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Associations Between Patella Lead and Blood Pressure in Lead Workers

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Abstract

Background—To compare associations of patella lead, a lead pool that may capture aspects of both current bioavailable and cumulative lead dose thus offering advantages over tibia or blood lead, with blood lead in models of blood pressure and hypertension and to examine effect modification by age, sex and polymorphisms of the genes encoding for the vitamin D receptor (VDR) and δ-aminolevulinic acid dehydratase (ALAD).

Methods—Cross-sectional data in 652 current and former lead workers were analyzed.

Results—Blood lead, but not patella lead, was positively associated with systolic blood pressure. Neither lead measure was associated with diastolic blood pressure or hypertension status. There was no evidence of effect modification.

Conclusions—In these workers, blood lead was more relevant to elevations in blood pressure than was patella lead. Additional research will be required to determine whether patella lead assessment provides unique information on vascular risk from lead exposure.

Keywords

blood lead; blood pressure; δ-aminolevulinic acid dehydratase; hypertension; occupational lead exposure; patella lead; vitamin D receptor

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INTRODUCTION

A substantial body of literature indicates that there is a causal relation between lead exposure and elevated blood pressure [Navas-Acien et al., 2007; Navas-Acien et al., 2008; Nawrot et al., 2002]. The clinical significance of this is apparent in research showing a 55% increase in cardiovascular mortality in National Health and Nutrition Examination Survey (NHANES) III participants whose blood lead levels were in the highest tertile compared to those in the lowest [Menke et al., 2006]. Lead dose assessment in most studies examining associations between lead exposure and vascular outcomes has relied solely on blood lead [Navas-Acien et al., 2007; Navas-Acien et al., 2008]. Blood lead reflects both current external exposure and lead released from bone where > 90% of this cumulative toxicant is stored in adults [Barrry and Mossman, 1970]. Measurement of lead in bone, particularly cortical bone such as the tibia, assesses cumulative lead dose [Hu et al., 1998]. Cumulative lead dose may be an important risk factor as well. Indeed, in data from the first evaluation of the workers reported herein, both blood and tibia lead were associated with systolic blood pressure but only tibia lead was associated with hypertension [Lee et al., 2001]. Lead in trabecular bone (commonly measured in the patella or calcaneus) is thought to be more bioavailable than lead in cortical bone [Hu et al., 1998; Tsaih et al., 2001]. Thus, trabecular lead, as a measure of both cumulative and bioavailable lead, may be the most important dose measure for increased risk from lead, especially if recent release of lead from bone and distribution to target organs explains the observed health effects.

Despite the potential importance of bioavailable and cumulative lead dose, few studies have assessed bone lead and neither measure is required in medical surveillance of workers under either Occupational Safety & Health Administration (OSHA) lead standard [OSHA. 29 Code of Federal Regulations 1926.62 and 1910.1025]. Patella lead was obtained at the third evaluation in this longitudinal lead worker study. Herein, we examine associations of patella lead with systolic and diastolic blood pressure and hypertension in a cross-sectional analysis of data from the lead workers who participated in that evaluation. We compare and contrast these relations with blood lead and examine effect modification by age, gender and vitamin D receptor (VDR) and δ-aminolevulinic acid dehydratase (ALAD) genotypes. To our knowledge, this is the first report of associations between patella lead and blood pressure measures in participants with occupational exposure to lead.

MATERIALS AND METHODS

Study overview and design

We performed a cross-sectional analysis of data from 652 current and former lead workers who completed the third annual evaluation in a longitudinal study of the adverse health effects of inorganic lead exposure. Evaluations were performed between December, 1999 and June, 2001. Participation in the study was voluntary and all participants provided written, informed consent. The study protocol was approved by Institutional Review Boards at the SoonChunHyang University School of Medicine and the Johns Hopkins University Bloomberg School of Public Health.

Study Population

As previously described [Schwartz et al., 2001], workers were recruited from 26 plants that produced lead batteries, lead oxide, lead crystal, or radiators; or were secondary lead smelters. Workers were designated as lead workers based on the potential for exposure to lead in the manufacturing process. No medical exclusionary criteria were applied.

Data Collection

Data collection procedures have been previously reported [Schwartz et al., 2001]. Briefly, study participants completed a standardized questionnaire on demographics and medical and occupational history and had their height and weight measured. As previously described [Lee et al., 2001], systolic and fifth Korotkoff diastolic blood pressures were measured using a Hawksley random zero sphygmomanometer (Hawksley, Sussex, England) in a standardized protocol. Each participant provided a blood specimen for blood lead and genotyping and had patella lead concentration measured by ^{109}Cd-induced K-shell X-ray fluorescence (XRF).

Laboratory Methods

The lead biomarkers and genetic polymorphisms were measured as previously reported [Lee et al., 2001; Schwartz et al., 2001]. Blood lead was measured with an Hitachi 8100 Zeeman background-corrected atomic absorption spectrophotometer (Hitachi Ltd. Instruments, Tokyo, Japan) at the Institute of Industrial Medicine, a certified reference laboratory for lead in South Korea [Fernandez, 1975]. Patella lead was assessed via a 30-min. measurement of the left medial patella using ^{109}Cd to fluoresce the K-shell X-rays of lead. The lead X-rays were recorded with a radiation detector and then quantified and compared to calibration data to estimate the concentration of lead in bone [Todd, 2000; Todd and Chettle, 2003; Todd et al., 2002]. All point estimates, including negative values, were retained in the statistical analyses in order to minimize bias and avoid censoring of data [Kim et al., 1995]. The ALAD polymorphism assayed has two alleles: ALAD^1 and the variant, ALAD^2, which has a G to C transversion at codon 177 and is cleaved by *Msp*1. The VDR *Bsm*I polymorphism in intron 8 includes a common allele, denoted b, and a variant, denoted B, in which the *Bsm*I restriction enzyme site is absent. Amplification used primers originating in exon 7 and intron 8.

Statistical Analysis

The goals of the analysis were: 1) to compare and contrast associations of patella lead with systolic and diastolic blood pressure and hypertension status to those with blood lead; and 2) to compare effect modification by VDR and ALAD genotypes on the same associations. Statistical analysis was performed using Stata® (StataCorp: Stata Statistical Software: Release 7.0, Stata Corporation, College Station, TX 2000) and SAS statistical software (SAS Institute, Inc., Cary, NC, USA).

Initially, variable distributions were examined for normality. Since the distribution of patella lead was skewed, with the potential for influential datapoints at high concentrations, associations of natural log transformed patella lead were also examined. The SAS t-test procedure (including the Satterthwaite test for unequal variances) was used to compare

means for the selected demographic, exposure and health outcome measures from the initial evaluation of the 652 lead workers who completed the third evaluation with those from the 153 who did not. Chi-square testing was used when these measures were dichotomous. Linear regression modeling was used to evaluate relations between lead dose and blood pressure. Covariates evaluated included age (linear and quadratic terms), gender, body mass index (BMI; weight in kilograms divided by the square of height in meters), diabetes (based on participant report of physician diagnosis), antihypertensive and analgesic medication use, lead job duration, work status (current vs. former lead worker), and tobacco and alcohol use. Tobacco and alcohol use were analyzed both in terms of never, previous or current use, and in quartiles of lifetime tobacco or alcoholic beverages consumption. Final blood pressure models were adjusted for age (linear and quadratic terms), gender, body mass index, job duration, antihypertensive medication use, and quartiles of cumulative lifetime drinks for current alcohol users. Continuous independent variables were centered at the mean, except in the effect modification-by-age models, discussed below, in which age was centered at the 67^{th} percentile.

Effect modification by genotype, lead dose, gender and age was assessed in separate interaction models. Cross-product terms of VDR or ALAD genotypes with lead dose measures were added to separate models for each genotype. Effect modification by gender was evaluated in the same manner. To evaluate whether blood lead modified associations of patella lead and blood pressure, a cross-product term of blood lead, dichotomized at the median, and continuous patella lead was entered into the patella lead and blood pressure model. The procedure was reversed for assessing influence of patella lead on the relation between blood lead and blood pressure (i.e., a cross-product term of patella lead, dichotomized at the median, with continuous blood lead was entered into the model of blood lead and blood pressure). Lastly, models with cross-product terms for patella lead and age, dichotomized at the 67^{th} percentile per previous work in this dataset [Weaver et al., 2005], were evaluated to assess effect modification by age. Main regression models and age and gender interaction models were repeated using natural log transformed patella lead in separate models.

Logistic regression was used to model relations between lead dose measures (blood, patella and ln patella lead) and hypertension status. Two definitions of hypertension were modeled separately: 1) systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 mm Hg or use of antihypertensive medications; 2) physician diagnosis of hypertension as noted in the patient questionnaire. To assess effect modification by age and gender on relations between lead dose and hypertension status, cross-product terms of gender and age, dichotomized at the median, with lead dose were evaluated in separate models.

Models were evaluated for linear regression assumptions and the presence of outlying points using added variable plots [Weisberg, 1985], which are graphical summaries of the relation between Y and a particular X, adjusted for all of the other covariates. Each plot displays residuals and two lines: the regression line, and a line determined by a scatter plot smoothing method (lowess) that calculates a locally weighted least-squares estimate for each point in the scatter plot [Cleveland, 1979]. This allows an examination of the data for outliers that are overly influential, as evidenced by inconsistency between the lowess and regression lines.

The “lowess” function of the S-plus statistical software program (MathSoft, Seattle, WA, USA) was used to produce these plots. When applicable, models were repeated without outliers. Models were also assessed for collinearity through examination of variance inflation factors and conditional indices.

RESULTS

Selected Demographics, Exposure, and Health Outcome Measures

Information on demographics, lead biomarkers, blood pressure, and selected covariates from the third evaluation is presented in Table I. Women and former lead workers were well represented. The mean blood lead level reflects moderate occupational exposure. Blood and patella lead were correlated (Spearman correlation coefficient = 0.66; $p < 0.0001$). Based on data from the first evaluation, the 652 lead workers who completed the third evaluation, compared to the 153 who did not, were, on average, older, more likely to be women, and to have worked longer in lead exposed jobs (Table II). Both participants with the variant VDR genotype and former lead workers were more common among those who went on to complete the third evaluation, although the differences only reached borderline statistical significance ($p = 0.09$). Mean levels of the lead biomarkers and the blood pressure measures were similar in the two groups.

Associations Between Lead Dose and Blood Pressure

Neither patella lead nor ln-transformed patella lead was significantly associated with systolic blood pressure (Table III, model 1). In contrast, blood lead was associated with systolic blood pressure, both when modeled separately and when modeled with patella lead (Table III, models 2 and 3). No lead measure was associated with diastolic blood pressure (data not shown). No effect modification by age on associations between lead dose and blood pressure was observed in interaction models utilizing age dichotomized at the 67^{th} percentile (Table III, models 4 and 5 for systolic blood pressure). The results were similar when participants taking one or more antihypertensive medications were excluded from the analyses (n = 27). Blood lead did not modify the association between patella lead and either blood pressure measure, nor did patella lead alter the association between blood lead and blood pressure. Associations between lead dose (blood, patella, and ln patella) and blood pressure were not modified by gender or ALAD or VDR genotypes (models assessing effect modification by genotype on associations with systolic blood pressure are presented in Table IV).

Associations Between Lead Dose and Hypertension Status

Finally, using logistic regression, no lead dose measure (blood, patella, and ln patella) was significantly associated with hypertension by either definition (elevated blood pressure and/or use of medications [n = 100] or physician diagnosis of hypertension [n = 51]). Associations between lead dose and the former hypertension definition were not modified by age or gender. Effect modification by these factors on the latter definition of hypertension was not examined due to the small number of participants involved.

DISCUSSION

In this cross-sectional analysis of data from the third evaluation in a longitudinal study of Korean lead workers, we compared associations of patella and blood lead with blood pressure measures. We also determined whether several factors, including age, gender, and genetic polymorphisms modified these associations. No significant associations between patella lead and any blood pressure measure were observed and no effect modifiers were identified. In contrast, and consistent with our findings at the first evaluation (conducted a mean of 2.2 years earlier in the original cohort of 803 lead workers [Lee et al., 2001]), blood lead was positively associated with systolic blood pressure although, as for patella lead, the relations were not modified by ALAD or VDR genotypes.

There were two major goals of this analysis. First, we wanted to evaluate associations between patella lead and blood pressure measures since lead in trabecular bone is an important endogenous source of circulating lead that also reflects cumulative dose [Hu et al., 1998; Tsaih et al., 2001]. In retired lead workers, blood lead is correlated with trabecular bone lead indicating the importance of this lead source [Gerhardsson et al., 1993]. Stable isotope technique studies have shown that, in stable or recently reduced environmental exposure, as much as 40–70% of blood lead arises endogenously from bone [Smith et al., 1996; Gulson et al., 1995]. The association between blood lead and blood pressure and/or hypertension has been extensively studied. There is general consensus that the data, overall, support an association between increasing blood lead and blood pressure [Navas-Acien et al. 2007; Nawrot et al., 2002]. However, far fewer data are available on the association between cumulative lead dose and blood pressure [Navas-Acien et al., 2008]. Since studies have shown that patella lead is significantly correlated with blood lead [Hernandez-Avila et al., 1996; Hu et al., 1996b], including in this population [Weaver et al., 2005], patella lead might also be expected to be positively associated with blood pressure. However, patella lead also reflects bioavailable cumulative lead dose and the bioavailability is dependent on several factors.

Associations between trabecular bone lead and blood pressure measures have only been studied previously in three populations. Similar to our results, a cross-sectional analysis of data from the Normative Aging Study (involving a subset of 590 men from the larger general population study in the Boston, MA area; average age = 67 years; mean [range] blood and patella lead levels = 6.3 [< 1 μg/dL to 28] μg/dL and 32.1 [1 μg/g to 142 μg/g], respectively) found no significant association between patella lead and hypertension [Hu et al., 1996]. An analysis of longitudinal data from the same ongoing study revealed a significant association between patella lead and risk for development of hypertension during the follow-up period (mean follow-up time not provided but within 6 years) [Cheng et al., 2001]. However, again, consistent with our data, patella lead was not associated with systolic blood pressure in non-hypertensives at baseline. A study of a subset of 284 women from the Nurses' Health Study (average age = 59 years; mean [range] blood and patella lead levels = 3 [< 1 to 14] μg/dL and 17.3 [−5 μg/g to 87] μg/g, respectively) found an increased odds ratio for hypertension with patella lead [Korrick et al., 1999]. A study of 668 pregnant Latina women (average age = 31 years; geometric mean blood lead levels = 1.9 and 2.3 μg/dL in the third trimester and postpartum, respectively; mean calcaneus lead level = 10.7 μg/g postpartum) found that

calcaneus lead, measured at postpartum, was associated with systolic and diastolic blood pressures and an increased odds ratio for hypertension in the third trimester but not postpartum [Rothenberg et al., 2002].

The inconsistencies in the limited research to date on patella lead and vascular outcomes may be related to several factors. Pregnancy and post-menopause are periods of higher bone turnover in women which may increase release of lead from bone resulting in more bioavailability of trabecular lead. This may account for the significant cross-sectional associations noted in pregnant Latina women and in the Nurses' Health Study. Older men are also at risk for osteoporosis but generally at an older age than women. This difference may be a factor in the negative cross-sectional results in our work and in the Normative Aging Study. However, as assessed in our population through interaction models, we did not see an association between patella lead and blood pressure measures in older participants or in women. Longitudinal bone lead data have revealed a longer half-life of lead in cortical bone in older participants (over age 40 years) and in those with higher lifetime lead exposure (average blood lead > 25 μg/dl) [Brito et al., 2001]. Those data also suggested that this may also be the case for trabecular bone although the differences were not significant. If confirmed in other populations, this would suggest that patella lead in occupationally exposed workers is less bioavailable than in environmentally exposed controls since the dose is higher. Finally, greater measurement error in trabecular lead may bias analyses towards the null [Hu et al., 1998; Gerhardsson et al., 1993]. However, we found consistent associations of patella lead compared to blood and tibia lead in models of renal function in this population [Weaver et al., 2005]. In our occupational population, vascular effects from acute rather than chronic lead mechanisms do not appear to be an explanation since tibia lead was associated with systolic blood pressure and hypertension in evaluation one data. Additional research with patella lead, particularly in the occupational setting, will be required to fully understand the reasons for inconsistencies in the data to date.

The second goal of this study was to examine mechanisms for relations between patella lead and blood pressure. As lead exposure declines, lead-related toxicity is more likely to occur in the setting of multifactorial disease. Thus, identification of susceptible populations, due to genetic factors or chronic diseases that increase risk for lead-related toxicity, is increasingly important. We addressed this goal through interaction models examining effect modification by ALAD and VDR genotypes and dichotomized lead dose measures, as well as by age and gender as discussed above. Effect modification was not apparent in these models although higher patella lead levels were observed in participants with the variant VDR *Bsm*I allele [Theppeang et al., 2004].

There were two main limitations to our study. First, 153 study participants did not complete the third evaluation. The individuals who completed the study were, on average, older by about three years, and had worked for approximately 2 years longer than those who did not complete the study (as determined by data from the first evaluation). They were also more likely to be women. However, blood pressure and lead dose measures did not differ significantly between the two groups. Our adjustment for age, job duration, and gender in the statistical analyses makes us reasonably confident that the differences in these parameters did not affect the validity of our results. Another potential limitation of our study

was the skewed distribution of the patella lead measurements. As outlined in the methods section, we performed many of our analyses with natural log transformed patella to determine whether our results were unduly influenced by the higher patella lead datapoints. Our conclusions remained the same in these analyses. Lastly, the overall health of this working population, evidenced by lower BMI and blood pressure in comparison to European and U.S. populations [Moens et al., 1999], may limit the generalizability of our findings.

In conclusion, the positive association between blood lead and blood pressure observed in this analysis of data from the third evaluation is consistent with previously published results from the first evaluation [Lee et al., 2001] and suggests that lead and blood pressure may be related by acute mechanisms. Further, patella lead does not appear to be a significant risk factor for elevated blood pressure among our study participants. Finally, none of the effect modifiers we examined, including VDR and ALAD genotypes, age, gender and dichotomized lead dose, modified associations of lead dose measures with blood pressure and/or hypertension. However, given the potential for trabecular lead to provide unique information on a lead pool that is both cumulative and bioavailable and the limited number of studies that have measured it to date, additional research is needed to further evaluate the potential of this lead dose measure for research and medical surveillance in lead workers.

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Abbreviations

ALAD	δ-aminolevulinic acid dehydratase
BMI	body mass index
VDR	vitamin D receptor

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TABLE I

Selected demographic, exposure, and health outcome measures from the third evaluation of current and former lead workers, 1999 to 2001, Republic of Korea, n = 652

Characteristic	Number	%
Male gender	503	77.2
Tobacco use		
Never smokers	222	34.1
Current smokers	326	50.2
Former smokers	102	15.7
Alcohol use		
Never drinkers	198	30.4
Current drinkers	408	62.8
Former drinkers	44	6.8
Hypertension diagnosis	53	8.1
Hypertension medication use	27	4.1
Work status		
Current lead worker	452	69.3
Former lead worker	200	30.7
	Mean	SD
Age, years	43.3	9.8
Body mass index, kg/m^2	23.5	3.0
Systolic blood pressure, mm Hg	120.7	16.3
Diastolic blood pressure, mm Hg	74.1	12.6
Lead work job duration, years	10.0	6.5
Blood lead, μg/dL	30.9	16.7
Patella lead, μg Pb/g bone mineral	75.1	101.1

TABLE II

Selected characteristics from the first evaluation of the 652 Korean lead workers who completed the third evaluation compared to the 153 workers who did not.

	Third Evaluation Completers (N = 652)		Third Evaluation Non-completers (N = 153)		p-value
First Evaluation Characteristic	**Number**	**%**	**Number**	**%**	
Sex					
Male	503	77.2	137	89.5	
Female	149	22.8	16	10.5	< 0.01
Work status					
Current lead worker	569	87.3	141	92.2	
Former lead worker	83	12.7	12	7.8	0.09
Hypertension	48	7.4	10	6.5	0.72
VDR Bb or BB genotype	78	12.1	11	7.3	0.09
ALAD$^{1-2}$ genotype	63	9.8	16	10.7	0.74
	Mean	SD	Mean	SD	
Age, years	41.1	9.7	37.8	11.4	< 0.01
Systolic blood pressure, mm Hg	123.1	16.2	123.9	16.9	0.61
Diastolic blood pressure, mm Hg	75.8	11.9	75.3	12.3	0.67
Lead job duration, years	8.4	6.4	6.6	6.7	< 0.01
Blood lead, μg/dL	31.9	14.8	32.4	16.0	0.71
Tibia lead, μg/g bone mineral	37.5	41.8	35.8	33.5	0.59

TABLE III

Linear regression models[a] of associations between lead dose and systolic blood pressure among 652 Korean lead workers

Independent variable	β coefficient	SE β	p-value	Model r^2
Model 1				
Patella lead, μg/g	0.0059	0.0071	0.41	0.19
Model 2				
Blood lead, μg/dL	0.1007	0.0404	0.01	0.20
Model 3				
Patella lead, μg/g	−0.0017	0.0078	0.82	0.20
Blood lead, μg/dL	0.1048	0.0444	0.02	
Model 4[b]				
Intercept	121.63	0.6034	<0.01	0.19
Age, years	0.4448	0.1043	<0.01	
Patella lead, μg/g	*0.0043*	*0.0078*	*0.59*	
Patella lead, μg/g × age cat[1]	0.0066	0.0139	0.64	
Model 5[b]				
Intercept	121.15	1.6001	<0.01	0.20
Age, years	0.4529	0.1021	<0.01	
Blood lead, μg/dL	*0.1196*	*0.0603*	*0.05*	
Blood lead, μg/dL × age cat[1]	−0.0301	0.0714	0.67	

[a]The models also controlled for age (linear and quadratic terms), gender, body mass index, lead job duration, antihypertensive medication use, and cumulative lifetime drinks in current alcohol users (divided into quartiles).

[b]The oldest tertile of workers is the reference group (italized); the beta coefficient for this term is therefore the slope for the association between the lead variable and systolic blood pressure in the older workers. The slope in the younger age category (age cat[1] which is the youngest 67th percent) is obtained by adding the beta coefficient of the cross-product term (below the reference category) to the beta coefficient of the reference category (i.e., the slope for the association between patella lead and systolic blood pressure in the younger age group is 0.0109 [*0.0043* + 0.0066]). P-values for the cross-product terms of age and lead dose reflect the statistical significance of the difference between the slopes of the regression lines in the younger age category and in the oldest age group.

TABLE IV

Linear regression models[a] of effect modification by VDR and ALAD genotypes on associations between lead dose and systolic blood pressure among 652 Korean lead workers

Independent variable	β coefficient	SE β	p-value	Model r^2
Model 1				
ALAD[12]	−0.2437	1.9578	0.90	0.18
Patella lead, μg/g	*0.0063*	*0.0085*	*0.46*	
Patella* ALAD[12]	−0.0127	0.0304	0.68	
Model 2				
VDR Bb or BB	−0.1503	1.7816	0.93	0.18
Patella lead, μg/g	*0.0030*	*0.0083*	*0.72*	
Patella* VDR Bb or BB	−0.0041	0.0160	0.80	
Model 3				
ALAD[12]	−0. 2323	1.9355	0.90	0.19
Blood lead, μg/dL	*0.1030*	*0.0415*	*0.01*	
Blood* ALAD[12]	−0.0447	0.1176	0.70	
Model 4				
VDR Bb or BB	−0.7937	1.8222	0.66	0.19
Blood lead, μg/dL	*0.0972*	*0.0426*	*0.02*	
Blood* VDR Bb or BB	−0.0068	0.0935	0.94	

[a]The models also controlled for age (linear and quadratic terms), gender, body mass index, lead job duration, antihypertensive medication use, and cumulative lifetime drinks in current alcohol users (divided into quartiles).

[b]The common gene allele is the reference group (italized); the beta coefficient for this term is therefore the slope for the association between the lead variable and systolic blood pressure in workers with the common genotype. The slope in workers with the variant allele is obtained by adding the beta coefficient of the cross-product term (below the reference category) to the beta coefficient of the reference category (i.e., the slope for the association between patella lead and systolic blood pressure in workers with the variant $ALAD^2$ allele is −0.0064 [0.0063 + −0.0127]). P-values for the cross-product terms of gene and lead dose reflect the statistical significance of the difference between the slopes of the regression lines in participants with the variant gene and those with the common gene.