Both the Environment and Genes Are Important for Concentrations of Cadmium and Lead in Blood

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Concentrations of cadmium and lead in blood (BCd and BPb, respectively) are traditionally used as biomarkers of environmental exposure. We estimated the influence of genetic factors on these markers in a cohort of 61 monozygotic and 103 dizygotic twin pairs (mean age = 68 years, range = 49–86). BCd and BPb were determined by graphite furnace atomic absorption spectrophotometry. Variations in both BCd and BPb were influenced by not only environmental but also genetic factors. Interestingly, the genetic influence was considerably greater for nonsmoking women (h^2 = 65% for BCd and 58% for BPb) than for nonsmoking men (13 and 0%, respectively). The shared familial environmental (c^2) influence for BPb was 37% for men but only 3% for women. The association between BCd and BPb could be attributed entirely to environmental factors of mutual importance for levels of the two metals. Thus, blood metal concentrations in women reflect not only exposure, as previously believed, but to a considerable extent hereditary factors possibly related to uptake and storage. Further steps should focus on identification of these genetic factors and evaluation of whether women are more susceptible to exposure to toxic metals than men. *Key words*: **aging, blood, cadmium, environment, genes, human, lead, twins.** *Environ Health Perspect* **108:719–722 (2000). [Online 23 June 2000]**
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The amount of the toxic metals cadmium and lead in the human environment has increased considerably during the last century because of anthropogenic activities (*1,2*). Both metals interact with tissue constituents at low concentrations, and the safety margins to exposure levels at which signs of toxic effects are seen are small (*1–4*). In the general population, diet is the main source of exposure to both Cd and Pb (*5*). Cigarette smoking is another source of Cd exposure (*6*). In Sweden and other countries where leaded gasoline has been phased out, human Pb exposure has declined significantly (*7*). However, leaded gasoline is still in use in many developing countries.

The assessment of human exposure to Cd and Pb has traditionally been based on biomarkers, in particular concentrations in blood and urine. For both metals, concentrations in blood (BCd and BPb, respectively) are believed to reflect mainly ongoing exposure (*1,3*). However, there is often considerable variation between individuals, indicating that factors other than exposure might be of importance. The twin study design is well suited to partitioning individual differences into genetic and environmental sources of variation (*8*). Thus, the aim of this project was to evaluate to what extent variation in blood concentrations of Pb and Cd are genetically influenced.

Using data from a sample of elderly twin pairs, we were interested in three research questions. First, what is the relative importance of genetic and environmental effects for BCd and BPb? Second, are there sex differences in the importance of these effects? Third, to what extent are the same genetic and environmental influences of importance for BCd and BPb?

Methods

Study group. The study group consisted of twins participating in The Swedish Adoption/Twin Study of Aging (SATSA) (*9,10*), a longitudinal research project based on a subsample of same-sex twins from the Swedish Twin Registry (*11*). The SATSA cohort consists of twins 50 years of age and older and who were either reared apart or together (*9,10*). Participants in SATSA responded to questionnaires and participated in in-person testing at regular 3-year intervals. A third test (which included 569 individuals and was conducted between 1992 and 1994) also involved the collection of blood samples for subsequent analysis of metal concentration. Details on the sample collection procedures were described previously (*12*). Blood samples for analysis of BCd and BPb were available from 424 individuals, of whom 328 were members of complete twin pairs [61 monozygotic (MZ) pairs and 103 dizygotic (DZ) pairs; mean age = 68 years, range = 49–86]. Descriptive statistics concerning influence on blood metal concentrations from smoking, sex, age, and occupation have previously been reported (*12*). We obtained informed consent from all participants and the study was approved by the ethics committee of Karolinska Institute (Stockholm, Sweden) and the Swedish National Data Inspection Authority (Stockholm, Sweden).

Metal analyses. We determined concentrations of BCd and BPb by graphite furnace atomic absorption spectrophotometry with Zeeman background correction (*12–14*). The detection limit (mean of blank ± 3 SD) was 0.05 µg/L for BCd and 1.7 µg/L for BPb. The analytical performance was evaluated by comparisons of sets of quality control samples and two external reference control samples (Seronorm trace elements, whole blood no. 205052 and 203056; Nycomed Pharma, Oslo, Norway).

Statistical analyses. Genetic analyses were based on quantitative genetic theory, which defines a phenotype as the sum of the effects of both genotype and environment (*8*). Similarity within twin pairs (measured by intraclass correlation) is compared between MZ and DZ pairs. For example, MZ twins share identical genotypes, so their environments theoretically cause any differences between them. Dizygotic twins, in contrast, share on average 50% of their segregating genes. The extent to which MZ twins are more alike than DZ twins should therefore reflect genetic influences. A common concept used in this context is heritability (h^2), which is the extent to which the phenotypic (observable) variation is attributable to genetic effects.

The environmental component of variance for a particular trait can be decomposed into two subcomponents—one shared by family members and the other not. Shared environmental influences (c^2) are those that make family members more similar to each other than people in general (*15*). The

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remainder of the environmental variance not shared by family members is called nonshared (e^2). Thus, total variation (V_p) can be apportioned into genetic and environmental influences as described by:

$$V_p = h^2 + c^2 + e^2$$

Estimates of genetic and environmental effects based on intraclass correlation have relatively large standard errors resulting in low power and do not use all available information simultaneously. Model-fitting approaches are more powerful and permit the analysis of several groups of twins simultaneously as tests of the relative fit of various models, and are now standard practice in twin research (*16*). In our study, covariance matrices for the two zygosity groups were subjected to structural-equation modeling with the LISREL 7 program (*17*) to estimate the genetic and environmental components of variance. The application of these techniques in the SATSA project has been described previously (*18,19*). In contrast to other analyses in SATSA in which we were able to evaluate a rearing environmental effect by comparing reared-apart pairs to reared-together pairs, sample sizes limited us to pooling over rearing status. However, we were able to analyze the data separately for men and women.

To achieve normal distribution of data BCd and BPb were log-transformed. We used residuals, adjusted for age and sex, from linear regression analyses in the calculation of intraclass correlation and model fitting. Analyses were first applied to the entire sample and then only to nonsmoking twin pairs, using new residuals for only nonsmoking twins. Because of the strong influence of smoking on the BCd concentrations (*12*), the genetic effects for smoking would confound those for Cd levels. When the sample was categorized by sex, residuals were adjusted for age only.

Results

Blood concentrations of Cd and Pb. The overall geometric mean BCd was 0.41 µg Cd/L (range = 0.05–6.8 µg Cd/L). Because smokers had highly elevated BCd, data for nonsmokers are given separately (Table 1). For nonsmokers, BCd was significantly higher for women than for men. Concentrations increased slightly across age. The geometric mean concentration of Pb in blood was 28 µg Pb/L (range = 5.6–150 µg/L). BPb was not influenced by smoking, and was slightly higher for men than for women (Table 1). Mean levels of BPb decreased slightly with age until approximately 70 years of age, after which they increased again. More importantly, total variance increased with age for BPb but was stabile across age groups for BCd. There were no differences in means or variances for the two zygosity groups, thus fulfilling one of the assumptions of the twin method.

Twin analyses: BCd. Intraclass correlations of BCd by sex and by age for the entire study group as well as for nonsmoking twins are given in Table 2. In general, MZ twins had higher correlations than DZ twins, indicating a genetic influence on BCd. Among nonsmokers, the pattern of correlations for women suggested a genetic effect whereas the considerably lower correlations for men suggested that environmental factors are of much greater importance than genetic effects.

Results from model-fitting analyses of BCd (Figure 1) mostly confirm the findings based on the comparison of intraclass correlations. When the entire sample was evaluated (regardless of smoking status), approximately 60% of the variation in BCd was due to genetic effects. Among nonsmoking twins, genetic effects were considerably more important for women than for men (65 and 13%, respectively). Analyses of nonsmoking twin pairs younger and older than 65 years of age showed no major cohort differences.

Twin analyses: BPb. The correlation for MZ twins was greater than that for DZ twin pairs among the women, suggesting the importance of genetic effects (Table 2). In contrast, the MZ and DZ correlations for men did not differ, indicating the importance of shared familial environment. The intraclass correlations for twin pairs (pooled across sex and smoking status) suggested a substantial cohort effect, with substantial genetic influences in the younger cohort and shared environmental influences in the older cohort. The sample size did not allow separate analyses by age group and sex simultaneously.

Model-fitting analyses indicated that approximately 44% of the variance in BPb in women was due to genetic factors, compared to only 3% in men (Figure 2). Shared environmental factors were significant for men but not for women (37 and 3%, respectively). There was essentially no genetic influence at older ages. This in large part reflected a decrease in genetic effects among the older women, as there was essentially no genetic variance for the men at any age.

Associations between Cd and Pb. There was a moderate association (r = 0.30, n = 210) between BCd and BPb in nonsmoking individuals. Thus, the next logical step was to evaluate whether this association can be attributed to the same genetic factors for BCd and BPb, or to environmental influences of importance for blood concentrations of both metals. We evaluated this association by computing cross-twin cross-trait correlations for nonsmoking twin pairs, i.e., the correlation of BPb in one twin with BCd in the cotwin. Because there were no differences in the cross-correlations for MZ and DZ pairs, only environmental influences could have contributed to the association. Thus, the association between BCd and BPb could be attributed entirely to environmental factors of mutual importance for levels of the two metals.

Discussion

To our knowledge, this is the first empirical demonstration that individual differences in concentrations of BCd and BPb in part

Table 1. BCd and BPb in blood by sex and zygosity.

Sex	Zygosity	Pairs (*n*)	Cd (µg/L)			Pb (µg/L)		
			Mean[a]	−1 SD	+1 SD	Mean[a]	−1 SD	+1 SD
Smoking pairs								
Men	MZ	27	0.40	0.16	0.99	31	19	49
	DZ	45	0.41	0.16	1.01	33	20	53
Women	MZ	34	0.41	0.21	0.81	24	14	40
	DZ	58	0.42	0.21	0.83	25	15	41
Nonsmoking pairs								
Men	MZ	17	0.27	0.13	0.53	31	18	52
	DZ	25	0.25	0.15	0.43	31	20	49
Women	MZ	26	0.35	0.22	0.54	23	14	37
	DZ	37	0.32	0.20	0.51	25	15	42

[a]Geometric mean.

Table 2. Intraclass correlations of BCd and BPb concentrations in MZ and DZ twin pairs by sex and age group.

Group[a]	Zygosity	Intraclass correlation		
		Cd		Pb
		All	Nonsmokers	all
Men	MZ	0.63	0.11	0.40
	DZ	0.34	–0.01	0.36
Women	MZ	0.58	0.62	0.45
	DZ	0.30	0.34	0.25
< 65 years	MZ	0.57	–0.37	0.63
	DZ	0.31	0.27	0.28
> 65 years	MZ	0.62	0.49	0.35
	DZ	0.33	0.13	0.27
All	MZ	0.61	0.31	0.42
	DZ	0.33	0.17	0.30

Data for BCd and BPb are given for all pairs. BCd data for nonsmokers are given separately.
[a]The number of twin pairs is given by sex in Table 1. In those younger than 65 years of age there were 18 and 39 MZ and DZ twin pairs, respectively. There were 11 MZ and 18 DZ nonsmoking pairs. In those older than 65 years of age there were 43 and 64 MZ and DZ twin pairs, respectively. There were 32 MZ and 44 DZ nonsmoking pairs.

reflect genetic variation. Interestingly, genetic effects were of greater importance for women than men. In men the variation in blood metal concentrations could be attributed almost entirely to environmental factors. Elucidation of the genetic mechanisms that influence blood metal concentrations in women would enable identification of risk groups that are particularly sensitive to toxic metal exposure.

Genes can act and interact in a variety of ways before their effects on the phenotype (BCd or BPb) are observable. Specific genetic factors influencing BCd and BPb have not yet been investigated, but may include genes regulating absorption, distribution, metabolism, and excretion. Heritability estimates were greater for the pooled sample of men than for nonsmokers only. This suggests that some of the genetic influences for BCd reflect genetic influences for smoking status. The pronounced genetic influence on BCd in nonsmoking women is particularly interesting because women in general have higher concentrations of Cd in blood and in the kidneys, the main target organ for Cd toxicity (*6,12,20*). The elevated Cd levels in women are at least partly related to increased Cd absorption with depleted iron stores (*21–23*), which frequently occur in women before menopause (*22,24,25*). The likely underlying mechanism is that both Cd and iron bind to the intestinal divalent metal ion transporter, DMT1, which is up-regulated in iron deficiency (*26,27*). This makes women with low iron stores a risk group for Cd-induced health effects (*2*).

BCd levels increase across age in men but not in women (*12*), which is consistent with improved iron stores and decreased Cd absorption after menopause. We were not able to evaluate the importance of genetic effects for iron status in these women. However, genetic influences are important for menstrual blood loss (*28*) and age at menopause (*29*). Thus, some of the genetic variation for BCd in women may reflect genetic influences for postmenopausal iron status. Metallothionein is the main Cd-binding ligand in the body and may be another genetically influenced factor of importance for BCd. There are different isoforms of metallothionein, which may differ in affinity to Cd and result in varying levels of BCd (*3,30*). However, little is known about the interindividual variation in metallothionein.

Genetic effects for BPb variation were also greater for women than for men. Pb is neurotoxic and very low concentrations may affect the central nervous system, especially during prenatal development (*1,31*). Pb passes the placenta and the fetus has approximately the same blood concentration as the mother. Thus it is important to identify factors influencing exposure and internal dose of Pb. Pb is accumulated in bone, which contains > 90% of the total body burden. Thus, candidate genes influencing BPb are, for example, those regulating bone formation and resorption. During situations of increased bone resorption relative to bone formation, in particular at menopause, stored Pb may be released to the bloodstream (*32*). The highest BPb concentration was found in the twins of immediate postmenopausal age [50–55 years (*12*)], which is similar to results reported for American women (*33*). The disappearance of the genetic influence on BPb with increasing age in the present study may be related to the decreased bone turnover. Unfortunately, these data are not longitudinal; hence it is not possible to determine whether the cohort effects obtained reflect true aging changes. Environmental levels of Pb have decreased substantially during the last decades (*7*). Nevertheless, it is notable that the increase in variation for BPb is entirely attributable to an increase in environmental variance, regardless of whether this is a cohort or an aging effect.

Variation in male BPb was mainly influenced by environmental factors. Part of the variation may reflect individual differences in dietary habits. Studies on the concentrations of Pb in diet, collected in duplicate during 7 consecutive days by 15 women (105 diets total), showed a total range of 5–80 µg Pb (*5*). Elevated Pb levels are found in canned food and wine and other foodstuffs (*5,34*). However, there may also be variation in sources of exposure. For example, it has been reported that rifle shooting (*35*) and automobile repair (*36*) may cause a significant increase in BPb. For men, shared environmental factors were considerably more important than genetic factors. The extent to which brothers or sisters share lifestyle factors may explain in part the shared familial influences in the present study.

There was a moderate association between BCd and BPb levels among nonsmokers that was entirely attributable to environmental influences. The lack of a genetic mediator for this covariation is notable and is in striking contrast to findings for components of the metabolic syndrome (*37*). The association is consistent with findings in children with environmental exposure to Cd and Pb (*38,39*). Some caution in interpretation of the cause of the association is warranted, particularly in light of the small sample sizes.

Although this is the first known report of genetic influences on blood metal concentrations in a large number of individuals, the number of pairs for the analyses was small by twin study standards. The classical twin study has much greater power to identify significant genetic rather than shared environmental effects (*40*). Comparisons across age groups were limited by power considerations. Perhaps the greatest limitation is the absence of unlike-sexed pairs. Their inclusion is essential to draw conclusions concerning whether or not the differences in heritability estimates reflect different genes operating in men and women or other forms of sex limitation (*16*).

Conclusions

Interindividual variation in BCd and BPb concentrations is not entirely attributable to environmental exposure. Genetic influences on blood concentrations of Cd and Pb were most pronounced in nonsmoking women. Thus blood metal concentrations are influenced by different factors in men and women and are not the direct indicators of exposure as previously believed. This new knowledge will improve the evaluation of exposure and internal dose—important parts in the risk assessment process. It is important to study the effect in a younger population and to characterize the genetic influences on metal concentrations to identify risk groups in the population.

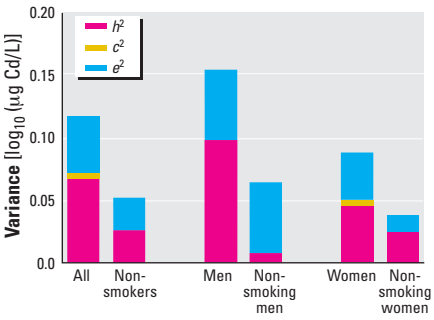

Figure 1. Sources of variation of concentration of cadmium in blood. Abbreviations: c^2, shared environmental factors; e^2, nonshared environmental factors; h^2, genetic factors. Data are given for both all twin pairs (including smokers) and separately for nonsmoking pairs and by sex.

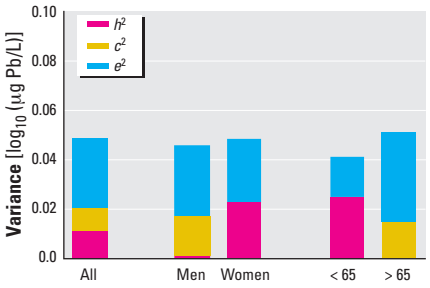

Figure 2. Sources of variation of concentration of lead in blood. Abbreviations: c^2, shared environmental factors; e^2, nonshared environmental factors; h^2, genetic factors. Data are presented both by sex and by age group (< 65 and > 65 years of age).

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