Exposure to Cadmium and Conventional and Ambulatory Blood Pressures in a Prospective Population Study

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This prospective population study investigated in a random sample of 692 subjects (age 20–83 years) how changing environmental exposure to cadmium influenced blood pressure (BP) and the incidence of hypertension. At baseline (1985 to 1989; participation rate, 78%) and follow-up (1991 to 1995; re-examination rate, 81%), blood pressure was measured by conventional sphygmomanometry (CBP; 15 readings in total) and, at follow-up, also by 24-h ambulatory blood pressure monitoring (ABP). Systolic/diastolic CBP at baseline averaged 128.4/77.3 mm Hg. At baseline, blood cadmium concentration (B-Cd) and urinary cadmium excretion (U-Cd) averaged (geometric means) 11.1 nmol/L and 10.2 nmol/24 h. Over 5.2 years (median follow-up), B-Cd fell by 29.6% and U-Cd by 15.2%. B-Cd fell less in subjects living closer to three zinc smelters and in premenopausal women. During follow-up, systolic CBP decreased by 2.2 mm Hg in men and remained unchanged in women, and diastolic CBP increased by 1.8 mm Hg in both sexes. No relationship could be demonstrated between the secular trends in CBP and B-Cd or U-Cd or between B-Cd or U-Cd at baseline and the incidence of hypertension. In addition, in cross-sectional analyses involving the average of all available CBP measurements in each participant or 24-h ABP at follow-up (mean, 119.1/71.4 mm Hg), blood pressure was not correlated with B-Cd or U-Cd. In conclusion, environmental exposure to cadmium was not associated with higher CBP or 24-h ABP or with increased risk for hypertension. The lesser fall in B-Cd in the residents living closer to the zinc smelters or in premenopausal women underscores the necessity to sanitize cadmium-polluted areas and to systematically reinforce the preventive measures to be adopted by exposed communities to reduce cadmium uptake. Am J Hypertens 2000;13:146–156 © 2000 American Journal of Hypertension, Ltd.

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Cadmium, a heavy metal with high toxicity, has an elimination half-life of 10 to 30 years.[1] It accumulates in the body, in particular the kidney, so that its 24-h urinary excretion is a biomarker[2] of lifetime exposure.[3,4] Blood cadmium reflects more recent exposure.[3,4]

The hypothesis that low-level environmental exposure to cadmium may lead to hypertension is mainly derived from animal experiments.[5,6] Prospective population studies on this subject are scarce. The cross-sectional CadmiBel (Cadmium in Belgium) survey (1985 to 1989) failed to demonstrate an independent positive correlation between blood pressure and environmental exposure to cadmium.[7] In a follow-up study (1991 to 1995) named Public Health and Environmental Exposure to Cadmium (PheeCad), the CadmiBel participants of two rural areas were invited for further examinations. This part of Belgium is polluted by the emissions of three zinc smelters, one of which was dismantled in 1974.[8] A second smelter ceased primary zinc production in 1992.[8] At the third smelter, zinc production has always been electrolytic; but, since 1991, ore has been transported and stored in dust-tight facilities.[8] Furthermore, starting from 1985, villagers have been informed as to how to reduce exposure to cadmium by using tap instead of well water, by liming the soil of their kitchen gardens, and by not growing leafy vegetables. These circumstances have created a unique setting to investigate the associations between changes in blood pressure and environmental exposure to cadmium. In the follow-up study, blood pressure was also measured by ambulatory monitoring,[9] a technique that provides more reproducible estimates of blood pressure than do conventional blood pressure readings.[10] In this report, the presumed associations between the biomarkers[2] of cadmium exposure, blood pressure and hypertension were re-examined both prospectively and cross-sectionally.

SUBJECTS AND METHODS

Subjects The study was conducted in two rural areas located in the northeast of Belgium close to the border with the Netherlands.[11,12] One region had an estimated population of 9840 inhabitants and bordered on three zinc smelters, whereas the other had 9390 inhabitants and was less polluted by cadmium. In the two areas, the geometric mean cadmium concentration in soil sampled from kitchen gardens averaged 4.9 ppm (n = 612) and 0.8 ppm (n = 56), respectively ($P < .001$ for difference).[12]

Baseline observations were collected from 1985 to 1989.[11,13] Of 1419 randomly selected subjects with a minimum age of 20 years, 1107 (78%) participated in the first phase of the study.[13] From 1991 to 1995, these subjects were invited for a follow-up study. After excluding subjects who had died (n = 83) and those who were severely ill (n = 3) or who had moved (n = 7), 1014 persons were left, of whom 823 (81%) participated.[14] Of these, 131 were excluded, either because of missing measurements (n = 115) or because, according to published criteria,[15] a 24-h urine sample was incomplete or overcollected (n = 16). Thus, for the present analysis, the study group totaled 692 subjects.

The distance and direction of each participant's home in relation to the smelters was determined from maps drawn at a scale of 1/10,000. Taking the nearest smelter as starting point, the bearings of the houses, proceeding compass-wise, could range from 0 degrees (going from south to north) to 360 degrees (going from north to south). The prevailing winds in Belgium blow from the southwest to the northeast (225 degrees).

Field Work Five specially trained nurses measured the participants' sitting blood pressure at baseline at two home visits 1 to 3 weeks apart[7] and at follow-up at one further home visit.[14] After the subjects had rested for 5 min, the nurses determined blood pressure (phase V diastolic) five times consecutively to the nearest 2 mm Hg.[16] Standard cuffs had a 12 × 24 cm inflatable portion, but if the upper arm girth exceeded 31 cm, larger cuffs with 15 × 35 cm bladders were used. Blood pressure changes and the incidence of hypertension were determined from the average blood pressure of the first set of five baseline measurements and the average of the five follow-up measurements. Normotension was an average blood pressure not higher than 140 mm Hg systolic and 90 mm Hg diastolic. Borderline hypertension included 141 to 159 mm Hg systolic or 91 to 94 mm Hg diastolic. Definite hypertension was an untreated blood pressure of ≥160 mm Hg systolic, or 95 mm Hg diastolic, or a condition requiring antihypertensive medication as determined by the subject's personal physician.

At follow-up, 658 participants had their ambulatory blood pressure measured within 1 week before or after the home visit. SpaceLabs (Redmond, WA) 90202 monitors[17] fitted with the same cuff size as for the conventional measurements were programmed for readings at intervals of 20 min from 8 AM until 10 PM and every 45 min from 10 PM to 8 AM.[14] The 24-h blood pressure was calculated from unedited recordings with weights according to the time interval between successive readings.[18]

The same questionnaire was used at baseline and follow-up. Social class,[19] energy spent in physical activity,[19] and menopausal status[20] were coded as previously described.

Biochemical Measurements At baseline and follow-up, the participants collected a 24-h urine sample in a wide-neck polyethylene container. A venous blood sample was obtained within 2 weeks of the home visit

TABLE 1. CHARACTERISTICS OF THE PARTICIPANTS AT BASELINE (1985–1989) AND FOLLOW-UP (1991–1995)

	Men (n = 336)		Women (n = 356)	
	Baseline	Follow-up	Baseline	Follow-up
Clinical characteristics				
Age (years)	46.5 ± 14.4	51.6 ± 14.3	45.5 ± 14.1	50.7 ± 14.1
Body mass index (kg/m^2)	26.0 ± 3.4	26.2 ± 3.5**	25.9 ± 5.1	26.4 ± 5.6***
Systolic pressure (mm Hg)†	133.2 ± 16.3	131.0 ± 17.5**	126.6 ± 17.7	126.1 ± 19.2
Diastolic pressure (mm Hg)†	78.4 ± 9.1	80.3 ± 10.9***	76.3 ± 9.2	78.0 ± 10.2**
24-h systolic pressure (mm Hg)‡	not measured	121.2 ± 11.4	not measured	117.0 ± 11.1
24-h diastolic pressure (mm Hg)‡	not measured	72.8 ± 7.8	not measured	70.1 ± 7.1
Biochemical measurements				
Serum total calcium (mmol/L)	2.36 ± 0.08	2.33 ± 0.10***	2.36 ± 0.09	2.33 ± 0.11***
γ-Glutamyltransferase (units/L)	12.4 (4–30)	16.7 (8–45)***	8.5 (4–24)	11.9 (5–34)***
Blood cadmium (nmol/L)	11.2 (3.6–40.0)	7.8 (1.8–30.2)***	10.9 (3.6–28.5)	7.8 (1.8–24.0)***
Urinary volume (mL)	1599 ± 589	1516 ± 585*	1682 ± 651	1567 ± 647***
Urinary calcium (mmol/24 h)	5.01 ± 2.64	4.40 ± 2.42***	4.10 ± 2.18	4.04 ± 3.38
Cadmium excretion (nmol/24 h)	11.8 (3.3–41.1)	9.9 (2.7–32.7)***	8.8 (2.9–28.2)	7.5 (2.4–21.3)***
Urinary sodium-to-potassium ratio	2.88 ± 1.29	2.87 ± 1.12	2.62 ± 1.19	2.97 ± 3.05*
Questionnaire data				
Tobacco use (n)	164 (48.8%)	124 (36.9%)***	119 (33.4%)	100 (28.1%)**
Alcohol use (n)	107 (31.8%)	108 (32.1%)	15 (4.2%)	21 (5.9%)
Low, middle, high social class (n)	98, 180, 58	103, 168, 65	242, 70, 44	240, 71, 45
Exposure to heavy metals (n)§	139 (41.4%)	142 (42.3%)	3 (0.8%)	8 (2.2%)
Treated with antihypertensive drugs (n)	32 (9.5%)	61 (18.2%)***	57 (16.0%)	84 (23.6%)***

Values are arithmetic means (±SD), geometric means (5th to 95th percentile interval), or number of subjects (%). Significance of the difference between baseline and follow-up: * $P < .05$; ** $P < .01$ *and* *** $P < .001$.

† *Average of five readings at the first baseline and follow-up visit.*

‡ *The 24-h blood pressure was measured at follow-up in 322 men and 336 women.*

§ *Reported exposure to heavy metals at work.*

and the 24-h urine collection. The biochemical methods were the same at baseline and follow-up.[11]

Blood and urinary cadmium were measured by electrothermal atomic absorption spectrometry with the use of a stabilized temperature platform and Zeeman background correction.[21] The detection limit for cadmium was 0.89 nmol/L.[11,21] Accuracy in the external quality control program was calculated as the annual mean (±SD) of detected cadmium concentrations expressed as a percentage of the true levels in the test samples.[21] Over the whole study period (1985 to 1995) accuracy ranged from 94.1% ± 4.8% to 100.9% ± 9.6% for blood cadmium (20 determinations per year; range of test concentrations 19 to 146 nmol/L). For urinary cadmium (16 determinations per year; range of test concentrations 3 to 300 nmol/L), accuracy ranged from 93.9% ± 8.3% to 98.5% ± 6.1%. Accuracy did not show a significant time trend, which excluded analytical bias (drift) in the cadmium measurements.

Statistical Analysis Database management and statistical analyses were performed with SAS software (SAS Institute Inc, Cary, NC). Non-normally distributed data were logarithmically transformed. To adjust for the baseline, longitudinal changes in continuous variables were assessed as dimensionless ratios of follow-up to baseline measurements. The difference of these ratios with unity, indicating change, was tested by the standard normal z test. Longitudinal changes in proportions were assessed by the McNemar test.[22] The statistical methods also included single and multiple linear regression, logistic regression, and analysis of covariance.

In stepwise linear regression with the level of blood pressure as the dependent variable, the linear and quadratic terms of age were forced into the model to fit the curvilinear associations observed across the quintiles of the age distribution. The other variables offered to the model were blood or urinary cadmium, the urinary calcium excretion, body mass index, serum zinc, total calcium and γ-glutamyl transferase, the sodium-to-potassium ratio in 24-h urine samples, energy expenditure by physical activity, reported exposure to heavy metals, social class, smoking and drinking habits, menstrual status, and the use of antihypertensive drugs, oral contraceptives, and hormonal replacement therapy. The secular trends in

TABLE 2. CORRELATES OF THE CHANGES (1985–1989 *V* 1991–1995) IN THE BIOMARKERS OF CADMIUM EXPOSURE IN STEPWISE MULTIPLE REGRESSION

	Change in Exposure Biomarkers*			
	Men (n = 336)		Women (n = 356)	
	Cadmium Excretion	Blood Cadmium	Cadmium Excretion	Blood Cadmium
R^2	0.039	0.219	0.021	0.275
Intercept	0.191	−0.228	−0.090	−0.271
Partial regression coefficients ± SE†				
Age at baseline (years)	−0.0021 ± 0.0007	0.0044 ± 0.0008	. . .	0.0063 ± 0.0015
	$P = .004$	$P < .001$	$P = .62$	$P < .001$
Body mass index at baseline (kg/m^2)	−0.0065 ± 0.0031	0.0064 ± 0.0036	. . .	. . .
	$P = .04$	$P = .08$	$P = .30$	$P = .41$
Logarithmic serum ferritin concentration	. . .	−0.096 ± 0.035	. . .	−0.096 ± 0.032
at baseline (pmol/L)	$P = .82$	$P = .007$	$P = .92$	$P = .003$
Menopausal status†	not applicable	not applicable	. . .	−0.090 ± 0.047
			$P = .48$	$P = .05$
Smoking at baseline‡	. . .	0.063 ± 0.026	0.063 ± 0.023	. . .
	$P = .17$	$P = .02$	$P = .006$	$P = .11$
Change in smoking status§	. . .	0.207 ± 0.035	. . .	0.287 ± 0.036
	$P = .32$	$P < .001$	$P = .53$	$P < .001$
Logarithmic distance between house	. . .	−0.132 ± 0.023	. . .	−0.137 ± 0.022
and nearest zinc smelter (km)	$P = .10$	$P < .001$	$P = .23$	$P < .001$
Logarithmic direction from nearest smelter	. . .	. . .	. . .	0.076 ± 0.041
to house (degrees)¶	$P = .82$	$P = .45$	$P = .95$	$P = .06$

Values of P *denote significance of the regression coefficients or probability of variables to enter into the model in stepwise regression. Reported exposure to heavy metals at work at baseline and change in reported exposure at work were considered for entry into the model in men, but were not significantly correlated with the changes in blood (*P = *.68 and* P = *.46, respectively) or urinary (*P = *.59 and* P = *.69) cadmium.*

* *Logarithm of the dimensionless ratio of follow-up to baseline measurements.*

† *Coded 0 in 181 premenopausal women, 0.5 in 44 perimenopausal women, and 1 in 138 postmenopausal women.*

‡ *Coded 0 for condition absent and 1 for condition present.*

§ *Coded 0 for no change in condition, −1 for reverting from condition, and 1 for acquiring condition.*

¶ *Coded from 0 degrees (from south to north) to 360 degrees (from north to south).*

these variables and duration of follow-up were regarded as possible covariates in stepwise regression, with the blood pressure changes from baseline to follow-up as the outcome variables. Because, over the life span, the age-related blood pressure change is not constant, initial age was also considered as a covariate in the latter regression procedure.

In stepwise regression with the secular trends in blood or urinary cadmium as the dependent variables, the potential covariates were age, body mass index, smoking habits, exposure to heavy metals at work, and menopausal status at baseline, as well as the changes in these variables over time. In addition, the serum ferritin concentration at baseline and the distance and direction of each participant's home to the nearest smelter were also taken into account.

RESULTS

Changes from Baseline (1985 to 1989) to Follow-Up (1991 to 1995) Age at baseline ranged from 20 to 83 years (Table 1). During follow-up (median 5.2 years; range 3.4–8.1 years) systolic blood pressure ($P < .01$) decreased in men (n = 336), but not in women (n = 356). In both sexes (Table 1) diastolic blood pressure, the percentage of individuals on antihypertensive drug treatment and body mass index increased ($P < .001$). The 24-h blood pressure, measured only at follow-up in 322 men and 336 women, was significantly lower than the conventional blood pressure (Table 1). In both sexes serum total calcium and urinary volume were slightly lower at follow-up than at baseline, whereas the opposite was observed for the activity of γ-glutamyl transferase in serum. The serum zinc and ferritin concentrations were measured only at baseline and were significantly ($P \leq .001$) higher in men than in women. Serum zinc averaged 12.8 μmol/L (5th to 95th percentile interval [PI]: 9.4–16.9 μmol/L) in men and 12.3 μmol/L (PI: 9.6–15.5 μmol/L) in women, and serum ferritin 378 pmol/L (PI: 116–1415 pmol/L) and 117 pmol/L (PI: 34–841 pmol/L), respectively.

In subjects living in the most polluted region (n = 376), the geometric mean distance and direction to the

nearest smelter were 1.2 km (PI: 0.4–3.0 km) and 169 degrees (PI: 19–283 degrees). For the inhabitants of the other region (n = 316), these values were 10.6 km (PI: 7.9–13.6 km) and 242 degrees (PI: 173–270 degrees), respectively.

At baseline, blood cadmium ranged from 0.95 to 85.4 nmol/L and urinary cadmium from 0.71 to 137 nmol/24 h. The blood cadmium concentration and the urinary excretion of cadmium decreased ($P < .001$) from baseline to follow-up. In men, blood cadmium fell by 30.8% (95% confidence interval [CI]: 26.6% to 34.8%) and urinary cadmium decreased by 15.7% (CI: 11.6% to 19.5%). In women, these reductions averaged 28.5% (CI: 24.2% to 32.6%) and 14.7% (CI: 10.4% to 18.8%), respectively. The fall in urinary cadmium was larger with higher initial age and body mass index in men, but was less pronounced in women who smoked at baseline (Table 2). In both sexes, the decrease in blood cadmium was less in older subjects, in persons who continued smoking during follow-up, in subjects with lower initial iron stores, and in persons living closer to the smelters. In men, blood cadmium also decreased less in subjects who smoked or who were obese at baseline. In women, blood cadmium diminished less in premenopausal subjects as well as in those residing closer down the direction of the prevailing winds.

During follow-up smoking became less prevalent ($P < .001$). No changes occurred in the percentage of subjects reporting alcohol intake or exposure to heavy metals, or in the daily energy expenditure due to physical activity (men 6388 kJ, women 5389 kJ). Throughout follow-up, male and female users of tobacco smoked 15 (median) cigarettes/day (range: 1–70 cigarettes/day). Daily alcohol consumption also remained unchanged, averaging 20 g (median) in men (range: 2–130 g) and 16 g in women (range: 3–40 g). Of the female participants, 179 were premenopausal, 43 perimenopausal, and 134 postmenopausal. Women took oral contraceptives (47 *v* 46, $P = .88$) or hormonal replacement therapy (three *v* seven, $P = .16$) in similar numbers at baseline and at follow-up.

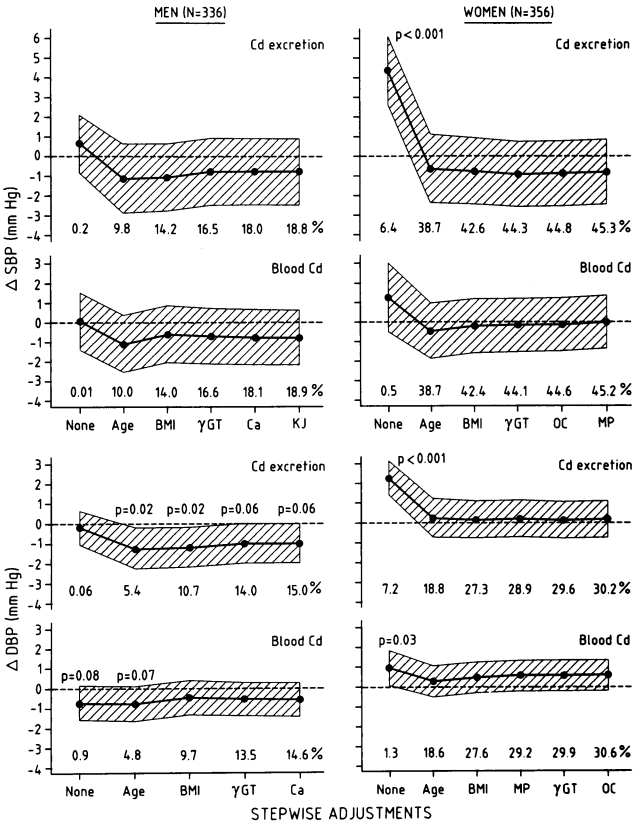

FIGURE 1. *Mean differences in conventional blood pressure (mm Hg, average of 15 readings), which, in a time-integrated (1985–1995) cross-sectional analysis, were associated with a two-fold increase in the 24-h urinary cadmium excretion (nmol/24 h) or in the blood cadmium concentration (nmol/L). The associations (with 95% confidence interval, depicted by shading) are shown before any adjustment and after cumulative adjustments for significant covariates identified by stepwise regression analysis. BMI, body mass index; Ca, serum total calcium concentration; MP, menopause; γGT, γ-glutamyl transferase activity in serum used as an index of alcohol intake; OC, use of contraceptive pills. The cumulative percentage of blood pressure variance explained by all variables in the model and the* P*-values of the regression coefficients for 24-h urinary cadmium or blood cadmium, if <0.10, are presented for single regression steps.*

Time-Integrated Conventional Blood Pressure The baseline and follow-up measurements were averaged to obtain time-integrated estimates of each subject's conventional blood pressure (15 readings/subject), exposure biomarkers (two determinations of blood and urinary cadmium) and possible confounders. In this analysis, systolic and diastolic blood pressure averaged 131.5 ± 14.2 mm Hg and 78.5 ± 8.3 mm Hg in men and 125.4 ± 15.9 mm Hg and 76.1 ± 7.8 mm Hg in women.

Of the systolic and diastolic blood pressure variances, age and body mass index combined explained 13.8% and 9.3% in men, and 42.4% and 27.2% in women. After stepwise adjustments for these major confounders and other significant covariates (Figure 1), blood pressure was not correlated with blood or urinary cadmium in all (n = 356) women. This was also the case in all (n = 336) men with the exception of diastolic pressure, which, after cumulative adjustment for age and body mass index, tended to be negatively correlated with the urinary excretion of cadmium (partial regression coefficient [±SE]: −3.88 ± 1.70 mm Hg [log nmol/24 h]$^{-1}$, $P = .02$). The latter association remained of borderline significance after further stepwise adjustments for γ-glutamyl transferase activity

TABLE 3. PARTIAL REGRESSION COEFFICIENTS FOR THE RELATION BETWEEN BLOOD PRESSURE AND THE BIOMARKERS OF CADMIUM EXPOSURE

	Conventional Blood Pressure (1985–1995)†			24-h Blood Pressure (1991–1995)		
	n	Systolic	Diastolic	n	Systolic	Diastolic
Logarithm blood cadmium (nmol/L)						
Men						
All	336	−2.67 ± 2.39	−1.97 ± 1.42	322	−1.55 ± 1.79	0.20 ± 1.21
Never exposed at work	173	−3.77 ± 3.83	−4.18 ± 2.30	164	−0.42 ± 2.66	−0.20 ± 1.72
Never on antihypertensive drugs	270	−3.84 ± 2.27	−3.10 ± 1.41*	259	−1.98 ± 1.71	−0.19 ± 1.28
Women						
All	356	−0.11 ± 2.32	1.97 ± 1.28	336	0.11 ± 1.68	−0.85 ± 1.52
Never on antihypertensive drugs	265	0.66 ± 2.20	1.30 ± 1.29	250	−1.76 ± 1.75	−2.00 ± 1.77
Premenopausal	179	4.83 ± 2.38*	3.84 ± 1.52*	173	0.84 ± 1.90	−1.71 ± 2.08
Perimenopausal or postmenopausal	177	−7.59 ± 4.13	−1.05 ± 2.12	163	−1.44 ± 3.10	−0.43 ± 2.31
Logarithm cadmium excretion (nmol/24 h)						
Men						
All	336	−2.54 ± 2.83	−3.22 ± 1.68	322	−3.16 ± 2.30	−0.50 ± 1.56
Never exposed at work	173	3.51 ± 5.44	−3.79 ± 3.27	164	6.57 ± 4.01	3.37 ± 2.60
Never on antihypertensive drugs	270	−5.55 ± 2.80*	−4.80 ± 1.73**	259	−3.55 ± 2.31	−0.55 ± 1.72
Women						
All	356	−2.55 ± 2.81	0.71 ± 1.56	336	−2.50 ± 2.20	−1.37 ± 1.61
Never on antihypertensive drugs	265	−1.32 ± 2.64	0.74 ± 1.56	250	−1.92 ± 2.26	−1.09 ± 1.81
Premenopausal	179	2.20 ± 3.01	2.69 ± 1.93	173	0.84 ± 2.60	−0.50 ± 2.11
Perimenopausal or postmenopausal	177	−8.24 ± 4.82	−1.69 ± 2.47	163	−7.19 ± 3.67*	−3.05 ± 2.48

Significance of the partial regression coefficients ± SE with cumulative adjustment for the covariates identified in Figures 1 and 2: * $P < .05$; ** $P < .01$.

† *Average of 10 readings at baseline (1985–1989) and five at follow-up (1991–1995).*

and the total calcium concentration in serum (−3.22 ± 1.68 mm Hg [log nmol/24 h]$^{-1}$, $P = .06$).

Across various subgroups of men, the correlations between blood pressure and blood or urinary cadmium were nonsignificant in most instances (Table 3). In men never treated with antihypertensive medications (n = 270), systolic blood pressure tended to be negatively correlated with urinary cadmium, and diastolic blood pressure was similarly negatively correlated with both blood and urinary cadmium (Table 3). The correlations between blood pressure and the exposure biomarkers were weak and nonsignificant in women. Only for systolic and diastolic blood pressure in premenopausal subjects (n = 179) were the correlations with blood cadmium positive and significant ($P < .05$), both before and after adjustment for age, body mass index, γ-glutamyl transferase activity in serum, and the use of oral contraceptives.

When both sexes were combined in the time-integrated analysis, the blood cadmium concentration and the urinary cadmium excretion were, on average, 16.8% (CI: 5.7% to 29.2%, $P = .003$) and 41.6% (CI: 26.4% to 58.6%, $P < .001$) higher in the most polluted of the two areas (geometric means 10.5 *v* 9.0 nmol/L and 11.3 *v* 8.0 nmol/24 h, respectively). The same geographic gradients were observed when men and women were analyzed separately (Table 4), although, in women, blood cadmium was only marginally elevated in the most polluted region. Despite these geographic differences in exposure, in men as well as in women, systolic and diastolic blood pressures were similar in the two areas.

Ambulatory Blood Pressure at Follow-Up (1991 to 1995) With the exception of the 24-h systolic blood pressure in women, age was only weakly correlated with the ambulatory blood pressures. Of the variance of the 24-h systolic and diastolic blood pressures, age explained 1.7% ($P = .07$) and 5.0% ($P < .001$) in men, and 19.4% ($P < .001$) and 1.1% ($P = .17$) in women. After stepwise adjustments for age and other significant covariates (Figure 2), blood pressure was not correlated with blood or urinary cadmium in men (n = 322) or women (n = 336). Furthermore, in various subgroups, with similar adjustments applied as in Figure 2, none of the partial regression coefficients between the 24-h ambulatory blood pressure and the biomarkers of exposure reached statistical significance (Table 3). The 24-h blood pressure means also did not follow the geographic gradients in the external exposure to cadmium (Table 4).

TABLE 4. BIOMARKERS OF CADMIUM EXPOSURE AND BLOOD PRESSURE IN TWO AREAS WITH DIFFERENT EXTERNAL EXPOSURE (1985–1995)

	Less Polluted	Heavily Polluted	*P* Value
Men			
Number	150	186	
Blood cadmium (nmol/L)*	8.8 (2.2–23.6)	10.9 (3.1–39.1)	<.01
Serum zinc (μmol/L)†	13.2 (8.9–17.9)	12.6 (9.8–15.8)	.02
Cadmium excretion (nmol/24 h)	8.8 (2.6–21.0)	13.4 (3.7–45.2)	<.001
Age (years)	50.0 ± 14.0	48.3 ± 14.6	.28
Systolic pressure (mm Hg)‡	131.8 ± 14.6	131.3 ± 14.0	.78
Diastolic pressure (mm Hg)‡	79.0 ± 8.3	78.1 ± 8.2	.33
24-h Systolic pressure (mm Hg)§	121.6 ± 10.9	120.8 ± 11.8	.55
24-h Diastolic pressure (mm Hg)§	73.7 ± 7.5	72.1 ± 8.0	.08
Women			
Number	166	190	
Blood cadmium (nmol/L)*	9.2 (3.6–23.1)	10.1 (3.1–24.9)	.18
Serum zinc (μmol/L)†	12.6 (9.3–16.1)	12.0 (9.8–14.9)	.007
Cadmium excretion (nmol/24 h)*	7.3 (2.6–18.7)	9.5 (3.0–25.5)	<.001
Age (years)	48.5 ± 13.5	47.8 ± 14.6	.64
Systolic pressure (mm Hg)‡	125.2 ± 17.0	125.6 ± 14.9	.81
Diastolic pressure (mm Hg)‡	75.2 ± 8.1	76.8 ± 7.5	.06
24-h Systolic pressure (mm Hg)¶	117.1 ± 11.4	117.0 ± 10.8	.95
24-h Diastolic pressure (mm Hg)¶	70.1 ± 7.1	70.1 ± 7.0	.98

Values are arithmetic means (± SD) or geometric means (5th to 95th percentile interval), unadjusted for covariates.

* *Blood cadmium concentration and urinary cadmium excretion were the averages of the baseline and follow-up measurements.*

† *Measured only at baseline (1985–1989).*

‡ *Average of 10 readings at baseline and 5 readings at follow-up.*

§ *Measured at follow-up in 142 and 180 men in the nonpolluted and polluted areas, respectively.*

¶ *Measured at follow-up in 159 and 177 women in the nonpolluted and polluted areas, respectively.*

Correlations Between the Changes in the Biomarkers of Cadmium Exposure and Conventional Blood Pressure To identify all covariates of potential importance, in this analysis (Table 5), the significance for the variables to enter and to stay in the model was set at $P = .10$. In men as well as in women, systolic blood pressure on conventional measurement increased more during follow-up with higher initial age, whereas the opposite tendency was observed for diastolic blood pressure. Changes in body mass index by 10% were on average accompanied by 2% to 4% blood pressure shifts in the same direction. In men, a 10% increase in the urinary sodium-to-potassium ratio was associated with a 0.1% to 0.2% rise in the conventional systolic blood pressure, or vice versa. In women, blood pressure increased by 5% to 6% in subjects starting hormonal contraception, and by 4% in those taking up smoking. In women, the initiation of antihypertensive drug treatment during follow-up led to nearly a 4% decrease in diastolic blood pressure, whereas a doubling in the serum activity of γ-glutamyl transferase was accompanied by a 1% to 2% rise in diastolic blood pressure, or vice versa.

After adjustment for these covariates, the relative changes in blood pressure over the follow-up period were not correlated with the concurrent alterations in blood or urinary cadmium (Table 5). The only exception observed was for diastolic blood pressure in women, in whom a 30% decrease in the blood cadmium concentration (geometric mean change −28.5%) was accompanied by a 1% fall in diastolic blood pressure (Table 5).

Incidence of Hypertension At baseline, either borderline or definite hypertension was present in 98 (14.1%) and 116 (16.7%) subjects, respectively, and at follow-up in 95 (13.7%) and 177 (25.5%) subjects ($P < .001$ for change from baseline). Of 479 initially normotensive subjects, 49 became borderline and 45 definitely hypertensive. The risk of becoming hypertensive was not associated with the blood cadmium concentration or the 24-h urinary cadmium excretion at baseline. After adjustment for sex, age, and body mass index, the risk ratio associated with a doubling of the baseline blood cadmium concentration was 1.08 (CI: 0.82 to 1.42, $P = .55$), and if subjects who developed only borderline hypertension were excluded 1.28 (CI: 0.87 to 1.88, $P = .37$). The corresponding risk ratios for a doubling of the 24-h urinary cadmium

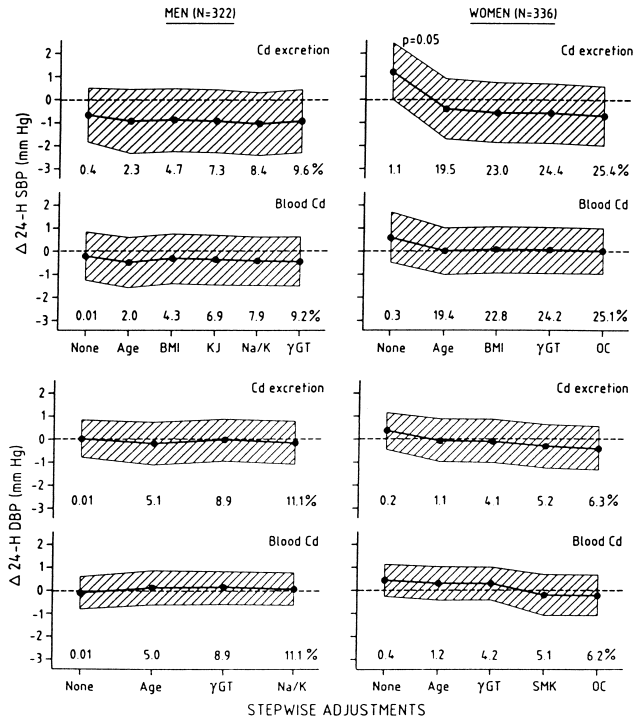

FIGURE 2. *Mean changes in the 24-h ambulatory blood pressure, which, in a cross-sectional analysis (1991–1995), were associated with a twofold increase in the 24-h urinary cadmium excretion (nmol/24 h) or in the blood cadmium concentration (nmol/L). kJ (kCal), indicates the daily energy expenditure in physical activity; Na/K, the urinary sodium-to-potassium ratio; SMK, smoking. (See Figure 1 for further explanation.)*

excretion at baseline were 0.93 (CI: 0.72 to 1.19, $P = .60$) and 1.16 (CI: 0.84 to 1.62, $P = .22$), respectively.

DISCUSSION

A representative population sample was examined twice at a median interval of 5.2 years, but no relationship could be demonstrated between the secular trends in conventional blood pressure and blood or urinary cadmium, or between exposure at baseline and the incidence of hypertension. Furthermore, in cross-sectional analyses involving all 15 conventional measurements or the 24-h ambulatory recordings at follow-up, blood pressure was not consistently correlated with blood or urinary cadmium. Among the general population, severe cadmium poisoning has only been observed in Japan.[23] Itai-Itai disease was endemic in the heavily polluted mining area around Fuchu town in Toyama Prefecture.[23] Patients with Itai-Itai disease had an average urinary cadmium excretion of nearly 30 μg per gram creatinine, but did not develop hypertension.[23] By comparison, men and women enrolled in the present study had a mean urinary cadmium excretion of only $\sim$1 μg per gram creatinine. These epidemiologic findings, covering a wide range of exposure, argue against the existence of a threshold above which cadmium exposure would lead to hypertension. The present longitudinal observations also confirm earlier cross-sectional studies in the general population of the US[24] or Belgium[7,25] and in British civil servants.[26]

Weak correlations may be obscured by intraindividual variability. Comparison of areas with different exposure, using group means rather than individual data, reduced this problem. Furthermore, individuals are better characterized if more measurements are averaged as presently done in the time-integrated cross-sectional analysis. Ambulatory blood pressure monitoring, compared with conventional sphygmomanometry, avoids arousal leading to the white coat phenomenon,[27–29] provides information on blood pressure during the whole day, and is characterized by higher reproducibility.[10] In spite of these advantages, blood and urinary cadmium were not more closely correlated with 24-h blood pressure than with conventional blood pressure. The present analysis not only accounted for age, body mass index, smoking and drinking habits, and the intake of medications, but also for physical activity, social class, and menstrual status.[20] Few studies measured all of these factors or showed how stepwise adjustments affected the correlations between blood pressure and the biomarkers of cadmium exposure.

Premenopausal women with low body iron stores readily absorb cadmium from the gastrointestinal tract,[4,30] and could therefore constitute a vulnerable subgroup. This may explain the positive correlations in younger women between the secular trends in diastolic blood pressure and the blood cadmium, and those between systolic and diastolic blood pressures and blood cadmium in the time-integrated analysis. However, in the same young women, the correlations between the 24-h blood pressure and blood cadmium were nonsignificant. In men, especially those never treated for hypertension, the conventional blood pressure tended to be negatively correlated with blood cadmium in the time-integrated analysis. Inhalation of tobacco smoke is a major source of cadmium exposure[7,31] and is therefore associated with higher blood cadmium levels. Smoking acutely raises blood pressure through sympathetic stimulation,[32–34] and is associated with higher blood pressure, at least if the latter is continuously recorded.[35] In contrast, in epidemiologic studies in which the conventional blood pressure is measured after a smoking-free interval, smokers show slightly lower blood pressure levels than do nonsmokers.[36–38] This may be due to the reduction in sympathetic activity in the intervals between smoking,[39] the development of tolerance,[40] or to the lower body weight of smokers. The presently observed negative correlations between conventional

TABLE 5. CORRELATES OF THE CHANGES (1985–1989 *V* 1991–1995) IN CONVENTIONAL BLOOD PRESSURE IN STEPWISE MULTIPLE REGRESSION

	Change in Conventional Blood Pressure*			
	Men (n = 336)		Women (n = 356)	
	Systolic	Diastolic	Systolic	Diastolic
R^2	0.079	0.065	0.076	0.121
Intercept	0.642	0.681	0.739	0.803
Partial regression coefficients ± SE				
Age at baseline (years × 10^{-2})	0.094 ± 0.040 $P = .02$	−0.119 ± 0.050 $P = .05$	0.067 ± 0.040 $P = .09$	−0.148 ± 0.050 $P = .03$
Change in body mass index*	0.300 ± 0.090 $P = .001$	0.400 ± 0.112 $P < .001$	0.229 ± 0.067 $P < .001$	0.287 ± 0.082 $P < .001$
Change in γ-glutamyltransferase activity in serum*	... $P = .13$	... $P = .21$	... $P = .61$	0.049 ± 0.029 $P = .09$
Change in urinary sodium-to-potassium ratio*	0.015 ± 0.004 $P = .005$	... $P = .38$	... $P = .68$	... $P = .82$
Antihypertensive treatment†	... $P = .11$	... $P = .30$	... $P = .16$	−0.036 ± 0.021 $P = .08$
Smoking†	... $P = .56$	... $P = .23$	0.041 ± 0.018 $P = .02$	0.041 ± 0.023 $P = .07$
Oral contraceptives†	not applicable	not applicable	0.050 ± 0.017 $P = .002$	0.068 ± 0.021 $P = .001$
Correlations with exposure biomarkers‡				
Change in urinary cadmium*	0.0142 ± 0.0297 $P = .63$	−0.0219 ± 0.0367 $P = .55$	−0.0047 ± 0.0274 $P = .86$	−0.0087 ± 0.0339 $P = .80$
Change in blood cadmium concentration*	0.0374 ± 0.0236 $P = .11$	0.0437 ± 0.0295 $P = .14$	0.0241 ± 0.0249 $P = .33$	0.0693 ± 0.0294 $P = .02$

Values of P *denote significance of the regression coefficients or probability of variables to enter into the model in stepwise regression.*

* *Dimensionless ratio of follow-up to baseline measurement (logarithm of ratios for γ-glutamyl transferase and cadmium measurements).*

† *Coded 0 for no change in condition, as −1 for reverting from condition, and as +1 for acquiring condition.*

‡ *Adjusted for the covariates with value of* $P < .1$ *(listed above).*

blood pressure and blood cadmium in men probably exemplify these chronic effects of smoking.

As a consequence of industrial reconversion and preventive measures implemented by the nonferrous industry and the inhabitants of the polluted region, blood cadmium fell on average by 29.6% and urinary cadmium by 15.2%. The proportionally larger reduction in blood than urinary cadmium was not unexpected, because the blood concentration is more influenced by recent exposure, whereas the urinary excretion correlates more closely with lifetime exposure.[3,4] After cessation of intensive long-term exposure, the decrease in whole blood cadmium displays a slow component with a half-life of approximately 10 years and a fast component with a half-life of 3 to 4 months.[4] The serum zinc concentration was significantly lower in the polluted than in the control area. This may be explained by the cadmium-stimulated induction of metallothionein in the liver and the kidneys. This main storage protein for cadmium also binds zinc.[41] Thus, exposure to cadmium may lead to a redistribution of zinc from the serum to the liver and the kidneys and, hence, to lower serum zinc levels.[41,42]

Urinary cadmium excretion decreased more in older and more obese men, but less in women who smoked at baseline. These observations probably reflect the larger initial body stores in taller and older men and smoking women.[31] Furthermore, blood cadmium fell less with higher age in both sexes, and in men also with higher initial body mass index. From the larger liver stores in older and obese persons, probably more cadmium is recirculated, thereby attenuating the fall in the blood concentration. Cadmium is redistributed in the body, so that with longer time after repeated or long-term contact, a larger proportion of whole body cadmium is found in the kidneys.[4] The blood cadmium concentration also diminished less in subjects with low serum ferritin concentration at baseline and in premenopausal women. Depleted iron stores may increase the gastrointestinal absorption of cadmium from 3% to 7% of the amount orally ingested up to 20%.[4,30] Furthermore, blood cadmium

decreased less in subjects whose houses were located nearest to the smelters and in women living closer down the direction of the prevailing winds. This observation suggests that industrial emissions and airborne particulate may have contributed directly to the cadmium body burden.

In conclusion, at the intensity studied, exposure to cadmium was not associated with increased conventional or 24-h blood pressure or with increased risk for hypertension. The observed decreases in blood and urinary cadmium may be attributed to industrial reconversion, improvement of the production process at the single nonferrous smelter remaining in operation, and the implementation of hygienic measures by the inhabitants of the most polluted area. However, the lesser fall in the body burden of cadmium in subjects living close to the smelters and in premenopausal women highlights the necessity to sanitize cadmium-polluted areas and to systematically reinforce the preventive measures to be adopted by environmentally exposed communities to reduce cadmium uptake.

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APPENDIX

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