to cadmium was much lower than that in Japanese studies.[3] After adjustment for confounders, urinary calcium rose by 0·25 mmol daily for each two-fold increment in urinary cadmium excretion.[4] More recently, Järup and colleagues[1] showed a 90% increase in calciuria in Swedish women aged 50–70 years whose urinary cadmium concentration exceeded 1 nmol per mmol creatinine.[1] A slightly negative calcium balance, if sustained over many years, may be sufficient to impair mineralisation of the skeleton and to increase bone fragility. As part of the Public Health and Enviromental Exposure to Cadmium (PheeCad) project,[5] we undertook a prospective study of whether moderate environmental exposure to cadmium is associated with low bone density and high risk of fractures.

Methods

The CadmiBel study (1985–89)[4,6] included 1107 (78%) of 1419 randomly selected participants with a minimum age of 20 years. Participants in that study lived in ten districts in northeast Belgium.[6,7] Six of the districts, with an estimated population of 9840 inhabitants, bordered on three zinc smelters (figure 1). Four of the districts, with 9390 inhabitants, were more than 10 km away from the smelters and were less polluted by cadmium. The inhabitants of all ten districts had similar baseline characteristics apart from exposure to cadmium.[5]

After exclusion of people who had died (83 people), those who were severely ill (three), and those who had moved (seven), 1014 CadmiBel participants were asked to take part in the PheeCad study (April, 1991, to February, 1994). They renewed their informed consent and were invited for measurement of their forearm bone density.

At baseline in our study, CadmiBel participants collected a urine sample over 24 h in a wide-neck polyethylene container. Urinary cadmium was measured by electrothermal atomic absorption spectrometry with a stabilised-temperature-platform furnace and Zeeman background correction.[6] In the external quality control programme, the accuracy of the cadmium measurements did not show a significant time trend.[8]

We measured bone density at the forearm just above the wrist by single photon absorptiometry that used the ND1100 bone-density scanner (Nuclear Data Inc, Schaumburg, Illinois, USA).[9] After immersion of the forearm in water, the scanner did software-

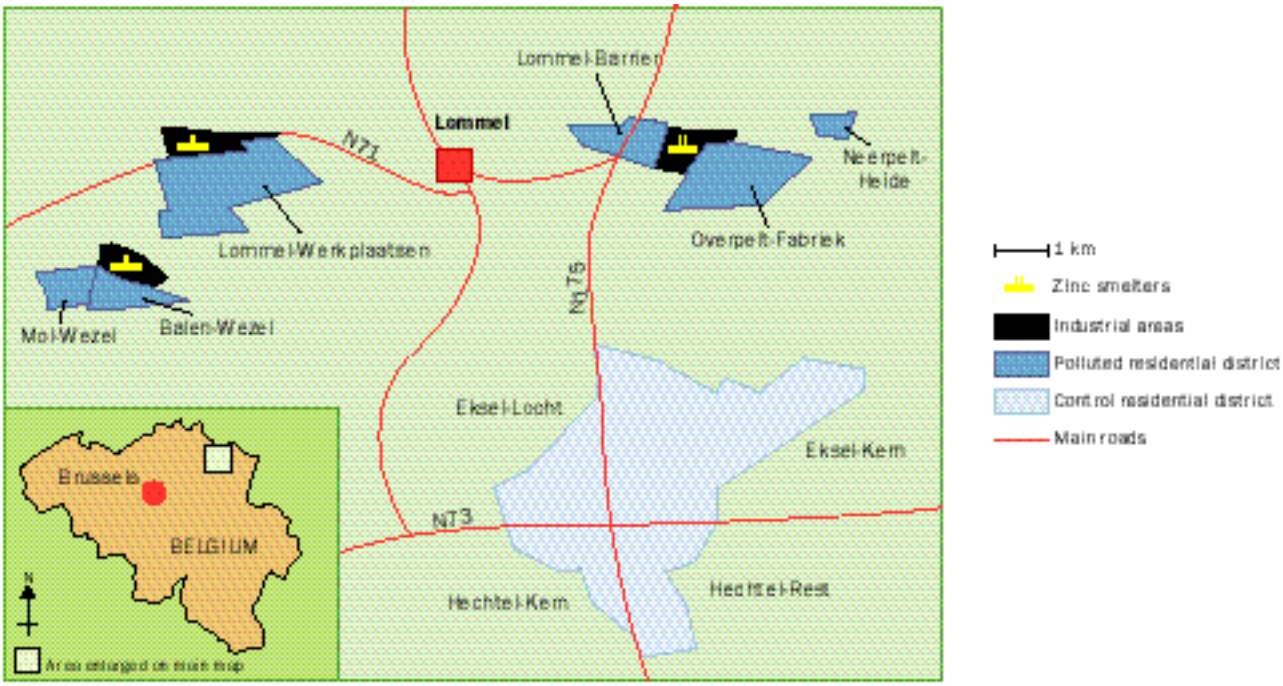

Figure 1: **Map of six polluted and four control districts, Belgium**
District names are shown.

controlled scout scans to locate the site at which the interosseal space between the ulna and the radius was 8·0 mm, 8·8 mm, or 9·6 mm. From the most distal starting point possible (smallest interosseal space) the scanner took six proximal and four distal scans at intervals of 4 mm and 2 mm, respectively.[9] Distal scans of adult forearms traverse a mean of 35% trabecular bone, whereas in proximal scans this proportion declines to nearly 5%.[9] The system was calibrated each week by use of an aluminium standard, and calibration was checked on every measurement day. Duplicate measurements in 34 participants at a median interval of 1·7 years (10th–90th percentile 1·6–2·2 years) showed that the repeatability of the results, expressed as the coefficient of variation,[9,10] was 1·2% for proximal bone density (mean of six scans) and 3·4% for distal bone density (mean of four scans). During the study, the iodine-125 source was renewed 12 times, but the lifestage of the ^{125}I source and the successive calibration coefficients did not correlate with the measurements of bone density.

In the PheeCad study, data on the incidence of fractures were obtained by questionnaire at a follow-up home visit, and these data were updated when bone density was measured. Fieldworkers contacted each patient's family physician to ascertain reported fractures. Body height was measured to the nearest 0·5 cm with a pliable measurer and the participants standing against a wall. In 1017 people whose height was measured twice at baseline[4] at a median interval of 1 week, the coefficient of variation was 0·1%. Participants wore light indoor clothing without shoes for bodyweight measurement. Body-surface area was calculated as weight ($kg^{0·425}$)×height ($cm^{0·725}$)×71·84.

We used the same standardised questionnaire at baseline and follow-up to collect information on participants' lifestyle and medication intake. Socioeconomic status was coded[11] and condensed into a scale with scores that ranged from 1 to 3. By use of published tables,[12] energy spent in physical activity was calculated from bodyweight, time devoted to sports and work, and type of physical activity. Premenopause was defined as an active menstrual cycle throughout follow-up, postmenopause as continuous amenorrhoea from baseline onwards, and perimenopause as the cessation of menstrual periods during follow-up.[13]

In 1985–89, soil samples were taken from 307 gardens owned by CadmiBel participants. Ten soil samples were taken from the top layer of soil in each garden at depths from 0 cm to 25 cm. Samples were dried for 24 h at 60°C, passed through a 2 mm sieve, blended, digested with aqua regia, and analysed for cadmium by atomic absorption spectrometry.[7] 127 of the households grew vegetables and provided samples of leek and celery. These leafy vegetables, which readily concentrate cadmium,[14] were dried for 24 h at 60°C, incinerated at low temperature, digested with 3 mol/L hydrochloric acid and measured for cadmium by atomic absorption spectrometry.[7]

Database management and statistical analysis used SAS software (version 6.12). Data that were not normally distributed were log-transformed, and described by the geometric mean and the 10th and 90th percentiles. Bone density was corrected for subcutaneous fat and bone width by a proprietary computer algorithm.[9,10] Means and proportions were compared by use of the standard normal z test and the χ^2 statistic, respectively. Longitudinal changes in proportions were assessed by McNemar's test. Statistical methods also included linear regression and Cox

	Men (n=199)	Women (n=307)	p
Characteristics at baseline (1985–1989)			
Age (years)	44·1 (14·0)	44·0 (13·1)	0·98
Body-mass index (kg/m^2)	25·3 (5·2)	25·5 (5·7)	0·73
Body surface area (m^2)	1·92 (0·15)	1·69 (0·15)	<0·001
Calcium excretion (mmol per day)	5·02 (2·80)	4·10 (2·16)	<0·001
Cadmium excretion nmol per day)	8·8 (3·5–19·1)	8·6 (3·5–22·0)	0·67
Creatinine excretion (mmol per day)	15·3 (3·7)	10·4 (2·5)	<0·001
Questionnaire data			
Physical activity (kcal per day)	673 (98–2983)	828 (206–2115)	0·26
Socioeconomic status*			
Low	60	218	<0·001
Middle	97	55	
High	42	34	
Smokers (%)			
1985–89	90 (45·2)	107 (34·8)	0·02
1991–94	68 (34·2)	90 (29·3)	0·25
Drinkers (%)			
1985–89	67 (33·7)	15 (4·5)	<0·001
1991–94	72 (36·2)	22 (7·2)	<0·001
Treatment with diuretics (%)			
1985–89	7 (3·5)	26 (8·5)	0·03
1991–94	11 (5·7)	36 (11·7)	0·02
Bone density (1992–95)†			
Proximal (g/cm^2)	0·54 (0·07)	0·44 (0·08)	<0·001
Distal (g/cm^2)	0·43 (0·06)	0·34 (0·07)	<0·001

Data are mean (SD) or geometric mean (10th to 90th percentile interval). *Coded according to guidelines of Office of Population Censuses and Surveys, UK.[11] †Mean of six proximal or four distal scans corrected for fat and bone width.

Table 1: **Characteristics of participants**

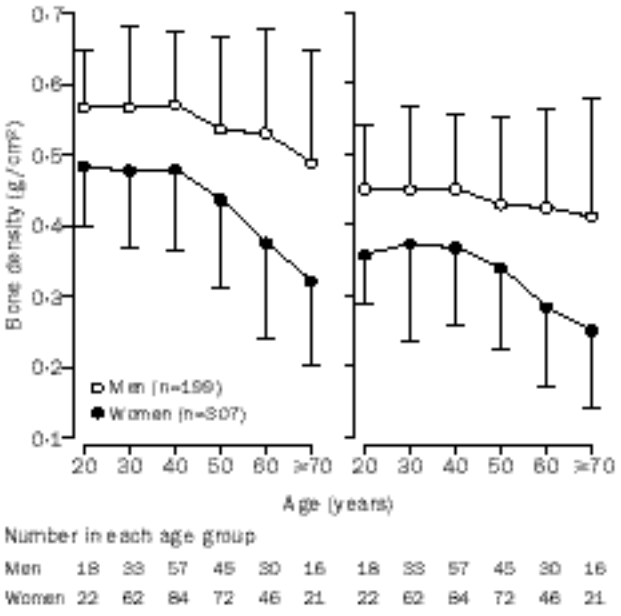

Figure 2: **Bone density according to sex and age**
Means of six proximal (left) or four distal (right) scans per participant.

regression. A stepwise procedure was used to select independent variables in multiple regression; significance for the explanatory variables to enter and to stay in the model was p=0·05. Unless stated otherwise, no variable was forced to enter the equations.

Results

Of the 1014 CadmiBel participants, 823 (81%) took part in the PheeCad study. Between January, 1992, and June, 1995, these 823 participants were invited for a measurement of forearm bone density. 614 (75%) participants responded, but seven were excluded because of missing exposure data, and 101 men who reported exposure to heavy metals at work and whose mean urinary cadmium excretion was 16·9 nmol daily (10th–90th percentile interval 4·7–44·0 nmol daily) were also excluded. Our analysis included 506 participants, whose exposure to cadmium was environmental alone.

Median follow-up was 6·6 years (range 5·3–10·5 years, table 1). During follow-up, the number of smokers declined (p<0·001), but there was no change in alcohol intake. In smokers, median tobacco use was 18 cigarettes daily (10th–90th percentile 6–30). In drinkers, median alcohol consumption was 20 g (1 unit) daily (10–50). 164 women were premenopausal, 40 perimenopausal, and 103 postmenopausal. Women took oral contraceptives at baseline and follow-up (42 *vs* 44; p=0·74) or hormonal replacement therapy (3 *vs* 7; p=0·16) in similar numbers.

The interosseal space at which bone-density measurements started was 8·0 mm in 86 men and 147 women, 8·8 mm in 70 men and 108 women, and 9·6 mm in 43 men and 52 women. Over the whole age range, proximal and distal bone densities were significantly greater in men than in women (figure 2). In single regression, proximal and distal bone densities were negatively correlated with urinary cadmium excretion in women but not in men (p<0·001, figure 3). Stepwise regression showed that in men proximal and distal bone densities were diminished linearly with age, were increased with body-surface area, were decreased with urinary calcium excretion at baseline, but were not correlated with urinary cadmium (table 2). In women, proximal and distal bone densities decreased in a curvilinear manner with age, but were raised with increased physical activity and the intake of diuretics, or with both increased body-surface area and higher socioeconomic position (table 2). The interaction term between cadmium excretion at baseline and menopausal status also entered both models, and showed that in postmenopausal women a twofold increase in cadmium exposure was associated with a decrease in proximal and distal bone density by nearly 0·01 g/cm^2. The following variables did not enter any of the regression models: season at the time of bone-density measurement, smoking, alcohol intake, intake of calcium or vitamin D supplements, menopause per se (without assessment of the interaction with cadmium excretion), use of oral contraceptives, or hormone replacement therapy.

20 bone fractures occurred in men and 24 in women. Fractures resulting from major trauma, such as car accidents, were not reported. Two men and three women had vertebral fractures, one woman had a fracture of the femoral neck, five men and 12 women had forearm fractures, and 13 men and eight women had fractures at other sites. Height loss that exceeded the 90th percentile (1·3% in both sexes) occurred in 20 men and 31 women. In stepwise Cox regression (table 3), a two-fold increase in cadmium excretion at baseline correlated with a 73% increased risk of fractures in women (p=0·007) and with a 60% increased risk of height loss in men (p=0·08). Age and socioeconomic position entered as significant covariates in several models. By contrast, the following variables did not enter any model: smoking, alcohol intake, urinary calcium excretion at baseline, energy spent in physical activity, menopausal status, and the use of diuretics, oral contraceptives, hormone replacement therapy, or supplements of calcium or vitamin D.

In a further step of the Cox regression analysis, urinary cadmium was replaced as the biomarker of internal exposure by each person's external exposure to cadmium,

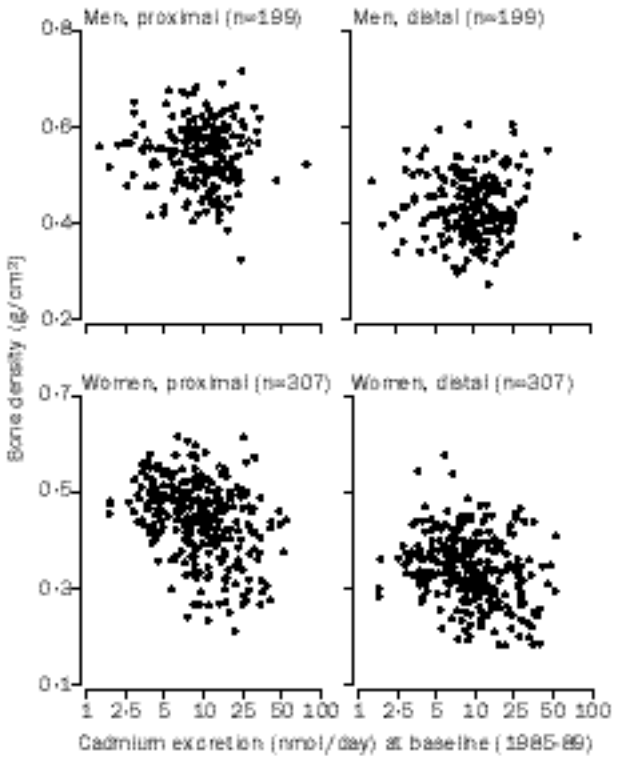

Figure 3: **Forearm bone density (1992–95) as a function of urinary cadmium excretion at baseline (1985–89)**

	Men (n=199)		Women (n=307)	
	Proximal	Distal	Proximal	Distal
Square of regression coefficient	0·198	0·107	0·455	0·379
Intercept	0·441	0·313	0·344	0·075
Partial regression coefficients (SE)				
Age (years)×10^{-3}	−1·665 (0·308)*	−0·957 (0·313)*	6·448 (1·813)*	6·769 (1·730)*
Age^2 (years^2)×10^{-3}	· ·	· ·	−0·092 (0·018)*	−0·082 (0·017)*
Body surface area (m^2)	0·104 (0·030)*	0·096 (0·030)†	· ·	0·083 (0·022)*
Diuretics intake (0, 1)	· ·	· ·	0·028 (0·013)‡	· ·
Physical activity (log kcal)×10^{-3}	· ·	· ·	9·470 (4·360)‡	· ·
Socioeconomic status§	· ·	· ·	· ·	0·010 (0·005)‡
Calcium excretion at baseline (mmol per day)×10^{-3}	−3·202 (1·563)‡	−3·147 (1·588)‡	· ·	· ·
Interaction between menopausal status and cadmium excretion (log nmol per day)¶	· ·	· ·	−0·028 (0·012)‡	−0·035 (0·011)†

Bone density (g/cm^2) corrected for fat and bone width was mean of six proximal or four distal scans. *p<0·001. †p≤0·01. ‡p≤0·05. §Coded 1, 2, and 3 for low, middle, or high socioeconomic position, respectively. ¶Coded 0, 0·5, and 1 for pre-, peri-, and postmenopausal women, respectively.

Table 2: **Correlates of forearm bone-density in stepwise multiple regression**

defined as the geometric mean concentration of cadmium in the soil and in the vegetables sampled in the relevant district of residence. Across the ten districts, the mean cadmium concentration in the soil ranged from 0·8 to 14·7 mg/kg. The mean cadmium concentration in leeks ranged from 0·1 to 0·6 mg/kg dry weight, and in celery from 0·4 to 4·0 mg/kg dry weight. The correlation coefficients between cadmium concentrations in soil and in vegetables were 0·83 (p=0·003) for leek and 0·88 (p<0·001) for celery. For both men and women, external exposure to cadmium was a significant predictor of the incidence of fractures and of height loss (table 3).

Urinary cadmium excretion in the 225 residents of the six districts near the smelters (mean 9·7 nmol/day [10th–90th percentile 6·9–24·1]) was 22·8% higher (p=0·001) than in the 281 inhabitants of the four other districts (7·9 [3·4–16·3]). Residence in a more polluted district rather than a less-polluted district increased the risk of fractures (16·0 *vs* 10·3 fractures per 1000 person-years). The population-attributable risk of fracture in the six polluted districts was 35·0%. For women with a urinary cadmium excretion above or below the age-adjusted median (9·3 nmol daily) the incidence rates of fracture were 13·5 and 9·6 per 1000 person-years, respectively. Thus, the risk attributable to above-median, age-adjusted internal cadmium exposure was 28·9%.

Discussion

This study shows that low to moderate environmental exposure to cadmium, as shown by urinary excretion, is associated with an increased risk of fractures in women, and possibly with a raised risk of height loss in men. Furthermore, environmental cadmium concentration was a predictor of the incidence of fractures and height loss in both sexes. Cadmium-induced bone disorders have previously been shown only in people with extreme exposure to cadmium. Japanese patients with Itai-Itai disease had mean urinary cadmium excretion of nearly 30 μg/g creatinine, whereas residents of the endemic area who did not have the disease excreted 20–25 μg/g creatinine.[3] By contrast, men and women in our study had mean urinary cadmium excretion of only about 1 μg/g creatinine.

In postmenopausal women, with adjustment for confounders, there was a negative correlation between forearm bone density and urinary cadmium concentration at baseline. In men there was a negative correlation only between forearm bone density and calcium excretion at baseline. Urinary cadmium reflects lifetime exposure to cadmium, and urinary calcium is an early-effect biomarker that shows renal tubular dysfunction in people exposed to cadmium.[1] Bone density of the distal radius partly reflects mineral content of the femur and of the entire skeleton (r=0·7–0·9), and does not correlate well with the amount of trabecular bone in the spine (r=0·4–0·6).[15–17] We did not measure dietary calcium intake. Thus, the inverse associations between forearm bone-density and the exposure or effect biomarkers shown in table 2 should be interpreted cautiously and do not necessarily imply causation. On the other hand, positive correlation between urinary cadmium and calcium was recorded at baseline[4] and at follow-up. Depleted iron stores due to menstrual blood loss might stimulate increased gastrointestinal absorption of cadmium from 5% up to 20% of the amount orally ingested.[18] This mechanism, together with parity and menopause, might make women susceptible to the demineralising effects of cadmium on bone tissue. Järup and colleagues[19] showed an inverse correlation (p=0·052) between forearm bone density and urinary cadmium (range 0·2–7·8 nmol/mmol creatinine) in workers assessed 15 years after their exposure to cadmium had ceased.

	Men (n=199)				Women (n=307)			
	Fracture	p	Height loss	p	Fracture	p	Height loss	p
Number of endpoints	20	· ·	20	· ·	24	· ·	31	· ·
Rate per 1000 person-years	14·7	· ·	14·7	· ·	11·5	· ·	14·9	· ·
Exposure indexes*								
Baseline cadmium excretion (nmol per day)†	1·20 (0·75–1·93)	0·44	1·60 (0·94–2·72)	0·084	1·73 (1·16–2·57)‡	0·007	1·15 (0·74–1·83)	0·51
Residence in polluted area (0·1)	2·76 (1·07–7·13)	0·036	2·72 (1·07–7·02)	0·035	4·30 (1·77–10·4)	0·001	2·92 (1·26–6·79)	0·013
Cadmium in soil (mg/kg)†	1·39 (1·04–1·86)	0·024	1·30 (0·98–1·74)	0·072	1·54 (1·19–2·00)	<0·001	1·29 (1·02–1·64)	0·035
Cadmium in leek (mg/kg dry weight)†	1·93 (1·05–3·53)	0·034	2·44 (1·31–4·57)	0·005	2·27 (1·31–3·94)	0·004	2·21 (1·30–3·78)	0·004
Cadmium in celery (mg/kg dry weight)†	1·69 (1·02–2·79)	0·039	1·34 (0·80–2·27)	0·27	2·07 (1·31–3·27)	0·002	1·83 (1·18–2·86)	0·007
Significant covariates								
10-year increase in age	· ·	· ·	1·38 (1·04–1·82)	0·021	1·41 (1·06–1·88)	0·019	1·45 (1·10–1·91)	0·003
1 point higher score for socioeconomic status	· ·	· ·	· ·	· ·	· ·	· ·	0·44 (0·22–0·87)	0·003

*Adjusted for significant covariates selected by stepwise regression. †Relative risk associated with a doubling of the cadmium concentration. ‡Age did not enter the model; if age was forced in the model, relative risk rate was 1·53 (95% CI 0·95–2·45; p=0·08) for urinary cadmium and 1·20 (0·84–1·71; p=0·31) for age.

Table 3: **Relative risk (95% CI) of fracture and height loss in stepwise Cox regression**

How fairly low amounts of cadmium absorbed over many years could lead to demineralisation of the skeleton and increased bone fragility is unknown. In rats exposed to a single subcutaneous injection of cadmium 0·4 mg/kg bodyweight, hypercalciuria preceded the development of proteinuria.[20] In those animals, cadmium more than halved calcium uptake by the proximal renal tubular cells.[20] These results are similar to epidemiological evidence that increased calciuria is a sensitive renal-tubular biomarker of a low degree of cadmium exposure in the general population.[1,21] At a higher degree of exposure, other mechanisms could also intervene. Cadmium reduces the generation of active vitamin D in renal tubular cells,[22,23] which in turn impedes calcium uptake in the duodenum[24] and active calcium reabsorption in the distal convoluted tubule.[25] Cadmium might also interact directly with bone cells,[26] diminish their ability to mineralise,[27] and inhibit procollagen C-proteinases[28] and collagen production.[27] Whatever the underlying mechanism, calcium loss and a negative calcium balance might indirectly accelerate bone-cell turnover, in particular bone resorption.[2]

Cadmium is a ubiquitous environmental pollutant, so our findings may have important public-health implications. In France, the cadmium concentration in human bones rose ten-fold during the 20th century.[29] Industrial sites are polluted by cadmium and are continuous sources of environmental cadmium, which is redistributed by lateral wind erosion of metal-loaded soil particles or by leaching of cadmium into groundwater. In less-developed countries, severe cadmium exposure can occur at the workplace or as a result of food intake (rice). Poor nutrition and underuse of hormone-substitution therapy after menopause also play a part. The precise transfer vector(s) must be defined in communities exposed to cadmium, and preventive measures should be adopted to lower exposure and individual susceptibility.

Contributors

Jan Staessen designed and coordinated the Public Health and Environmental Exposure to Cadmium (PheeCad) study, did statistical analysis, and wrote the first draft of the paper with Dmitri Emelianov and Tatyana Kuznetsova. Lutgarde Thijs reviewed statistical calculations. Harry Roels, Jaco Vangronsveld, and Robert Fagard took part in results interpretation and in preparation of the final paper.

PheeCad investigators

Hilde Celis, Dmitri Emelianov, Robert Fagard, Jerzy Gąsowski, Tatyana Kuznetsova, Paul Lijnen, Karel Pardaens, Victor Petrov, Lutgarde Thijs, Jan A Staessen, Wouter Vinck, Sofia Voyaki, Ji G Wang, Roger Bouillon, Dirk Vanderschueren, Marc De Ley (Katholieke Universiteit Leuven, Leuven, Belgium); Alfred Bernard, Jean-Pierre Buchet, Robert Lauwerys, Dominique Lison, Harry A Roels (Université catholique de Louvain, Bruxelles, Belgium); Hugo Clijsters, Jaco Vangronsveld (Limburgs Universitair Centrum, Diepenbeek, Belgium); Francis Dondeyne, Anne Forier, Guido Vyncke, Dirk Wildemeersch (Ministerie van de Vlaamse Gemeenschap, Brussel, Belgium); Jurian Hoogewerff (Bundesforschungs-und Prüfzentrum, Wien, Austria).

Acknowledgments

The PheeCad study was supported by the Nationaal Fonds voor Wetenschappelijk Onderzoek Vlaanderen (Brussel, Belgium), by the municipality Hechtel-Eksel (Belgium), and by the International Lead Zinc Research Organization (Research Triangle Park, NC, USA). We thank all the family physicians for their assistance. Fieldwork was coordinated by Sylvia Van Hulle, and done with the assistance of Lut Depauw, Lieve Gijsbers, Alida Hermans, Marie-Jeanne Jehoul, Karin Rombouts, Yvette Toremans, Marleen Vandermaesen, and Renilde Wolfs.

References

1 Järup L, Berglund M, Elinder CG, Nordberg G, Vahter M. Health effects of cadmium exposure—a review of the literature and a risk estimate. *Scand J Work Environ Health* 1998; **24** (suppl 1): 1–51.

2 Kjellström T. Effects on bone, on vitamin D, and calcium metabolism. In: Friberg L, Elinder CG, Kjellström T, Nordberg GF, eds. Cadmium and health: a toxicological and epidemiological appraisal, volume II: effects and response. Boca Raton: CRC Press, 1985: 111–58.

3 Kjellström T. Appendix: Itai-Itai disease. In: Friberg L, Elinder CG, Kjellström T, Nordberg GF, eds. Cadmium and health: a toxicological and epidemiological appraisal, volume II: exposure, dose, and metabolism, Boca Raton: CRC Press, 1985: 257–90.

4 Staessen J, Amery A, Bernard A, et al. Effects of exposure to cadmium on calcium metabolism. *Br J Ind Med* 1991; **45:** 710–14.

5 Staessen JA, Roels H, Fagard R, for the PheeCad Investigators. Lead exposure and the conventional and ambulatory blood pressure: a prospective population study. *JAMA* 1996; **275:** 1563–70.

6 Lauwerys R, Amery A, Bernard A, et al. Health effects of environmental exposure to cadmium: objectives, design and organization of the Cadmibel study: a cross-sectional morbidity study carried out in Belgium from 1985 to 1989. *Environ Health Perspect* 1990; **87:** 283–89.

7 Staessen JA, Lauwerys RR, Ide G, Roels HA, Vyncke G, Amery A. Renal function and historical environmental cadmium pollution from zinc smelters. *Lancet* 1994; **343:** 1523–27.

8 Claeys F, Ducoffre G, Sartor F, Roels H. Analytical quality control of cadmium and lead in blood and cadmium in urine: results of its implementation during a five-year epidemiological study. In: Nordberg GF, Herber RFM, Alessio L, eds. Cadmium in the human environment: toxicity and carcinogenicity. Lyon: International Agency for Research on Cancer, 1992: 83–92.

9 Nilas L, Borg J, Gotfredsen A, Christiansen C. Comparison of single- and dual-photon absorptiometry in postmenopausal bone mineral loss. *J Nucl Med* 1985; **26:** 1257–62.

10 Valkema R, Bloklund JAK, Papapoulos SE, Bijvoet OLM, Pauwels EKJ. The reproducibility of single photon absorptiometry in a clinical setting. *Eur J Nucl Med* 1989; **15:** 269–73.

11 Office of Population Censuses and Surveys. Classification of occupations and coding index. London: HMSO, 1980.

12 McArdle WD, Katch FI, Katch VL. Exercise physiology: energy, nutrition, and human performance. Philadelphia: Lea and Febiger, 1991: 804–11.

13 Staessen JA, Ginocchio G, Thijs L, Fagard R. Conventional and ambulatory blood pressure and menopause in a prospective population study. *J Hum Hypertens* 1997; **11:** 507–14.

14 Sherlock JC. The intake by man of cadmium from vegetables grown on sludged land. In: Wilson D, Volpe RA, eds. Cadmium 83. Proceedings of the Fourth International Cadmium Conference. New York: International Lead Zinc Research Organization, 1983: 107–09.

15 Mazess RB, Peppler WW, Chesney RWI, Nelp WP, Cohn SH, Zanzi I. Total body bone mineral and lean body mass by dual-photon absorptiometry; II: comparison with total body calcium by neutron activation analysis. *Calcif Tissue Int* 1981; **33:** 361–63.

16 Christiansen C, Rödbro P. Estimation of total body calcium from bone mineral content of the forearm. *Scand J Clin Lab Invest* 1975; **35:** 425–31.

17 Cummings SR, Kelsey JL, Nevitt MC, O'Dowd KJ. Epidemiology of osteoporosis and osteoporotic fractures. *Epidemiol Rev* 1985; **7:** 178–208.

18 Nordberg GF, Kjellström T, Nordberg M. Kinetics and metabolism. In: Friberg L, Elinder CG, Kjellström T, et al, eds. Cadmium and health: a toxicological and epidemiological appraisal, vol I: exposure, dose and metabolism. Boca Raton: CRC Press, 1985: 103–78.

19 Järup L, Alfvén T, Persson B, Toss G, Elinder CG. Cadmium may be a risk factor for osteoporosis. *Occup Environ Med* 1998; **55:** 435–39.

20 Jin T, Leffler P, Nordberg GF. Cadmium-metallothionein nephrotoxicity in the rat: transient calciuria and proteinuria. *Toxicology* 1987; **45:** 307–17.

21 Buchet JP, Lauwerys R, Roels H, et al. Renal effects of cadmium body burden of the general population. *Lancet* 1990; **336:** 699–702.

22 Lorentzon R, Larsson SE. Vitamin D metabolism in adult rats at low and normal calcium intake and the effect of cadmium exposure. *Clin Sci Mol Med* 1977; **53:** 439–46.

23 Chalkley SR, Richmond J, Barltrop D. Measurement of vitamin D3 metabolites in smelter workers exposed to lead and cadmium. *Occup Environ Med* 1998; **55:** 446–52.

24 Bronner F, Pansu D, Stein WD. An analysis of intestinal calcium transport across the rat intestine. *Am J Physiol* 1985; **250:** G561–69.

25 Bronner F. Renal calcium transport: mechanisms and regulation—an overview. *Am J Physiol* 1989; **257:** F707–11.

26 Bhattacharyya MH, Whelton BD, Stern PH, Peterson DP. Cadmium accelerates bone loss in ovariectomized mice and fetal rat limb bones in culture. *Proc Natl Acad Sci USA* 1988; **85:** 8761–65.

27 Miyahara T, Yamada H, Takeuchi M, Kozuka H, Kato T, Sudo H. Inhibitory effects of cadmium on in vitro calcification of a clonal osteogenic cell, Mc3T3-E1. *Toxicol Appl Pharmacol* 1988; **96:** 52–59.

28 Hojima Y, Behta B, Romanic AM, Prockop DJ. Cadmium ions inhibit procollagen C-proteinase and cupric ions inhibit procollagen N-proteinase. *Matrix Biol* 1994; **14:** 113–20.

29 Jaworowski Z, Barbacan F, Blain C, Pere E. Heavy metals in human and animal bones from ancient and contemporary France. *Sci Tot Environ* 1985; **43:** 103–26.