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Blood Pressure, the Prevalence of Cardiovascular Diseases, and Exposure to Cadmium: A Population Study

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In a population study conducted from 1985 to 1989 in Belgium, the authors investigated whether exposure to cadmium is associated with blood pressure elevation and with an increased prevalence of cardiovascular diseases. The participants, aged 20–88 years, constituted a random sample of the households living in two low exposure areas (n = 803) and two high exposure areas (n = 1,283). For each exposure level, a rural and an urban district were selected. The cadmium levels in blood (8.5 vs. 11.0 nmol/liter) and urine (7.2 vs. 8.7 nmol/24 hours) were significantly ($p < 0.001$) raised in the two high exposure areas compared with the two low exposure areas ($p < 0.001$). Systolic pressure was similar in both rural areas, but in the urban area with high exposure systolic pressure was 5 mmHg ($p < 0.001$) higher than in the control town. Diastolic pressure was similar in the four districts and the same was true for the prevalence of hypertension and of other cardiovascular diseases. Adjustment of systolic pressure for blood and urinary cadmium did not remove the difference in systolic pressure between both urban areas, suggesting that it was not related to the cadmium burden on the environment. Further analyses in individual subjects showed that neither blood pressure nor the presence of cardiovascular diseases were significantly and positively correlated with blood and urinary cadmium. Thus, the present population study did not confirm the hypothesis that increased exposure of the population to cadmium is associated with blood pressure elevation and with a higher prevalence of cardiovascular diseases. *Am J Epidemiol* 1991;134:257–67.

blood pressure; cadmium; cardiovascular diseases; coronary disease; hypertension; lead

The cadmium hypothesis postulates that long-term environmental exposure to cadmium may lead to hypertension (1–3), and that cadmium via blood pressure elevation, or possibly via other mechanisms, may contribute to the pathogenesis of cardiovascular diseases in industrialized countries (4–7). The concept that exposure to cadmium may be a causal factor in human hypertension is mainly rooted in animal experiments (1, 8–11). Indeed, studies in exposed workers (12–14), in patients with hypertension (15–18),

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Conversion of units: cadmium, 1 nmol = 112.4 ng; creatinine, 1 mmol = 113.1 mg; lead, 1 μmol = 207.1 μg.

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and in small groups of individuals (19–23) have failed to corroborate the hypothesis. In addition, some of the positive studies (24–30) relied on less accurate techniques to measure cadmium, or did not satisfactorily control for possible confounders, such as smoking (31–33). Thus, more than two decades after Schroeder and Vinton (1) and Schroeder (2, 3) published their pioneering animal studies, the cadmium hypothesis still awaits confirmation or rejection at the population level.

Belgium, the principal cadmium producer in Europe, has areas with high cadmium pollution, mainly as a consequence of past emissions; the latter are only a short distance away from districts with lower environmental exposure levels. The present study, named CADMIBEL (Cadmium in Belgium) (34, 35) took advantage of these geographic circumstances. This article reports on the influence of environmental cadmium exposure on blood pressure and on the prevalence of hypertension and cardiovascular diseases in the general population.

MATERIALS AND METHODS

Study population

As described in detail elsewhere (34), the study was conducted from 1985 to 1989 in four Belgian districts, representing two areas with low environmental exposure to cadmium and two with high environmental exposure to cadmium. For each exposure level, a rural and urban district were selected. In Liège (polluted town), the 95th percentile of the airborne cadmium concentration during operation of the local zinc and/or cadmium producing plants amounted to 1.47 nmol/m^3 and in Noorderkempen (polluted rural district), the 95th percentile of airborne cadmium reached 0.36 nmol/m^3, whereas in Charleroi (control town) and Hechtel-Eksel (control rural area) the 95th percentiles of airborne cadmium never exceeded 0.27 and 0.09 nmol/m^3, respectively (34). In the Liège area, the cadmium concentration in the soil ranged from 36 to 320 μmol/kg (dry weight) and that in grass ranged from 4 to 222 μmol/kg (dry weight); in Noorderkempen, these concentrations ranged from 4 to 213 and from 1 to 258 μmol/kg, respectively, whereas in both nonpolluted districts they did not exceed 9 and 18 μmol/kg, respectively (34).

In each district, a random sample of the households was identified, with the goal to recruit an equal number of subjects in each of six subgroups by sex and age (20–39, 40–59, 60–79 years). All household members with a minimum age of 20 years were invited to participate, provided the quota of the sex-age group to which they belonged had not yet been satisfied (34).

In the four districts, a total of 4,532 subjects were eligible for the study, of whom 2,327 took part. The participation rate was 78 percent in the two rural districts and 39 percent in the two urban districts. Subjects were excluded from analysis when not all relevant measurements could be obtained (n = 149), when the 24-hour urine sample was judged under- or overcollected (n = 44) on the basis of previously published criteria (36), or when either occupational exposure to heavy metals (n = 41) or smoking habits (n = 7) could not be ascertained from the questionnaire.

Field work

Each household was visited several times by the same observer. The first home visit consisted of five consecutive blood pressure readings in the sitting position with an ordinary sphygmomanometer. The blood pressure measurements were followed by a pulse rate count over one minute and a measurement of body weight and height. The participants were asked to complete in the interval between the first and second home visit a self-administered questionnaire, inquiring into their medical history, current and past occupations, smoking habits, consumption of alcohol, and intake of medications. They were also asked to collect a 24-hour urine sample in a wide neck metal-free polyethylene container, after having been instructed how to avoid external contamination of the urine with cadmium.

At a second visit 1–2 weeks later, the questionnaire and the 24-hour urine sample were collected and the measurements of blood pressure, pulse rate, body weight, and height were repeated. Each subject was thus characterized by the mean of 10 blood pressure readings and of two determinations of pulse rate, body weight, and height. On a separate occasion, but usually within 2 weeks after the urine collection, a physician or nurse visited the households to draw 20 ml of venous blood.

One team of observers operated in the rural areas and another team in the two towns. However, all observers were tested for the accuracy of their blood pressure measurements at 6-month intervals in two steps (34). They had to record first the pressures from a film showing a falling mercury column with Korotkoff sounds (Measuring Blood Pressure, Production no. B-132, The Audio-Visual Centre, University of London, London, United Kingdom, 1973). Thereafter, they were tested using live subjects and stethoscopes with double ear-pieces. The observers were considered to have passed the test when for both the sound film and the measurements in live subjects, each of their pressure readings was within 5 mmHg compared with those of experienced medical staff.

Biochemical measurements

Blood was analyzed for cadmium, lead, and serum gamma-glutamyltranspeptidase (37), and 24-hour urine samples for cadmium, sodium (38), potassium (38), and creatinine (39). Cadmium and lead were measured by electrothermal atomic absorption spectrometry with the use of a stabilized temperature platform furnace and Zeeman background correction (34).

Two laboratories shared the burden of the biochemical determinations, but, for each measurement, all samples were processed by the same laboratory (34). In the two laboratories, all tests were performed in duplicate and certified reference standards were run along each series of samples. Ten percent of the measurements of cadmium and lead were performed in both laboratories. A series of measurements was repeated whenever the precision of the duplicate determinations or the accuracy of the measurements of the standards fell outside previously published limits (34), or whenever one sample differed more than 10 percent among the two laboratories (34). For the cadmium and lead measurements, the precision had to be within 5 percent and the accuracy within 10 percent (for blood cadmium concentrations of 45 nmol/l or more, 10 and 15 percent, respectively).

Definitions

Hypertension was defined as having either a systolic or a diastolic pressure in excess of 140 and 90 mmHg, or both, or as being on antihypertensive treatment, regardless of the measured blood pressure level. Cardiovascular diseases, reported by the subjects themselves, included *Internationational Classification of Diseases* (ICD) 8th revision codes 390–450, and ischemic heart disease included ICD codes 410–414 and 425–429.

Statistical methods

For statistical analysis, the SAS software package was used (40). The distributions of blood and urinary cadmium, blood lead, and serum gamma-glutamyltranspeptidase were normalized by a logarithmic transformation; for these measurements, the geometric means and ranges are reported.

Blood pressure was first represented graphically by quintiles of blood and urinary cadmium in men and women separately to ensure that there was no threshold phenomenon and that linear correlation techniques were appropriate. Preliminary analyses also indicated that systolic and diastolic blood pressures and urinary cadmium were curvilinearly related to age, and that the quadratic term of age significantly improved the linear correlations of these measurements with age. Age adjustments of blood pressure and of urinary cadmium therefore included both a linear and quadratic term of age.

A following step of the analyses consisted of the comparison of the two control areas

with the two polluted districts by analysis of covariance with district as the classification variable and age, body mass index, blood and urinary cadmium, blood lead, smoking and log gamma-glutamyltranspeptidase (used as index of alcohol intake) as covariates.

The relations between blood pressure and the cadmium levels in individual subjects were investigated by single and multiple linear regression, and the correlations between cadmium and the odds of having a cardiovascular illness by logistic regression. Significant covariates of blood pressure were traced by a stepwise regression procedure terminating when all regression coefficients in the model were significant at the 5 percent level.

RESULTS

Characteristics of the subjects

The 2,086 subjects included in the present analysis were 48 ± 16 (standard deviation) years old (range, 20–88 years). Pulse rate averaged 75 ± 9 beats/minute, urinary volume 1.66 ± 0.72 liters/24 hours and the urinary sodium:potassium ratio 2.7 ± 1.3. Urinary creatinine output was 14.6 ± 3.8 mmol/24 hours in men and 10.0 ± 2.6 mmol/24 hours in women. The geometric mean of serum gamma-glutamyltranspeptidase activity was 11 units/liter (range, 2–335 units/liter). Among men, current smoking was reported by 49 percent of the subjects, past smoking by 31 percent, and daily intake of alcohol by 36 percent. Current and past smoking, regular alcohol consumption and the use of birth control pills were reported by 35, 14, 15, and 20 percent of the women.

All of the above mentioned characteristics were similarly distributed among the inhabitants of the four districts. Only body mass index (26.0 vs. 25.1 kg/m^2; $p < 0.001$) was higher in the control district than in the polluted districts, whereas the opposite tendency was observed for the percentage of men reporting exposure to heavy metals at work (20 vs. 38 percent; $p < 0.001$).

Determinants of blood and urinary cadmium

Urinary cadmium was higher in men than in women (geometric mean, 9.2 vs. 7.2 nmol/24 hours; $p < 0.001$), whereas blood cadmium was similar in both sexes (10.1 vs. 9.9 nmol/liter, respectively).

Age, smoking, and exposure to heavy metals at work were important determinants of blood and urinary cadmium (figure 1). Blood and urinary cadmium were higher in past and current smokers combined than in never smokers (geometric mean, 12.0 vs. 7.1 nmol/liter and 9.1 vs. 6.6 nmol/24 hours, respectively; $p < 0.001$). Subjects reporting exposure to heavy metals at work (313 men and 20 women) had a blood cadmium of 12.2 nmol/liters, and a urinary cadmium of 12.6 nmol/24 hours, which was respectively 28 and 70 percent higher ($p < 0.001$) than individuals not exposed at work (9.5 nmol/liter and 7.4 nmol/24 hours, respectively).

Comparison of high and low exposure areas

Blood and urinary cadmium. Blood and urinary cadmium were raised in the two high exposure areas compared with the two low exposure areas (table 1), but blood and urinary cadmium were also higher in the two rural districts compared with the two urban districts (11.2 vs. 9.0 nmol/liter, and 10.2 vs. 6.6 nmol/24 hours; $p < 0.001$ for both comparisons).

Figure 2 illustrates the geographic trends in blood and urinary cadmium, standardized for age and body mass index. After adjustment for sex, age, body mass index, present and past smoking habits, residence in a rural or urban district and occupational exposure, blood and urinary cadmium were, respectively, raised 32 and 24 percent ($p < 0.001$) in the two high exposure areas compared with the two low exposure areas.

Blood pressure. Women living in the two polluted districts had a higher systolic blood pressure than those residing in the two control districts (table 1). The same tendency was also observed in men, but in both sexes these differences in systolic pressure were

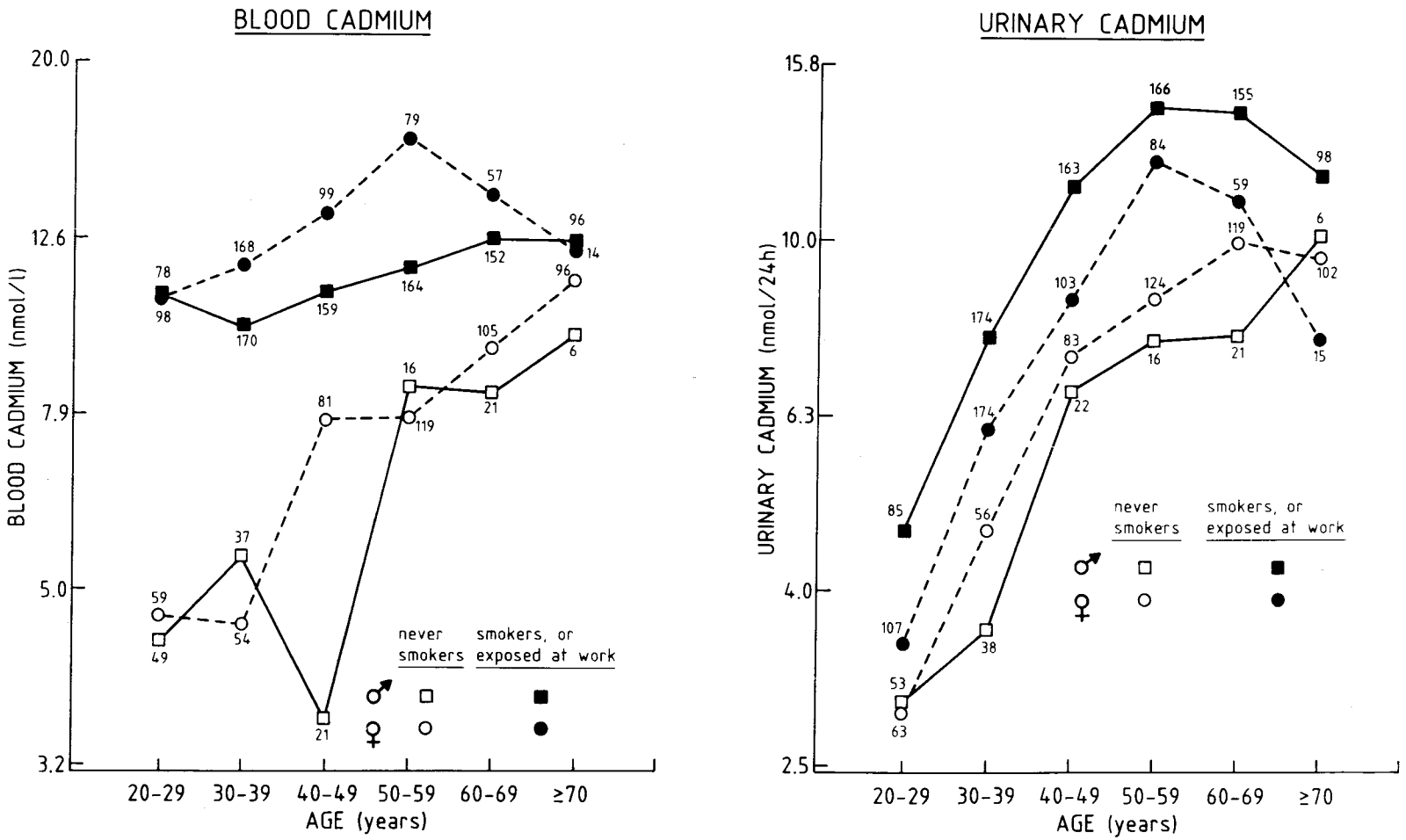

Figure 1. The association between blood and urinary cadmium and age in men and women in a Belgian population study, 1985–1989. The data are presented for never smokers (no evident exposure to cadmium) and the remainder of the subjects (exposure via smoking or at work).

TABLE 1. Comparisons between the low and high exposure districts in a Belgian population study, 1985–1989

	Men		Women	
	Low exposure	High exposure	Low exposure	High exposure
No.	370	627	433	656
Systolic pressure (mmHg)†	132 ± 17 (95–204)	133 ± 16 (95–192)	126 ± 18 (96–198)	128 ± 18* (93–214)
Diastolic pressure (mmHg)†	78 ± 9 (46–112)	77 ± 10 (37–116)	75 ± 9 (51–104)	76 ± 9 (47–111)
Hypertensive (%)	16.0	18.2	22.4	23.2
Antihypertensive treatment (%)	11.7	15.4	20.8	20.9
Cardiovascular disease (%)	17.6	16.0	21.2	17.4
Ischemic heart disease (%)	8.1	8.0	9.9	7.5
Blood cadmium (nmol/liter)‡,§	8.5 (0.9–67.6)	11.0*** (0.9–129.9)	8.3 (0.9–40.9)	11.0*** (0.9–81.0)
Blood lead (μmol/liter)‡	0.47 (0.14–1.59)	0.62*** (0.11–3.50)	0.33 (0.08–1.66)	0.38*** (0.08–2.91)
Urinary cadmium (nmol/24 hours)‡	7.9 (0.7–48.2)	10.2*** (0.4–325.2)	6.6 (0.1–70.8)	7.6*** (0.5–47.3)

Significance of the difference between low and high exposure areas: * $p < 0.05$ and *** $p < 0.001$.
† Values are means ± standard deviation with range between parentheses.
‡ Geometric mean with range between parentheses.
§ Blood cadmium available in 351 and 618 men and in 405 and 624 women, respectively.

probably too small to be biologically meaningful. The level of diastolic pressure was similar in the four districts (table 1).

Analysis of covariance with low versus high environmental exposure as the main classification variable showed that the difference in systolic pressure between the two low exposure districts and the two high exposure districts was not abolished, when covariates, such as rural versus urban residence, age, body mass index, smoking, alcohol intake, blood lead and cadmium, and urinary cadmium were accounted for. After cumulative adjustment for these covariates, the difference ($p < 0.001$) still averaged 2.8 mmHg in men and 2.6 mmHg in women. The observation that the difference in systolic pressure was not removed by adjustment for blood and urinary cadmium suggests that it was not related to the body burden of cadmium.

Further analysis demonstrated that blood pressure was similar in the two rural areas (high vs. low exposure area, 130/77 vs. 131/76 mmHg) and that the difference in systolic pressure in association with a high environmental exposure to cadmium was only observed in the urban districts (126/76 vs. 131/76 mmHg).

The prevalence of cardiovascular diseases. The prevalence of cardiovascular diseases, hypertension, and ischemic heart disease was similar in the low and high exposure districts (table 1).

Analyses in individual subjects

Blood pressure. Preliminary analyses had demonstrated that there was no threshold phenomenon when blood pressure was plotted by quintiles of blood and urinary cadmium in the two sexes separately and that

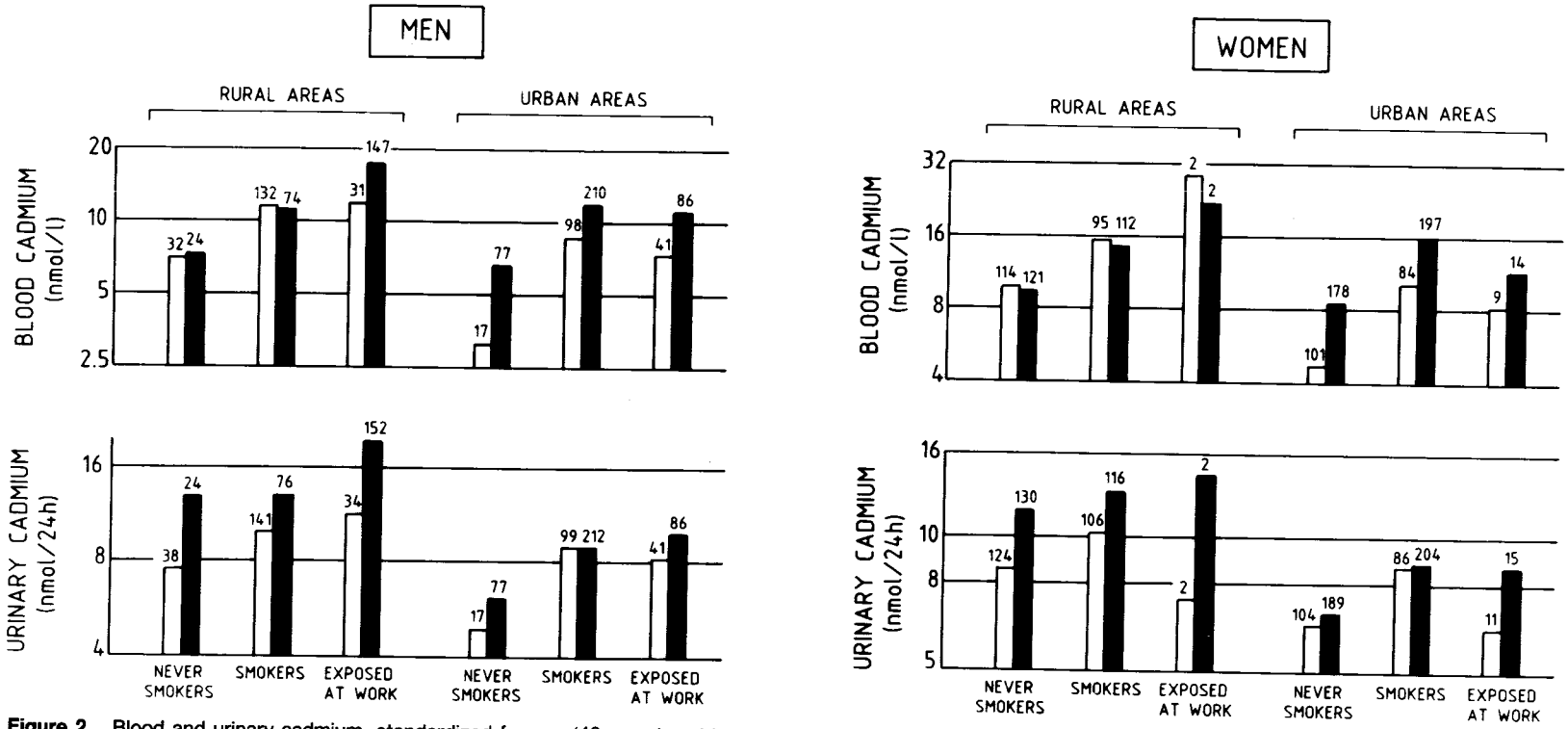

Figure 2. Blood and urinary cadmium, standardized for age (48 years) and body mass index (25.5 kg/m^2) in two districts with low environmental exposure to cadmium (open columns) and two districts with high environmental exposure to cadmium (closed columns) in a Belgian population study, 1985–1989. For each exposure level, an urban and rural district were selected. The data are presented according to smoking status and exposure at work in men and women, separately. Past and current smokers are combined. Subjects exposed at work include both smokers and nonsmokers. For each subgroup, the number of subjects contributing to the geometric mean is shown. Blood cadmium measurements were not available for 88 subjects.

TABLE 2. Relations between blood pressure and its determinants in a Belgian population study, 1985–1989†

	Men (n = 964)		Women (n = 1,016)	
	SBP	DBP	SBP	DBP
R^2	0.218	0.191	0.412	0.234
Intercept	98.8	28.7	95.7	46.2
Partial regression coefficients‡				
Log urinary cadmium	NS	−2.522**	NS	NS
Log blood cadmium	−2.085§	−2.422**	NS	NS
Log blood lead	NS	NS	NS	+2.130§
Age	−0.886***	+0.856***	−0.363*	+0.486***
Age^2	+0.012***	−0.007***	+0.010***	−0.003***
Body mass index	+1.040***	+0.690***	+0.710***	+0.497***
Pulse rate	+0.191***	+0.103***	NS	+0.049+
Urban residence§	NS	NS	NS	+0.982+
Sodium:potassium ratio	NS	NS	NS	NS
Log gamma-glutamyltranspeptidase‖	+3.852*	+4.233***	+4.290**	+1.957*
Being current smoker§	NS	NS	+2.993**	NS
Being past smoker§	NS	NS	NS	−1.421*
Contraceptive pill§			+2.568*	+1.400*

+0.1 < p < 0.05; * p < 0.05; ** p < 0.01; *** p < 0.001.
† Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; NS, not significant.
‡ Significant blood pressure covariates were identified by stepwise regression. Regression coefficients were derived for a model including either blood or urinary cadmium (not both).
§ Coded 0 or 1 for condition absent or present.
‖ Used as index of alcohol intake.

a linear model was adequate to study the relations between blood pressure and cadmium.

Stepwise multiple regression showed that systolic and diastolic blood pressures in the two sexes were significantly correlated with age, (linear and quadratic term), body mass index, and serum gamma-glutamyltranspeptidase (or alcohol intake as assessed by the questionnaire) (table 2). Systolic and diastolic blood pressures were also positively correlated with pulse rate in men, and with the use of birth control pills in women. After adjustment for the aforementioned covariates, blood and urinary cadmium were negatively correlated with diastolic pressure in men; the partial regression coefficients indicated that a twofold increase in blood or urinary cadmium was associated with a decrease in diastolic blood pressure by approximately 1 mmHg (table 2).

Exclusion of subjects on antihypertensive treatment did not alter the variables identified as significant covariates of blood pressure. After these exclusions, the partial regression coefficient of diastolic pressure on blood cadmium in men was −2.424 mmHg/log(nmol/liter) (p = 0.007) and on urinary cadmium it was −2.259 mmHg/log(nmol/24 hours) (p = 0.01).

Cardiovascular disease. Logistic regression showed that blood cadmium was not related to the presence of hypertension and of self-reported cardiovascular diseases in individual subjects. A positive relation existed between the presence of these diseases and urinary cadmium, but these associations disappeared after adjustment for sex and age.

DISCUSSION

Methodological issues

The question, whether cadmium at usual levels of environmental exposure may lead to blood pressure elevation, and therefore to a higher prevalence of hypertension in the population at large, remains unresolved (41). Indeed, earlier studies involved mainly laboratory animals (1, 8–11, 41), or investigated selected workers at workplace exposure levels (14, 29). Moreover, confounding

factors, such as smoking, were not always accounted for, and occasionally the published analytical results were not in agreement with modern standards (41).

The present population study recruited its participants from a random sample of households. The sampling procedure made it possible to visit several participants at the same address, thereby reducing the amount of field work and the financial cost of the study. The present study was conducted over 5 years as a collaborative project by four research units (34). The results of the intensive quality checks of the clinical and biochemical measurements met the objectives set during the planning stage of the project (34).

The participation rate in the two urban districts was low (39 percent). Selection bias may possibly limit the generalizability of the results obtained in the two urban areas, but the low participation does not invalidate comparisons restricted to only the subjects included in the study. In addition, the overall conclusions of this study were not altered if we compared only the two rural areas, where the participation rate of 78 percent could be considered to be satisfactory. As far as this could be assessed, there were no socioeconomic differences between respondents and nonrespondents, but nonrespondents in the two urban areas were on average 12 years older than the subjects taking part in the study.

In the present study, a 25–30 percent increase in blood and urinary cadmium was found to be associated with higher environmental exposure to cadmium. In general, the present blood and urinary cadmium levels (figure 2) are comparable with those reported for other industrialized countries (42, 43). Indeed, in a review of blood cadmium measurements in 17 studies performed on three continents and in eight countries (43), nonsmokers were reported to have a median concentration in whole blood on the order of 3.6 to 8.9 nmol/liter.

Cadmium and blood pressure

In the two urban districts, a high environmental exposure to cadmium was associated with an elevation of systolic pressure by 5 mmHg, whereas in the two rural districts such an association was not observed. Selection bias due to the low participation rate may have contributed to the observed difference in systolic pressure between the two towns.

Since on average both systolic pressure and the body burden of cadmium were lowest in the control urban area, the hypothesis that a threshold cadmium concentration exists above which blood pressure suddenly rises was investigated. These analyses showed that there was no threshold phenomenon and that, at least for the ranges observed in the present study, a linear model was adequate for studying the association between blood pressure and blood and urinary cadmium. Whatever the underlying mechanism, the observation that the difference in systolic pressure between the two towns was not removed by adjusting for blood and urinary cadmium suggests that it was not related to cadmium exposure.

The interpretation that the difference in systolic pressure between the two towns was not due to cadmium was also corroborated by the results in individual subjects, showing that diastolic pressure was negatively correlated with blood and urinary cadmium at least in men. Blood and urinary cadmium have a different pathophysiologic significance, the former being more related to recent intake and the latter to lifetime exposure, i.e., the body burden of cadmium, but both increase with smoking (41, 42). In population studies (44–46), blood pressure tends to be lower among smokers than among nonsmokers, whereas smoking acutely raises blood pressure, probably as a consequence of sympathetic stimulation (47–49). It is therefore possible that the negative correlations between blood pressure and the measurements of cadmium exposure in men reflect to some extent the chronic effects of smoking.

Cadmium and the prevalence of cardiovascular diseases

The present findings did not confirm the hypothesis that cadmium accumulation in

the body leads to increased mortality from cardiovascular diseases in areas with an increased potential for environmental exposure, for instance, via polluted air (5), or via soft drinking water (7).

In agreement with the present findings, a large Japanese cohort study (50) has demonstrated that the mortality from cerebrovascular accidents and hypertension tended to be lower in four polluted districts compared with four control districts. Similarly, Armstrong and Kazantzis (12) found in a cohort of occupationally exposed workers no excess mortality from hypertension, and a decreased mortality from cerebrovascular causes. By contrast, among the residents of the cadmium-polluted village of Shipham, United Kingdom, there was in comparison with a nearby control village a slight excess mortality from cardiovascular causes, and a significantly elevated mortality from cerebrovascular disease (51). However, in the Shipham study, the number of deaths was small and individual exposure measurements were not available (51).

Conclusion

This study did not confirm the hypothesis that increased exposure of the population to cadmium may lead to blood pressure elevation and to a higher prevalence of cardiovascular diseases. These findings contradict the original hypothesis, which was mainly based on animal experiments (1, 8–11), but are in agreement with earlier reports on cerebrovascular mortality in exposed workers (12) and in the Japanese population (50).

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