Lead exposure, polymorphisms in genes related to oxidative stress and risk of adult brain tumors

Parveen Bhatti[1,2], **Patricia A. Stewart**[3], **Amy Hutchinson**[4], **Nathaniel Rothman**[1], **Martha S. Linet**[1], **Peter D. Inskip**[1], and **Preetha Rajaraman**[1]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, DHHS, Bethesda, MD

[2]Program in Epidemiology, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA

[3]Stewart Exposure Assessments, LLC, Arlington, Virginia

[4]Core Genotyping Facility, Division of Cancer Epidemiology and Genetics, Advanced Technology Program, SAIC Frederick, Inc., National Cancer Institute, Frederick MD

Abstract

There is some evidence that oxidative stress plays a role in lead-induced toxicity. Mechanisms for dealing with oxidative stress may be of particular relevance in the brain, given the high rate of oxygen metabolism. Using a hospital-based case-control study, we investigated the role of oxidative stress in the potential carcinogenicity of lead through examination of effect modification of the association between occupational lead exposure and brain tumors by single nucleotide polymorphisms (SNPs) in genes with functions related to oxidative stress. The study included 362 patients with glioma [176 of which had glioblastoma (GBM)], 134 patients with meningioma and 494 controls. Lead exposure was estimated by expert review of detailed job history data for each participant. We evaluated effect modification with 142 SNPs using likelihood ratio tests that compared nested unconditional logistic regression models that did and did not include a cross-product term for cumulative lead exposure and genotype. When the analyses were restricted to cases with GBM, *RAC2* rs2239774 and two highly correlated *GPX1* polymorphisms (rs1050450 and rs18006688) were found to significantly modify the association with lead exposure ($p \leq 0.05$) after adjustment for multiple comparisons. Furthermore, the same *GPX1* polymorphisms and *XDH* rs7574920 were found to significantly modify the association between cumulative lead exposure and meningioma. While the results of this study provide some evidence that lead may cause GBM and meningioma through mechanisms related to oxidative damage, the results must be confirmed in other populations.

Keywords

glioma; meningioma; lead exposure; oxidative stress; polymorphism

Introduction

Inorganic lead is classified as a "probable" human carcinogen by the International Agency for Research on Cancer, but results from epidemiologic studies are mixed, and a mechanism for

*Correspondence and reprint requests to: Parveen Bhatti, Program in Epidemiology, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, P.O. Box 19024 M4-B874, Seattle, WA 98109, TEL: 206-667-7803, FAX: 206-667-4787, E-MAIL: pbhatti@fhcrc.org.

the potential carcinogenicity of lead has not been confirmed (1). There is some evidence that oxidative stress plays a role in lead-induced toxicity; lead has been shown to deplete antioxidant proteins and induce the production of reactive oxygen species (ROS) (2,3). However, the relevance of these mechanisms to lead-induced carcinogenesis remains uncertain (1,3).

Mechanisms for dealing with oxidative stress may be of particular relevance in the brain, given the high rate of oxygen metabolism (4). Epidemiologic studies investigating associations with lead exposure and brain tumors, however, have reported conflicting results which may be attributed to various factors including the use of crude exposure assessment techniques for lead (i.e. Job exposure matrix linked to occupation and industry titles or self-reported exposure) (5-12). Two previous studies have used blood lead measurements; however, the numbers of brain tumor cases were small (13,14). Lack of consideration of brain tumor subtypes by some of the studies may also contribute to the inconsistent results (5,10,12).

Using a large hospital based case-control study, we aimed to further elucidate the role of oxidative stress in the potential tumorigenicity of lead by examining effect modification of the association between job-related lead exposure and brain tumors, specifically glioma and meningioma, by single nucleotide polymorphisms (SNPs) in genes with functions related to oxidative stress.

Materials and Methods

Study population

The design and population for the NCI Brain Tumor Study have been described previously (15,16). Briefly, subjects were enrolled between 1994 and 1998 from three hospitals that were regional referral centers for brain tumors, located in Phoenix, Arizona; Boston, Massachusetts; and Pittsburgh, Pennsylvania. Eligible patients were 18 years of age or older with a first intracranial glioma, meningioma or acoustic neuroma. Because of the small numbers of acoustic neuroma cases, our analysis focused on glioma and meningioma only. Four hundred and eighty-nine patients with glioma and 197 patients with meningioma were successfully enrolled. Controls were selected from patients admitted to the same hospitals as cases for various non-neoplastic conditions (e.g. circulatory system disorders, musculoskeletal disorders, digestive disorders, injuries) and were frequency matched to cases based on age at interview, race/ethnicity, sex, hospital and residential proximity to the hospital. Seven hundred and ninety-nine controls were successfully enrolled. Study protocols were approved by the institutional review board of each participating institution, and written informed consent was obtained from each patient or proxy.

The present analysis is restricted to non-Hispanic whites that were genotyped for 9 SNPs in a candidate study of genes related to oxidative stress [362 patients with glioma, including 176 cases with glioblastoma (GBM), 134 patients with meningioma and 494 controls] (17). Genotype data for an additional 133 SNPs were available for a subset of participants with sufficient DNA (>750 ng) [263 patients with glioma (116 patients with GBM), 101 patients with meningioma and 330 controls] to be included in a study of "tag" SNPs in genes related to innate immunity.

Collection of work history data

Data collection for this study has been described in detail previously (16). A trained research nurse administered an in-person standardized questionnaire to each patient or proxy. For all patients, a life-time occupational history was obtained along with information on other potential risk factors for brain tumors. Job-specific questions developed by an expert industrial hygienist were asked for jobs with expected exposure to specific agents (18).

Lead exposure assessment

Information on occupational lead exposure from over 500 peer-reviewed articles and technical reports was summarized by job and decade (16). Using this information, each job reported by a study participant was assigned an estimated average airborne concentration (0, 5-9, 10-29, 30-49, 50-249 or $\geq$250 $\mu g/m^3$), an estimated average frequency of time exposed to lead (<1, 1-9, 10-29 or 30-40 hours/week) and an estimated probability of lead exposure (0, 1-9, 10-49, 50-89 or $\geq$90%), that was specific to each subject (e.g. tasks performed and workplace environment). Participants were considered lead-exposed if they had ever worked in a job with an exposure probability of >10%. Lifetime cumulative lead exposure ($\mu g/m^3$-y) was calculated by summing the product of the number of years in each lead exposed job, the midpoint of the estimated airborne concentration range and the midpoint of the estimated frequency across all jobs. Cumulative lead exposure was set to missing for individuals with incomplete information for any job in their lifetime job history (n = 15 for glioma cases, n = 2 for meningioma cases, n = 3 for controls), and these individuals were excluded from further analysis. The exposure assessment conducted for this analysis represents a refinement of the previous lead exposure assessment (16), which used ordinal values rather than midpoint concentration levels in the derivation of the cumulative lead exposure metric and did not exclude individuals with incomplete job history information.

Genetic analyses

One-hundred and forty-two SNPs within 21 genes with functions related to oxidative stress were selected and included in all analyses. Nine of these SNPs were chosen as potential functional candidates and were genotyped using a medium-throughput TaqMan assay (17). The remaining 133 SNPs were selected as part of an Illumina GoldenGate OPA panel of 1536 SNPs designed to tag 148 candidate innate immunity genes and their surrounding regions. Genes for the innate immunity panel were selected from known innate immune pathways (including oxidative response), and less than five percent of SNPs were forced into the choice of tag SNPs based on prior evidence from association studies. Tag SNPs were chosen from the SNPs that were genotyped as part of the International HapMap using the TagZilla algorithm with the following parameters: minor allele frequency > 5% among HapMap Caucasian samples; r^2 0.8; and greater weighting for SNPs with a design score of 1.1 (SNPs with a design score of less than 0.4 were designated as "obligate excludes"). All study subjects were genotyped at the National Cancer Institute Core Genotyping Facility (CGF: Advanced Technology Corporation, Gaithersburg, MD). All SNPs passed testing for Hardy-Weinberg Equilibrium (p > 0.001).

Quality control specimens included replicate samples from three non-study participants and blinded duplicate samples from 21 to 89 study subjects interspersed among cases and controls. Percent agreement among the replicates ranged from 97.9 to 100% and concordance for duplicates ranged from 99.3 to 100%.

Statistical analyses

Unconditional logistic regression was used to evaluate the association between lifetime cumulative lead exposure and risk of glioma and meningioma and the association between all 142 SNPs and risk of glioma and meningioma. All analyses were repeated, restricting the cases definition to those individuals diagnosed specifically with GBM. To increase the power of the analyses, cumulative lead exposure was evaluated as a continuous variable, and a dominant model of effect was assumed for all SNPs. We chose not to evaluate cumulative lead exposure as a categorical variable given the small numbers of cases that would have remained in each category of exposure when stratifying by genotype. Based on visual inspection, the association between categories of cumulative lead exposure and the log odds of glioma and meningioma among the entire group of cases and controls was consistent with a linear dose-response

relationship (results not shown). Thus, evaluation of cumulative lead exposure as a continuous variable in our models was deemed appropriate. The study matching variables age, sex, hospital and residential proximity to the hospital were included in all analyses. All statistical analyses were completed in STATA (Version 10, College Station, Texas).

Effect modification was evaluated with likelihood ratio tests comparing nested unconditional logistic regression models that did and did not include a cross-product term for cumulative lead exposure and genotype. Odds ratios (ORs) and 95% confidence intervals for the association between cumulative lead exposure and glioma and meningioma were calculated for carriers and non-carriers of each variant. Adjusted p-values for SNP effects and effect modification taking into account multiple comparisons within each tumor type were calculated using the false discovery rate (19). To evaluate potential bias introduced by using hospital-based controls, analyses were repeated excluding one major subset of disease controls at a time.

Results

Table 1 provides the distribution of sex, age, recruitment site and cumulative lead exposure among cases and controls. For those individuals with complete exposure information among this group, the mean values (standard deviations) for cumulative lead exposure among glioma cases (n = 347), GBM cases (n = 165), meningioma cases (n=132) and controls (n=491) were 70.5 (193.8), 97.5 (233.9), 101.1 (408.7) and 69.7 $\mu g/m^3$-y (248.8), respectively. For glioma, GBM and meningioma, a 100 $\mu g/m^3$-y increase in cumulative lead exposure was associated with ORs of 1.0 (95% CI: 0.9, 1.1), 1.0 (95% CI: 0.9, 1.1) and 1.1 (95% CI: 1.0, 1.2), respectively. The point estimates for these associations remained relatively unchanged after excluding different groups of disease controls from the analysis one at a time (results not shown).

SNP associations and genotype frequencies are presented in Table 2 for those SNPs that demonstrated a statistically significant association (p ≤ 0.05) with one or more brain tumor types or those SNPs that demonstrated statistically significant effect modification of the association between cumulative lead exposure and one or more brain tumor types. Results for the remaining SNPs can be made available upon request. None of the SNP-tumor associations remained significant after adjusting for multiple comparisons.

The results for SNPs demonstrating statistically significant effect modification of the relationship between lead and one or more of glioma, GBM or meningioma are summarized in Table 3. Results for the remaining SNPs can be made available upon request. None of the interactions with glioma shown in Table 3 remained significant after adjustment for multiple comparisons. However, after restricting the analysis to cases with GBM, two *GPX1* polymorphisms (rs1050450 and rs18006688) and *RAC2* rs2239774 were found to significantly modify the association with cumulative lead exposure (p = 0.03 for all three SNPs). Using data from the SNP500 website (http://snp500cancer.nci.nih.gov) with the Haploview software package (20), the two *GPX1* polymorphisms were found to be highly correlated ($r^2 = 0.9$). These *GPX1* polymorphisms (rs1050450 and rs18006688) and *XDH* rs7574920 were found to significantly modify the association between cumulative lead exposure and meningioma (p = 0.03, p = 0.03, p = 0.05, respectively) (Table 3).

Carriers of the *GPX1* variants were found to have increased lead-GBM and lead-meningioma dose-response relationships compared to the homozygous wildtype subjects (Table 3). Carriers of the *RAC2* variant were found to have a decreased lead-GBM dose-response relationship compared to homozygous wildtype subjects. For the *XDH* polymorphism, carriers were found to have a decreased lead-meningioma dose-response relationship compared to homozygous wildtype subjects. The point estimates provided in Tables 3 were similar after different groups

of disease controls from the analysis were excluded one at a time, with the point estimate for risk of meningioma among homozygous wildtype subjects for the *XDH* polymorphism being slightly higher when controls with circulatory system disorders were excluded (results not shown).

Discussion

After adjustment for multiple comparisons, there were no significant associations between any of the 142 SNPs involved in oxidative stress pathways and either glioma or meningioma. This remained true even when restricting the analyses to patients with GBM, the most common and aggressive sub-type of glioma. However, polymorphisms in the *RAC2* and *GPX1* genes were found to significantly modify the association between cumulative lead exposure and risk of GBM even after adjustment for multiple comparisons. In addition to a polymorphism in the *XDH* gene, two highly correlated polymorphisms in the *GPX1* gene were also found to significantly modify the association between cumulative lead exposure and risk of meningioma.

Among studies that specifically examined glioma or looked at all brain tumor types (of which glioma was typically the most frequent), results have been mixed (5,6,9-14,16,21). We did not observe a statistically significant association between cumulative lead exposure and risk of glioma or GBM. However, we did observe statistically significant evidence of differential lead-GBM dose-response associations among carriers and non-carriers of three SNPs.

Given the rarity of meningioma, not many studies have evaluated the association of these tumors with lead exposure. Nonetheless, three previous studies, as well as a previously published analysis of these data, have demonstrated positive associations between lead exposure and risk of meningioma (6,7,9,16). Consistent with our previous analysis that used a slightly different method of exposure categorization, we observed a statistically significant association between cumulative lead exposure and risk of meningioma.

RAC2 is an enzyme involved in regulating the production of reactive oxygen species (22). While over-expression and mutations of *RAC2* has been previously reported in brain tumors (23,24), the results of a recent study found *RAC2* to be rarely mutated in gliomas (22). In that study, all six coding exons of *RAC2* were sequenced among 78 gliomas (including 18 GBMs), and the rs2239774 polymorphism was most frequently observed (20%), but there was no association with any particular subtype of glioma (22). Further work is required to determine the impact of this polymorphism and lead exposure on RAC2 activity.

GPX1 is a ubiquitously expressed enzyme that protects tissues from oxidative damage (25). While the two *GPX1* polymorphisms that we examined in our study may be linked with other SNPs or gene regions that are in fact causing the observed effect modification, *GPX1* rs1050450 has been shown to have a functional impact on GPX1 enzyme activity (8), and, as such, may be the causal variant. The variant GPX1 enzyme is less responsive to stimulation and may promote the development of cancer because of reduced levels of protection against oxidative damage from ROS that may be generated by lead. Lead has also been shown to decrease the activity of GPX1 by binding to the enzyme (26). This action, coupled with the decreased responsiveness of the GPX1 variant enzyme to selenium, may also result in reduced levels of protection against oxidative damage.

We also observed effect modification of the relationship between lead and meningioma by the rs7574920 polymorphism of the *XDH* gene. XDH is converted to xanthine oxidase, which is known to generate ROS in mammalian cells (27). In hamster cell lines, exposure to lead has been shown to stimulate the activity of xanthine oxidase (28). Thus, the rs7574920 polymorphism in *XDH* (or another SNP or region that is in linkage disequilibrium) may make

the xanthine oxidase enzyme less responsive to stimulation by lead, resulting in the reduced production ROS, and thus less cellular damage.

Our findings for GBM and meningioma persisted after controlling for multiple comparisons. Our analyses with exclusion of specific subsets of controls one at time suggested that a systematic bias in our results due to the use of hospital controls was unlikely. Nonetheless, given the small numbers of GBM and meningioma cases and the exploratory nature of the study, chance may explain our results.

Use of a biomarker for cumulative lead exposure such as bone lead measurements rather than exposure assessment based on self-report would have been ideal. However, evaluation of the association between lead exposure and brain tumors was not the primary objective of this study when it was initiated, and, as such, biomarker data for lead exposure were not collected.

While the results of our study provide evidence that lead may exert carcinogenic effects through mechanisms related to oxidative damage, the results must be confirmed in other populations. Pooled analyses from several epidemiologic studies would be helpful to allow for more conclusive examinations of potential effect modification of the lead-GBM and lead-meningioma associations by specific genotypes. However, this will require concerted efforts to obtain high quality occupational lead exposure data. Future studies may consider evaluating markers of oxidative stress in lead exposed populations to evaluate the role of oxidative stress as a mechanism for lead-induced carcinogenicity, though it may be difficult to determine which biomarkers are most relevant.

Acknowledgments

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Table 1

Demographic and cumulative lead exposure distributions for participants with glioma, glioblastoma, meningioma and controls in the NCI Adult Brain Tumor Study

Characteristic	Glioma (n = 362)	Glioblastoma[*] (n = 176)	Meningioma (n = 134)	Controls (n = 494)
Sex, n (%)				
Male	198 (55)	92 (52)	30 (22)	227 (46)
Female	164 (45)	84 (48)	104 (78)	267 (54)
Age at interview, n (%)				
18-29	41 (11)	3 (2)	1 (1)	55 (11)
30-49	137 (38)	37 (21)	53 (40)	209 (42)
50-69	121 (33)	83 (47)	57 (43)	171 (35)
70-90	63 (17)	53 (30)	23 (18)	59 (12)
Hospital site, n (%)				
Phoenix, AZ	160 (44)	70 (40)	58 (43)	229 (46)
Boston, MA	133 (37)	63 (36)	65 (49)	181 (37)
Pittsburgh, PA	69 (19)	43 (24)	11 (8)	84 (17)
Cumulative lead exposure ($\mu g/m^3$-y), n (%)				
0	201 (56)	92 (52)	93 (69)	281 (57)
>0 – 150	102 (28)	45 (26)	24 (18)	149 (30)
>150 - 300	19 (5)	10 (6)	5 (4)	29 (6)
>300 – 450	10 (3)	6 (2)	3 (2)	14 (3)
>450 – 600	3 (1)	2 (1)	2 (2)	3 (1)
>600	12 (3)	10 (6)	5 (4)	15 (3)
Unknown	15 (4)	11 (6)	2 (2)	3 (1)

[*] Cases with glioblastoma are a subset of the cases with glioma

Table 2

Risk of glioma, glioblastoma and meningioma with single nucleotide polymorphisms in genes related to oxidative stress in the NCI Brain Tumor Study

Gene	rs#	Genotype	Controls (%)‡	Glioma		Glioblastoma*		Meningioma	
				Cases (%)‡	OR (95% CI)	Cases (%)‡	OR (95% CI)	Cases (%)‡	OR (95% CI)
CAT	rs769214[†]	AA	207 (45)	152 (47)	1	75 (49)	1	52 (44)	1
		AG/GG	250 (55)	172 (53)	0.9 (0.7, 1.2)	79 (51)	0.9 (0.6, 1.3)	66 (56)	1.1 (0.7, 1.7)
CAT	rs1001179[†]	TT	249 (57)	186 (58)	1	85 (57)	1	72 (61)	1
		TC/CC	186 (42)	132 (42)	1.0 (0.7, 1.3)	65 (43)	1.0 (0.7, 1.5)	46 (39)	0.8 (0.5, 1.2)
GPX1	rs1050450[†§]	CC	236 (52)	158 (48)	1	74 (47)	1	55 (46)	1
		CT/TT	221 (48)	169 (52)	1.1 (0.8, 1.5)	83 (53)	1.1 (0.8, 1.6)	66 (55)	1.3 (0.8, 1.9)
LPO	rs8178407[†]	AA	131 (40)	92 (37)	1	43 (37)	1	29 (29)	1
		AG/GG	196 (60)	159 (63)	1.2 (0.9, 1.7)	73 (63)	1.2 (0.7, 1.9)	70 (70)	1.6 (1.0, 2.7)
MPO	rs4401102[†]	GG	183 (56)	137 (55)	1	60 (52)	1	55 (55)	1
		GA/AA	144 (44)	114 (45)	1.0 (0.7, 1.4)	56 (48)	1.2 (0.8, 1.9)	45 (45)	1.0 (0.6, 1.7)
NCF2	rs11579965	GG	291 (89)	211 (84)	1	102 (88)	1	79 (79)	1
		GC/CC	37 (11)	40 (16)	1.5 (0.9, 2.5)	14 (12)	1.1 (0.5, 2.3)	21 (21)	2.0 (1.1, 3.9)
NCF2	rs11588654[†]	AA	150 (46)	125 (50)	1	52 (45)	1	52 (53)	1
		AG/GG	178 (54)	126 (50)	0.8 (0.6, 1.2)	64 (55)	1.0 (0.6, 1.6)	47 (47)	0.7 (0.4, 1.2)
NCF4	rs2075938[†]	AA	181 (55)	143 (57)	1	70 (60)	1	54 (54)	1
		AG/GG	146 (45)	108 (43)	1.0 (0.7, 1.4)	46 (40)	0.8 (0.5, 1.3)	46 (46)	1.1 (0.7, 1.8)
NCF4	rs5756381[†]	AA	185 (56)	147 (59)	1	70 (60)	1	55 (55)	1
		AG/GG	143 (44)	104 (41)	0.9 (0.7, 1.3)	46 (40)	0.8 (0.5, 1.3)	45 (45)	1.1 (0.7, 1.8)
NCF4	rs8137602[†]	CC	261 (80)	216 (86)	1	101 (87)	1	87 (87)	1
		CG/GG	67 (20)	35 (14)	0.6 (0.4, 1.0)	15 (13)	0.5 (0.3, 1.0)	13 (13)	0.6 (0.3, 1.2)
NOS1	rs483589[†]	CC	119 (37)	96 (38)	1	48 (41)	1	37 (37)	1
		CT/TT	207 (64)	155 (62)	1.0 (0.7, 1.3)	68 (59)	0.9 (0.6, 1.5)	63 (63)	1.0 (0.6, 1.6)
NOS1	rs545654[†]	GG	92 (28)	56 (22)	1	29 (25)	1	27 (27)	1
		GA/AA	235 (72)	195 (78)	1.3 (0.9, 2.0)	87 (75)	1.1 (0.7, 1.9)	73 (73)	1.0 (0.6, 1.7)
NOS1	rs816293[†]	GG	109 (33)	93 (38)	1	47 (41)	1	40 (40)	1
		GC/CC	218 (67)	155 (63)	0.9 (0.6, 1.2)	69 (59)	0.9 (0.5, 1.4)	60 (60)	0.7 (0.4, 1.1)

Gene	rs#	Genotype	Controls (%)‡	Glioma			Glioblastoma*			Meningioma	
				Cases (%)†‡	OR (95% CI)		Cases (%)†‡	OR (95% CI)		Cases (%)†‡	OR (95% CI)
NOS1	rs816351	TT	269 (82)	219 (87)	1		104 (90)	1		78 (79)	1
		TC/CC	59 (18)	32 (13)	0.6 (0.4, 1.0)		12 (10)	0.5 (0.3, 1.0)		21 (21)	1.4 (0.8, 2.6)
NOS1	rs1123425†	TT	114 (35)	76 (30)	1		42 (36)	1		24 (24)	1
		TC/CC	212 (65)	175 (70)	1.2 (0.8, 1.7)		74 (64)	0.8 (0.5, 1.3)		76 (76)	1.7 (1.0, 3.0)
NOS1	rs1353939†	GG	206 (63)	154 (61)	1		68 (59)	1		61 (61)	1
		GA/AA	121 (37)	97 (39)	1.1 (0.8, 1.5)		48 (41)	1.2 (0.8, 1.9)		39 (39)	1.2 (0.7, 2.0)
NOS1	rs2291908†	AA	162 (50)	112 (45)	1		49 (42)	1		44 (44)	1
		AG/GG	164 (50)	139 (55)	1.3 (0.9, 1.7)		67 (58)	1.4 (0.9, 2.2)		56 (56)	1.4 (0.8, 2.2)
NOS1	rs4767535†	GG	94 (29)	65 (26)	1		29 (25)	1		26 (26)	1
		GA/AA	233 (71)	186 (74)	1.1 (0.8, 1.6)		87 (75)	1.0 (0.6, 1.8)		74 (74)	1.1 (0.6, 1.9)
NOS1	rs6490121†	CC	147 (45)	104 (42)	1		50 (43)	1		41 (41)	1
		CT/TT	181 (55)	146 (58)	1.1 (0.8, 1.6)		66 (57)	1.1 (0.7, 1.7)		59 (59)	1.2 (0.7, 1.9)
NOS1	rs7298903†	AA	271 (83)	206 (82)	1		97 (84)	1		82 (83)	1
		AG/GG	55 (17)	44 (18)	1.0 (0.7, 1.6)		19 (16)	0.9 (0.5, 1.7)		17 (17)	1.2 (0.6, 2.3)
NOS1	rs10850803	TT	272 (83)	198 (79)	1		91 (78)	1		72 (72)	1
		TC/CC	54 (17)	52 (21)	1.3 (0.9, 2.0)		25 (22)	1.4 (0.8, 2.5)		28 (28)	2.0 (1.1, 3.6)
NOS2A	rs944725†	GG	117 (36)	92 (37)	1		42 (36)	1		40 (40)	1
		GA/AA	211 (64)	159 (63)	1.0 (0.7, 1.4)		74 (64)	0.8 (0.5, 1.3)		60 (60)	0.7 (0.4, 1.2)
NOS2A	rs2297516†	TT	119 (37)	99 (39)	1		46 (40)	1		37 (37)	1
		TG/GG	207 (64)	152 (61)	0.9 (0.7, 1.3)		70 (60)	0.9 (0.6, 1.4)		63 (63)	1.0 (0.6, 1.6)
NOS2A	rs2779252†	CC	298 (91)	231 (92)	1		109 (94)	1		91 (91)	1
		CA/AA	29 (9)	20 (8)	0.8 (0.5, 1.5)		7 (6)	0.6 (0.3, 1.6)		9 (9)	1.2 (0.5, 2.7)
NOS2A	rs4795067†	TT	141 (43)	104 (41)	1		55 (47)	1		38 (38)	1
		TC/CC	187 (57)	147 (59)	1.0 (0.7, 1.5)		61 (53)	0.8 (0.5, 1.3)		62 (62)	1.1 (0.7, 1.9)
NOS2A	rs8072199	GG	124 (38)	79 (31)	1		40 (34)	1		28 (28)	1
		GA/AA	203 (62)	172 (69)	1.3 (0.9, 1.8)		76 (66)	1.0 (0.6, 1.6)		71 (72)	1.7 (1.0, 3.0)
NOS3	rs1799983†	TT	203 (44)	150 (46)	1		73 (47)	1		52 (43)	1
		TG/GG	261 (56)	176 (54)	0.9 (0.7, 1.2)		84 (54)	1.0 (0.6, 1.4)		69 (57)	0.9 (0.6, 1.4)

Gene	rs#	Genotype	Controls (%)[†‡]	Glioma		Glioblastoma[*]		Meningioma	
				Cases (%)[†‡]	OR (95% CI)	Cases (%)[†‡]	OR (95% CI)	Cases (%)[†‡]	OR (95% CI)
NOS3	rs4496877[†]	GG	107 (33)	88 (35)	1	35 (30)	1	39 (39)	1
		GT/TT	219 (67)	163 (65)	0.9 (0.6, 1.3)	81 (70)	1.1 (0.7, 1.8)	61 (61)	0.7 (0.4, 1.1)
NOS3	rs12703107[†]	GG	188 (57)	136 (54)	1	66 57	1	51 (52)	1
		GT/TT	140 (43)	115 (46)	1.1 (0.8, 1.6)	50 (43)	1.1 (0.7, 1.8)	48 (48)	1.3 (0.8, 2.1)
RAC1	rs836554[†]	CC	193 (59)	146 (58)	1	68 (59)	1	52 (52)	1
		CT/TT	134 (41)	105 (42)	1.1 (0.8, 1.5)	48 (41)	0.9 (0.6, 1.5)	48 (48)	1.3 (0.8, 2.2)
RAC1	rs6463554[†]	GG	235 (72)	198 (79)	1	95 (82)	1	69 (69)	1
		GC/CC	93 (28)	53 (21)	0.7 (0.5, 1.0)	21 (18)	0.5 (0.3, 0.9)	31 (31)	1.1 (0.7, 1.9)
RAC1	rs3729790[†]	GG	193 (59)	148 (59)	1	68 (59)	1	64 (64)	1
		GA/AA	135 (41)	103 (41)	1.0 (0.7, 1.5)	48 (41)	1.1 (0.7, 1.8)	36 (36)	0.7 (0.5, 1.2)
RAC2	rs6572[†]	GG	108 (33)	80 (32)	1	37 (32)	1	26 (26)	1
		GC/CC	220 (67)	171 (68)	1.0 (0.7, 1.5)	79 (68)	1.2 (0.7, 1.9)	74 (74)	1.4 (0.8, 2.4)
RAC2	rs1476002[†]	AA	248 (76)	191 (76)	1	90 (78)	1	68 (68)	1
		AG/GG	79 (24)	60 (24)	1.0 (0.7, 1.4)	26 (22)	0.8 (0.5, 1.4)	32 (32)	1.6 (0.9, 2.7)
RAC2	rs2213430	AA	102 (31)	69 (27)	1	30 (26)	1	37 (27)	1
		AG/GG	226 (69)	182 (73)	1.3 (0.9, 1.8)	86 (74)	1.2 (0.7, 2.0)	63 (63)	0.5 (0.3, 0.8)
RAC2	rs2239774[†]	CC	239 (73)	186 (74)	1	89 (77)	1	73 (73)	1
		CG/GG	89 (27)	65 (26)	0.9 (0.6, 1.4)	27 (23)	0.9 (0.6, 1.6)	27 (27)	1.2 (0.7, 2.1)
RAC2	rs2239775[†]	GG	240 (73)	202 (80)	1	88 (76)	1	66 (66)	1
		GT/TT	87 (27)	49 (20)	0.6 (0.4, 0.9)	28 (24)	0.8 (0.5, 1.3)	34 (34)	1.8 (1.1, 3.1)
RAC2	rs4820274[†]	GG	252 (77)	185 (74)	1	87 (75)	1	67 (67)	1
		GC/CC	75 (23)	66 (26)	1.2 (0.8, 1.8)	29 (25)	1.3 (0.8, 2.2)	33 (33)	1.9 (1.1, 3.3)
RAC2	rs4821609[†]	TT	161 (49)	132 (53)	1	61 (53)	1	48 (48)	1
		TC/CC	165 (51)	119 (47)	0.9 (0.6, 1.2)	55 (47)	0.9 (0.6, 1.4)	52 (52)	1.1 (0.6, 1.8)
RAC2	rs9607432[†]	AA	267 (82)	199 (79)	1	94 (81)	1	75 (75)	1
		AG/GG	60 (18)	52 (21)	1.2 (0.8, 1.8)	22 (19)	1.3 (0.7, 2.4)	25 (25)	1.9 (1.0, 3.4)
SOD1	rs202445[†]	TT	209 (64)	165 (65)	1	72 (62)	1	72 (72)	1
		TC/CC	117 (36)	86 (34)	0.9 (0.6, 1.3)	44 (38)	0.9 (0.6, 1.5)	28 (28)	0.7 (0.4, 1.2)

Gene	rs#	Genotype	Controls (%)[‡]	Glioma		Glioblastoma[*]		Meningioma	
				Cases (%)[‡]	OR (95% CI)	Cases (%)[‡]	OR (95% CI)	Cases (%)[‡]	OR (95% CI)
SOD2	rs4880[†]	TT	121 (27)	79 (25)	1	37 (24)	1	39 (33)	1
		TC/CC	327 (73)	240 (75)	1.1 (0.8, 1.6)	117 (76)	1.1 (0.7, 1.8)	80 (67)	0.8 (0.5, 1.2)
SOD2	rs2758352	TT	194 (59)	156 (62)	1	78 (67)	1	54 (54)	1
		TC/CC	133 (41)	94 (38)	0.9 (0.6, 1.3)	38 (33)	0.6 (0.4, 1.0)	46 (46)	1.1 (0.7, 1.8)
SOD2	rs5746136[†]	GG	163 (50)	119 (47)	1	49 (42)	1	44 (44)	1
		GA/AA	164 (50)	132 (53)	1.1 (0.8, 1.5)	67 (58)	1.4 (0.9, 2.3)	56 (56)	1.4 (0.9, 2.2)
SOD2	rs5746151[†]	GG	289 (88)	219 (87)	1	100 (86)	1	83 (83)	1
		AG/AA	39 (12)	32 (13)	1.1 (0.7, 1.8)	16 (14)	1.6 (0.8, 3.2)	17 (17)	1.9 (0.9, 3.9)
SOD3	rs699473[†§]	CC	208 (45)	125 (39)	1	66 (42)	1	41 (34)	1
		CT/TT	251 (55)	199 (61)	1.3 (1.0, 1.8)	90 (58)	1.1 (0.8, 1.7)	80 (66)	1.7 (1.1, 2.6)
XDH	rs206849	TT	102 (31)	99 (39)	1	49 (42)	1	38 (38)	1
		TC/CC	224 (69)	152 (61)	0.7 (0.5, 1.0)	67 (58)	0.6 (0.4, 1.0)	62 (62)	0.9 (0.6, 1.5)
XDH	rs207444	TT	290 (89)	226 (90)	1	103 (89)	1	96 (96)	1
		TC/CC	37 (11)	25 (10)	0.9 (0.5, 1.6)	13 (11)	1.0 (0.5, 2.0)	4 (4)	0.3 (0.09, 0.8)
XDH	rs494852	GG	235 (72)	157 (63)	1	71 (61)	1	62 (62)	1
		GA/AA	92 (28)	94 (37)	1.5 (1.1, 2.2)	45 (39)	1.6 (1.0, 2.7)	38 (38)	1.4 (0.9, 2.4)
XDH	rs1429376[†]	TT	175 (53)	133 (53)	1	61 (53)	1	51 (51)	1
		TG/GG	152 (46)	118 (47)	1.0 (0.7, 1.4)	55 (47)	1.0 (0.6, 1.6)	49 (49)	1.0 (0.6, 1.6)
XDH	rs7574920[†]	CC	77 (24)	63 (25)	1	21 (18)	1	20 (20)	1
		CG/GG	250 (76)	187 (75)	0.9 (0.6, 1.3)	95 (82)	1.4 (0.8, 2.5)	80 (80)	1.2 (0.6, 2.1)
XDH	rs6718606[†]	GG	221 (67)	157 (63)	1	66 (57)	1	66 (66)	1
		GC/CC	107 (33)	94 (37)	1.3 (0.9, 1.8)	50 (43)	1.8 (1.1, 2.8)	34 (34)	1.0 (0.6, 1.7)
XDH	rs17038412[†]	AA	222 (68)	174 (69)	1	77 (66)	1	66 (66)	1
		AT/TT	106 (32)	77 (31)	0.9 (0.6, 1.3)	39 (34)	1.0 (0.6, 1.6)	34 (34)	1.1 (0.6, 1.8)

[*] Cases with glioblastoma are a subset of the cases with glioma

[†] See Table 3 for effect modification results with cumulative lead exposure

[‡] Same group of controls used for each tumor type; Final numbers consist of individuals with non-missing data for cumulative lead exposure that were successfully genotyped

[§]*GPX1* rs1050450 is highly correlated with rs1800668 ($r^2 = 0.9$); *SOD3* rs699473 is highly correlated with rs2284659 ($r^2 = 0.9$)

Table 3

Risk of glioma, glioblastoma and meningioma with cumulative exposure to lead by genotype for single nucleotide polymorphisms in genes related to oxidative stress in the NCI Brain Tumor Study[*]

		Continuous Cumulative Lead (OR/100 µg/m³·y)								
		Glioma			Glioblastoma[†]			Meningioma		
Gene	rs#	Homozygous wildtype OR (95% CI)	Heterozygous/ Homozygous variant OR (95% CI)	p-int	Homozygous wildtype OR (95% CI)	Heterozygous/ Homozygous variant OR (95% CI)	p-int	Homozygous wildtype OR (95% CI)	Heterozygous/ Homozygous variant OR (95% CI)	p-int
CAT	rs769214	1.1 (0.9, 1.2)	0.9 (0.8, 1.0)	0.1	1.1 (1.0, 1.3)	1.0 (0.9, 1.1)	0.1	1.3 (1.1, 1.6)	1.0 (0.9, 1.1)	0.003
CAT	rs1001179	0.9 (0.8, 1.0)	1.0 (0.9, 1.2)	0.3	1.0 (0.9, 1.1)	1.1 (1.0, 1.3)	0.05	1.1 (1.0, 1.1)	1.2 (1.0, 1.4)	0.4
GPX1	rs1050450[†‡]	0.9 (0.8, 1.0)	1.1 (1.0, 1.3)	0.007	0.9 (0.8, 1.1)	1.3 (1.1, 1.5)	0.0004[§]	0.9 (0.7, 1.2)	1.4 (1.1, 1.8)	0.0002[§]
LPO	rs8178407	1.0 (0.9, 1.2)	1.0 (0.9, 1.1)	0.7	1.1 (0.9, 1.2)	1.0 (0.9, 1.1)	0.4	0.04 (0.0004, 3.5)	1.1 (1.0, 1.1)	0.002
MPO	rs4401102	1.1 (0.9, 1.2)	0.9 (0.8, 1.1)	0.2	1.1 (0.9, 1.3)	0.9 (0.8, 1.1)	0.09	0.4 (0.1, 1.6)	1.1 (1.0, 1.1)	0.02
NCF2	rs11588654	1.0 (0.9, 1.2)	1.0 (0.9, 1.1)	0.7	1.0 (0.8, 1.2)	1.0 (0.9, 1.1)	0.8	1.3 (1.0, 1.6)	1.0 (0.9, 1.1)	0.03
NCF4	rs2075938	1.0 (0.8, 1.1)	1.0 (0.9, 1.1)	0.7	1.0 (0.8, 1.2)	1.0 (0.9, 1.1)	0.9	1.2 (1.0, 1.3)	0.9 (0.6, 1.4)	0.02
NCF4	rs5756381	1.0 (0.8, 1.1)	1.0 (0.9, 1.1)	0.8	1.0 (0.9, 1.2)	1.0 (0.9, 1.1)	0.8	1.2 (1.0, 1.3)	0.9 (0.6, 1.4)	0.02
NCF4	rs8137602	1.0 (0.9, 1.1)	0.9 (0.8, 1.1)	0.4	1.0 (0.9, 1.2)	0.9 (0.7, 1.2)	0.4	1.1 (1.0, 1.3)	0.4 (0.03, 4.7)	0.02
NOS1	rs483589	1.0 (0.9, 1.1)	1.0 (0.9, 1.1)	0.6	1.0 (0.8, 1.1)	1.1 (0.9, 1.3)	0.3	0.6 (0.2, 1.5)	1.2 (1.0, 1.3)	0.003
NOS1	rs545654	0.7 (0.5, 1.1)	1.0 (0.9, 1.1)	0.09	0.5 (0.2, 1.2)	1.0 (0.9, 1.1)	0.02	1.0 (0.8, 1.4)	1.1 (1.0, 1.1)	0.9
NOS1	rs816293	0.9 (0.8, 1.1)	1.0 (0.9, 1.2)	0.2	1.0 (0.8, 1.1)	1.1 (0.9, 1.3)	0.2	0.9 (0.7, 1.2)	1.2 (1.0, 1.3)	0.02
NOS1	rs1123425	1.1 (0.9, 1.2)	0.9 (0.8, 1.1)	0.1	1.1 (0.9, 1.3)	1.0 (0.8, 1.1)	0.2	1.2 (1.0, 1.4)	1.0 (0.9, 1.1)	0.05
NOS1	rs1353939	1.0 (0.9, 1.2)	0.9 (0.8, 1.1)	0.2	1.1 (0.9, 1.2)	1.0 (0.8, 1.1)	0.3	1.1 (1.0, 1.3)	1.0 (0.8, 1.2)	0.04
NOS1	rs2291908	1.0 (0.9, 1.2)	1.0 (0.9, 1.1)	0.4	1.1 (0.9, 1.3)	1.0 (0.9, 1.1)	0.3	1.1 (1.0, 1.3)	1.0 (0.9, 1.1)	0.05
NOS1	rs4767535	1.0 (0.8, 1.2)	1.0 (0.9, 1.1)	0.9	1.0 (0.8, 1.3)	1.0 (0.9, 1.1)	0.9	1.2 (1.0, 1.5)	1.0 (0.9, 1.1)	0.05
NOS1	rs6490121	1.0 (0.8, 1.1)	1.0 (0.9, 1.1)	0.9	1.0 (0.9, 1.2)	1.0 (0.9, 1.1)	0.9	0.6 (0.2, 1.5)	1.1 (1.0, 1.1)	0.05
NOS1	rs7298903	1.0 (0.9, 1.1)	0.7 (0.5, 1.1)	0.05	1.0 (0.9, 1.1)	0.8 (0.6, 1.2)	0.3	1.1 (1.0, 1.1)	1.1 (0.9, 1.4)	0.5
NOS2A	rs944725	1.1 (0.9, 1.3)	1.0 (0.9, 1.1)	0.2	1.1 (0.9, 1.4)	1.0 (0.9, 1.1)	0.2	1.3 (1.0, 1.6)	1.0 (0.9, 1.1)	0.03
NOS2A	rs4795067	1.1 (0.9, 1.2)	1.0 (0.9, 1.1)	0.3	1.1 (1.0, 1.3)	0.9 (0.8, 1.1)	0.05	1.2 (1.0, 1.6)	1.0 (0.9, 1.1)	0.02
NOS2A	rs2297516	0.9 (0.7, 1.1)	1.1 (0.9, 1.2)	0.05	0.9 (0.8, 1.1)	1.1 (0.9, 1.3)	0.2	1.0 (0.9, 1.1)	1.1 (0.9, 1.2)	0.7
NOS2A	rs2779252	1.0 (0.9, 1.1)	0.9 (0.8, 1.1)	0.5	1.0 (0.9, 1.2)	1.0 (0.8, 1.1)	0.7	1.1 (1.0, 1.3)	0.2 (0.001, 36.1)	0.03

Continuous Cumulative Lead (OR/100 μg/m³-y)

Gene	rs#	Glioma Homozygous wildtype OR (95% CI)	Glioma Heterozygous/ Homozygous variant OR (95% CI)	Glioma p-int	Glioblastoma[†] Homozygous wildtype OR (95% CI)	Glioblastoma[†] Heterozygous/ Homozygous variant OR (95% CI)	Glioblastoma[†] p-int	Meningioma Homozygous wildtype OR (95% CI)	Meningioma Heterozygous/ Homozygous variant OR (95% CI)	Meningioma p-int
NOS2A	rs8072199	1.0 (0.8, 1.2)	1.0 (0.9, 1.1)	0.9	1.0 (0.8, 1.2)	1.0 (0.9, 1.1)	0.9	0.1 (0.005, 3.7)	1.1 (1.0, 1.1)	0.03
NOS3	rs1799983	0.9 (0.7, 1.1)	1.0 (0.9, 1.1)	0.1	0.9 (0.7, 1.1)	1.1 (1.0, 1.2)	0.04	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)	0.4
NOS3	rs4496877	1.0 (0.8, 1.3)	1.0 (0.9, 1.1)	0.6	1.2 (0.9, 1.5)	1.0 (0.9, 1.1)	0.1	1.3 (1.0, 1.8)	1.0 (1.0, 1.1)	0.02
NOS3	rs12703107	0.8 (0.7, 1.0)	1.0 (0.9, 1.1)	0.04	0.7 (0.6, 1.0)	1.0 (0.9, 1.1)	0.007	1.1 (0.9, 1.2)	1.0 (0.9, 1.1)	0.6
RAC1	rs836554	1.0 (0.9, 1.1)	1.0 (0.9, 1.1)	0.7	1.1 (0.9, 1.2)	1.0 (0.8, 1.1)	0.3	1.2 (1.0, 1.4)	0.9 (0.7, 1.2)	0.01
RAC1	rs6463554	1.0 (0.9, 1.1)	1.0 (0.9, 1.1)	0.8	1.0 (0.9, 1.2)	1.0 (0.8, 1.1)	0.5	1.2 (1.0, 1.3)	0.9 (0.6, 1.3)	0.01
RAC1	rs3729790	1.0 (0.9, 1.1)	0.9 (0.7, 1.1)	0.2	1.0 (0.9, 1.1)	0.8 (0.6, 1.1)	0.2	1.0 (0.9, 1.1)	1.2 (1.0, 1.5)	0.04
RAC2	rs6572	1.0 (0.9, 1.2)	1.0 (0.9, 1.1)	0.7	1.1 (0.9, 1.3)	1.0 (0.9, 1.1)	0.3	1.2 (1.0, 1.3)	1.0 (0.9, 1.1)	0.04
RAC2	rs1476002	1.0 (0.9, 1.1)	1.0 (0.9, 1.1)	0.6	1.0 (0.9, 1.2)	1.0 (0.9, 1.1)	0.6	1.2 (1.0, 1.3)	0.9 (0.7, 1.3)	0.02
RAC2	rs2239774	1.1 (1.0, 1.2)	0.6 (0.4, 0.9)	0.0006	1.1 (1.0, 1.3)	0.3 (0.08, 1.2)	0.0002[§]	1.1 (1.0, 1.3)	1.0 (0.9, 1.1)	0.1
RAC2	rs2239775	1.0 (0.9, 1.1)	1.0 (0.9, 1.1)	0.8	1.0 (0.8, 1.1)	1.0 (0.9, 1.1)	0.7	1.2 (1.0, 1.4)	0.8 (0.4, 1.5)	0.005
RAC2	rs4820274	1.0 (0.9, 1.1)	0.8 (0.6, 1.1)	0.2	1.0 (0.9, 1.1)	0.2 (0.02, 1.1)	0.002	1.1 (1.0, 1.1)	1.3 (0.9, 2.0)	0.3
RAC2	rs4821609	1.0 (0.8, 1.1)	1.0 (0.9, 1.1)	0.8	1.0 (0.8, 1.2)	1.0 (0.9, 1.1)	0.9	1.2 (1.0, 1.3)	0.9 (0.7, 1.3)	0.02
RAC2	rs9607432	1.0 (0.9, 1.1)	0.6 (0.4, 1.0)	0.04	1.0 (0.9, 1.1)	0.2 (0.03, 1.3)	0.005	1.1 (1.0, 1.1)	1.3 (0.9, 2.0)	0.3
SOD1	rs202445	0.9 (0.8, 1.1)	1.1 (0.9, 1.3)	0.1	0.9 (0.8, 1.1)	1.2 (1.0, 1.4)	0.03	1.0 (0.9, 1.1)	1.2 (1.0, 1.5)	0.2
SOD2	rs4880	0.9 (0.8, 1.1)	1.0 (0.9, 1.1)	0.1	0.8 (0.6, 1.1)	1.1 (1.0, 1.2)	0.02	1.1 (1.0, 1.2)	1.1 (0.9, 1.3)	0.7
SOD2	rs5746136	1.0 (0.9, 1.1)	0.9 (0.8, 1.1)	0.4	1.0 (0.9, 1.1)	0.9 (0.8, 1.1)	0.3	0.9 (0.5, 1.4)	1.2 (1.0, 1.3)	0.02
SOD2	rs5746151	1.0 (0.9, 1.1)	1.3 (0.7, 2.3)	0.4	1.0 (0.9, 1.1)	0.9 (0.4, 1.9)	0.8	1.0 (0.9, 1.1)	1.7 (0.8, 3.5)	0.02
SOD3	rs699473[†]	0.9 (0.8, 1.1)	1.0 (0.9, 1.1)	0.1	0.9 (0.8, 1.1)	1.1 (1.0, 1.2)	0.1	0.8 (0.4, 1.3)	1.2 (1.1, 1.3)	0.003
XDH	rs7574920	1.0 (0.8, 1.2)	1.0 (0.9, 1.1)	0.9	1.0 (0.8, 1.3)	1.0 (0.9, 1.1)	0.8	1.3 (1.0, 1.6)	0.8 (0.6, 1.2)	0.001[§]
XDH	rs1429376	1.0 (0.9, 1.2)	1.0 (0.9, 1.1)	0.4	1.1 (1.0, 1.3)	0.9 (0.8, 1.1)	0.06	1.2 (1.0, 1.4)	0.9 (0.6, 1.3)	0.005
XDH	rs17038412	1.0 (0.9, 1.1)	1.0 (0.8, 1.2)	0.7	1.0 (0.9, 1.1)	1.2 (0.9, 1.5)	0.1	1.1 (1.0, 1.1)	0.3 (0.05, 1.8)	0.03
XDH	rs671806	1.0 (0.9, 1.1)	1.0 (0.9, 1.1)	0.5	1.0 (0.9, 1.2)	1.0 (0.8, 1.1)	0.4	1.1 (1.0, 1.3)	1.0 (0.8, 1.2)	0.04

*
See Table 2 for genotype frequencies and associations with brain tumor types

†
Cases with glioblastoma are a subset of the cases with glioma

‡
GPX1 rs1050450 is highly correlated with rs1800668 ($r^2 = 0.9$); *SOD3* rs699473 is highly correlated with rs2284659 ($r^2 = 0.9$)

§
$p \leq 0.05$ after adjustment for multiple comparisons