Environmental Health Perspectives
Vol. 78, pp. 43–46, 1988

Blood Lead and Coronary Heart Disease Risk Among Elderly Men in Zutphen, the Netherlands

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Information about blood lead and other coronary heart disease risk factors was collected in 1977 among 152 men aged 57 to 76 years in the town of Zutphen, the Netherlands. Blood lead was determined by atomic absorption spectrometry. The blood lead distribution was skewed to the right. The median blood lead concentration was 167 µg/L, and the mean was 183 µg/L. Blood lead levels above 300 µg/L were present among 8.6% and levels above 400 µg/L among 1.3% of the Zutphen men. Blood lead was of borderline significance to cigarette smoking. After both univariate and multivariate analyses, a significant association was found between blood lead and blood pressure. This relation was stronger for systolic than for diastolic blood pressure. Of the 141 elderly men free of coronary heart disease in 1977, 26 developed coronary heart disease between 1977 and 1985. Blood lead was not associated with coronary heart disease incidence in both univariate and multivariate analyses.

Introduction

Descriptive data on serum and blood trace-metal distributions in elderly populations are scarce. Trace metals are of interest in relation to coronary heart disease risk because lead and cadmium have been suggested to play a role in the etiology of hypertension (*1–4*). Zinc, copper, and lithium may also be related to coronary heart disease risk (*5,6*). It was therefore decided to collect information on these trace elements in blood in a subgroup of 152 men aged 57 to 76 who participated in 1977 in the 15th round of the Zutphen Study. The major risk factors for coronary heart disease, e.g., blood pressure, serum total cholesterol, cigarette smoking, and Quetelet Index (weight/height^2) were also measured. Information about coronary heart disease incidence was collected during the period 1977 to 1985. In this paper the relation between blood lead, blood pressure, and coronary heart disease incidence will be described.

Materials and Methods

Since 1960, a longitudinal investigation of the relations between diet, other risk factors, and coronary heart disease has been carried out among middle-aged men from the town of Zutphen, the Netherlands. The Zutphen Study forms the Dutch contribution to the Seven Countries Study (*7–9*). In 1960, a random sample of 1088 men born between 1900 and 1919 who had lived for at least 5 years in Zutphen was selected for the study, and, of these 1088 men, 919 (84.5%) were medically examined.

Between 1960 and 1973, the men underwent a medical examination yearly. In 1977 and 1978, the 15th round took place, and, of all the men who were still alive, 611 (92%) were re-examined. Among the 473 men examined in 1977, a sample was selected of 152 men aged 57 to 76 years who had lived since 1960 in the same house. In this sample, relations were investigated between the type of waterpipes (e.g., lead or copper) and some trace metal levels in blood. Information about coronary heart disease risk factors was also collected. Statistically significant differences in coronary heart disease risk factor levels were not found between the men who participated in the trace metal study and all other men examined in 1977.

Information about smoking habits was obtained by a questionnaire completed by the men at home. Height and weight were determined according to a standardized protocol by a trained staff (*7*). Blood pressure was measured according to a standardized protocol by one internist using a mercury sphygmomanometer (*7*). Blood pressures were taken from the right arm with the men in a supine position. The first recording was made at the beginning of the examination, and the

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second and third recordings were made at the end of the medical examination. Only the systolic and diastolic (fifth phase) values of the third measurement were recorded.

To prevent contamination, cadmium- and lead-free disposable syringes and polyethylene tubes were used for blood collection. Lead-free heparin was used to prevent blood clotting, and the blood samples were deep frozen until analysis. Blood lead was determined by electrothermal atomization atomic absorption spectrometry, with improvements in precision by using a peakshape monitoring device (*10*). Serum lithium was determined by flamed emission spectrometry. The accuracy of blood lead was checked by participation in international round robin studies. The inaccuracy was ≤ 50 μg/L for blood lead.

Between 1960 and 1985 there was a continuous mortality and morbidity follow-up of the Zutphen men. Of the 141 elderly men without coronary heart disease in 1977, 26 men developed coronary heart disease, including definite or possible myocardial infarction, angina pectoris, or sudden death.

For the statistical analyses, SPSS package programs were used (*11*). In addition to descriptive statistics, means and standard deviations, correlation coefficients were calculated for continuous variables. Analysis of variance was used if the dependent variable was continuous and the independent variable was categorical. Multiple comparisons were tested by the Scheffé method (*11*). Multiple regression analyses were carried out using coronary heart disease risk factors as dependent variables and blood trace metals and other determinants of these risk factors as independent variables. For variables with skewed distributions, log transformations were used in univariate and multivariate regression analyses. No difference was observed whether transformed or untransformed variables were used. Therefore, only the results of untransformed variables will be reported. The relation between blood lead and coronary heart disease was analyzed by Mantel-Haenszel test and Cox survival regression analyses (*12*).

Results

The mean for blood lead was higher than the median, indicating that the distribution was skewed to the right (Table 1). Blood lead levels > 300 μg/L were present among 8.6%, and levels > 400 μg/L were present among 1.3% of the elderly men in Zutphen. The prevalence of systolic hypertension (> 160 mm Hg) was 34.4% and that of diastolic hypertension (> 95 mm Hg) was 37.1%. The prevalence of obesity (Quetelet Index > 27 kg/m^2) was 26.5%. The percentage of current smokers was 64.9%.

Cigarette smoking was of borderline significance to blood lead concentration (Table 2). A dose-response relation was not present. Men smoking 10 or more cigarettes per day tended to have higher blood lead levels than men who smoked fewer than 10 cigarettes per day or who did not smoke cigarettes. This difference, tested by Scheffé, was, however, not statistically significant.

Table 1. Coronary heart disease risk factor distributions of 152 men aged 57 to 76 years in Zutphen, the Netherlands, 1977.

Risk factor	Mean	SD	P10[a]	P50	P90
Blood lead, μg/L	183	74	108	167	280
Systolic blood pressure, mm Hg	154.3	22.0	126	149	184
Diastolic blood pressure, mm Hg	91.8	14.0	75	91	107
Quetelet Index, kg/m^2	25.4	2.8	22	26	29

[a]P, percentile.

Table 2. Analysis of variance of blood lead on cigarette smoking in 151 men aged 57 to 76 in Zutphen, the Netherlands, 1977.

No. of cigarettes smoked/day	No. of men	Blood lead, μg/L (mean + SD)
None	53	172 ± 63
<10	58	176 ± 64
10	40	209 ± 93
		$F = 3.5, p = 0.032$

Blood lead was significantly positively associated to systolic blood pressure ($r = 0.24, p < 0.01$) and diastolic blood pressure ($r = 0.18, p < 0.05$). Multiple regression analysis with systolic blood pressure as the dependent variable and blood lead, age, and Quetelet Index as independent variables showed that the standardized regression coefficient for blood lead was reduced to 0.21 ($p < 0.01$). When a similar model was used for diastolic blood pressure, the standardized regression coefficient for blood lead was reduced to 0.15 ($p = 0.05$).

The multiple regression coefficient for blood lead on blood pressure after adjustment for age and Quetelet Index suggests that an increase of 10 μg/L blood lead is associated with an increase of 0.6 mm Hg in systolic and an increase of 0.3 mm Hg in diastolic blood pressure (Table 3). The relation between blood lead and blood pressure might be influenced by the skewed distribution of blood lead. In order to gain insight into the stability of this relation, the individual with the highest blood lead level (525 μg/L), who also had

Table 3. Regression coefficients for blood lead on blood pressure among 149 men aged 57 to 76 in Zutphen, the Netherlands in 1977.[a]

Dependent variable	Model[b]	β	SE (β)
Systolic	UV	0.071†	0.024
	MV	0.063†	0.024
Diastolic	UV	0.035*	0.015
	MV	0.029*	0.015

[a]Blood pressure = blood lead + age + Quetelet Index.
[b]UV, univariate model; MV, multivariate model.
*$p \leq 0.05$.
†$p \leq 0.01$.

hypertension (218/138 mm Hg), was excluded from the analysis. Thereafter, a borderline significant correlation was found between blood lead and systolic blood pressure, and the correlation between blood lead and diastolic blood pressure became insignificant. The relation between blood lead and systolic blood pressure was no longer statistically significant after adjusting for age and Quetelet Index. The multiple regression coefficient was reduced from 0.06 before exclusion of the person with high blood lead and high blood pressure levels to 0.04 after exclusion of this person.

Of the 141 elderly men free of coronary heart disease in 1977, 26 developed coronary heart disease between 1977 and 1985. Univariate analyses suggested a U-shaped relation between blood lead and coronary heart disease incidence. The lowest risk ratio was observed among men in the second and third quartile of the blood lead distribution. The relation between blood lead and coronary heart disease did not reach statistical significance in univariate analysis nor in multivariate analyses adjusting for systolic blood pressure, cigarette smoking, serum total cholesterol, and Quetelet Index (Table 4).

Discussion

Blood lead levels found in the present study can be compared with those observed among men aged 56 to 72 in Sweden (*3*). The blood lead level of the Swedish men was 76 μg/L, compared to 167 μg/L among the men in Zutphen. In a carefully standardized international cooperative study among men of an unspecified age range (*14,15*), median levels below 100 μg/L were found among men from Sweden, China, and Japan. Levels between 100 and 200 μg/L were observed in men from the United States, Yugoslavia, India, and Peru. The highest median value, 271 μg/L, was found in Mexico City. Middle-aged men from England and West Germany had average values around 150 μg/L (*16,17*). Comparisons between countries are difficult due to the confounding effects of alcohol, smoking, and traffic intensity on blood lead levels (*13–15,17*). In spite of these difficulties, it may be concluded that the blood lead levels of the elderly men in Zutphen ranked high internationally, with a median of 167 μg/L and 8.6% with levels above 300 μg/L and 1.3% with levels above 400 μg/L.

Table 4. Relation between blood lead and 8-year incidence of coronary heart disease among 141 men aged 57 to 76 in 1977 in Zutphen, the Netherlands.

	Quartiles of blood lead		
	1	2–3	4
Risk ratio[a]	1.00	0.81	1.34
		(0.31–2.12)[b]	(0.46–3.94)[b]

[a]Adjusted for age, systolic blood pressure, cigarette smoking, total cholesterol and Quetelet Index in Cox survival analysis.
[b]95% confidence limits.

Cigarette smoking was of borderline significance to blood lead. No dose-response relation was present. In other studies (*13–15*), generally, a weak relation was also found between cigarette smoking and blood lead.

In the present study a positive association was found between blood lead and blood pressure. The association was stronger for systolic than for diastolic blood pressure. Additional analyses showed that this relation was influenced by one person with a high blood lead level who also had severe hypertension. After exclusion of this person, the regression coefficient was reduced from 0.06 to 0.04. These results suggest that in the elderly population of Zutphen a weak association was present between blood lead and blood pressure when blood lead levels were below 400 μg/L. The results also suggest that exposure to blood lead levels above 500 μg/L was associated with hypertension.

Consistency among results of different studies is one of the criteria to judge whether an association may be causal. Therefore, the results of Zutphen Study will be compared with those of the two largest epidemiologic studies on the relation between blood lead and blood pressure, the British Regional Heart Study and the NHANES II Study carried out in the U.S. (*18,19*). These studies also showed a stronger relation between blood lead and systolic blood pressure than between blood lead and diastolic blood pressure. After additional multivariate analyses with adjustment for site, similar statistically significant regression coefficients were observed for the relation between the natural logarithm of blood lead and systolic blood pressure, e.g., 2.09 and 3.23 (*20*). The multiple regression coefficient for the natural logarithm of blood lead (μg/dL) on systolic blood pressure after adjusting for age and Quetelet Index in the Zutphen Study was 10.85 (95% confidence limits, 1.40–20.30). These results are consistent with the hypothesis that blood lead is related to systolic blood pressure. Nevertheless, blood lead is probably a less important determinant of blood pressure than age and Quetelet Index.

In the present study, no relation was found between blood lead and 8-year incidence of coronary heart disease after both univariate and multivariate analysis. A similar result was obtained in the British Regional Heart Study (*21*). These results suggest that blood lead seems not to be related to coronary heart disease incidence.

The blood lead measurements were carried out at the Coronel Laboratory for Occupational and Environmental Health, Faculty of Medicine, University of Amsterdam, the Netherlands. This study was supported by the Praeventiefonds in the Netherlands

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