SUPPLEMENTARY INFORMATION

Mendelian randomisation study of the relationship between vitamin D and risk of glioma

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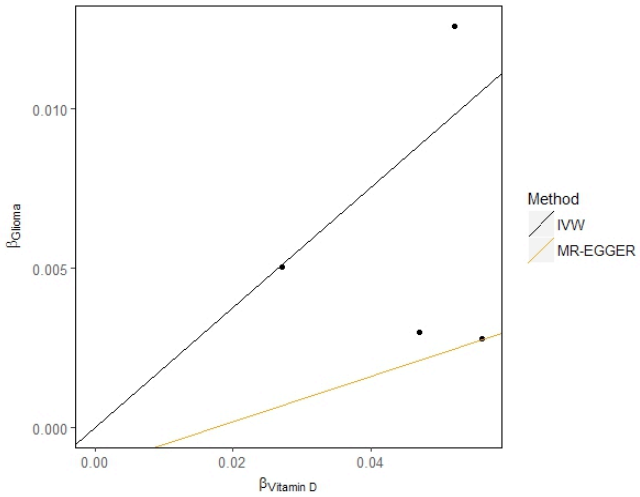
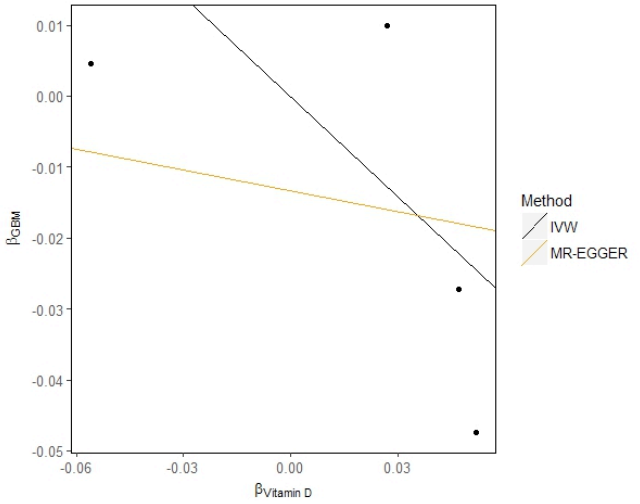
Supplementary Figure 1: Egger plots showing association estimates and intercepts for IVW and MR-Egger methods. (a) All glioma, (b) GBM and (c) non-GBM glioma. Individual SNP results (x axis, association between genetic variant and exposure; y axis, association between genetic variant and outcome) for MR-Egger represented as dots.

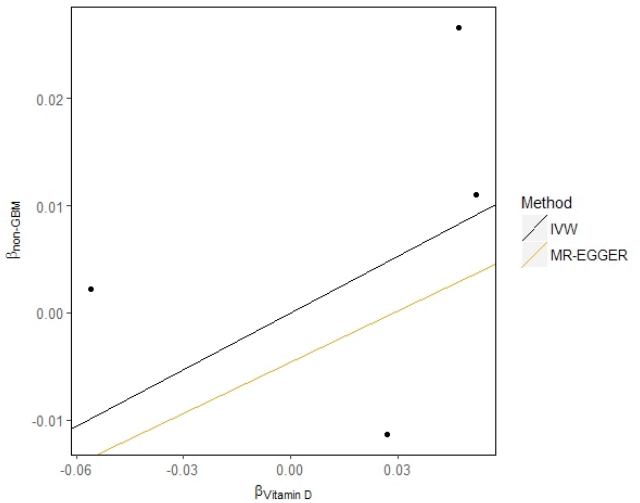
a)



b)



c)



Supplementary Table 1: Summary data taken from the eight glioma GWAS cohorts for all glioma, GBM and non-GBM glioma.

		β (SE)							
	SNP ID	**FRE**	**GER**	**GICC**	**MDA**	**NIH**	**UCSF Mayo**	**UCSF**	**UK**
All glioma									
	rs2282679	-0.041014 (0.061236)	0.133969 (0.0722672)	0.0312392 (0.0370895)	-0.0201926 (0.0583145)	-0.0334083 (0.0502593)	-0.0852 (0.078)	0.026953 (0.0666535)	-0.083326 (0.068562)
	rs10741657	-0.043771 (0.084085)	-0.0231973 (0.0104501)	0.0471905 (0.0343338)	0.0227122 (0.065825)	0.0827191 (0.0459571)	0.0280 (0.0701)	0.0155846 (0.0626787)	-0.066564 (0.063921)
	rs12785878	0.010056 (0.091535)	0.0670007 (0.0731303)	0.103648 (0.0376908)	-0.184117 (0.0741074)	-0.0277272 (0.049879)	-0.0794 (0.0785)	-0.077447 (0.0701056)	-0.046863 (0.075283)
	rs6013897	0.069519 (0.096596)	-0.135191 (0.0804649)	-0.0238725 (0.0450309)	-0.0288026 (0.0643046)	0.0826986 (0.0555012)	-0.11586 (0.0891)	0.0171522 (0.0737805)	-0.0022402 (0.078694)
GBM									
	rs2282679	-0.04843 (0.087789)	0.194952 (0.091289)	0.0428872 (0.0426909)	-0.0248584 (0.0715876)	0.0531505 (0.0616334)	-0.0569 (0.0927)	0.052768 (0.0750633)	-0.050416 (0.086665)
	rs10741657	0.04091 (0.084085)	-0.0433447 (0.084627)	0.0838341 (0.0398032)	0.0227122 (0.065825)	0.136855 (0.0563093)	0.0299 (0.084)	-0.0159823 (0.070422)	-0.095132 (0.092758)
	rs12785878	-0.032299 (0.091535)	-0.0329982 (0.091797)	0.0898337 (0.0438104)	-0.184117 (0.0741074)	0.0587657 (0.0615237)	-0.1273 (0.0931)	-0.0522656 (0.0791768)	-0.061052 (0.10893)
	rs6013897	0.20486 (0.096596)	-0.220451 (0.0999851)	-0.0515566 (0.0521191)	-0.00551889 (0.0788602)	0.0656293 (0.0680447)	-0.1620 (0.1059)	0.0109484 (0.0830175)	0.078138 (0.11336)
Non-GBM									
	rs2282679	-0.037759 (0.066931)	0.0659646 (0.0925085)	0.0181318 (0.0467723)	-0.00983184 (0.0788454)	-0.13506 (0.0799106)	-0.1066 (0.0917)	-0.0557449 (0.125407)	-0.050416 (0.086665)
	rs10741657	-0.080648 (0.064092)	-0.00334915 (0.0856417)	-0.0131532 (0.0431055)	0.000852212 (0.0718896)	0.00882211 (0.0725762)	0.02888 (0.083)	0.137603 (0.119067)	-0.045619 (0.080722)
	rs12785878	0.029065 (0.070909)	0.0538005 (0.0946434)	0.111379 (0.0475173)	-0.136224 (0.0815494)	-0.146313 (0.0785833)	-0.0601 (0.0935)	-0.159781 (0.132543)	-0.036517 (0.095481)
	rs6013897	0.0094937 (0.075201)	-0.042059 (0.101502)	0.029179 (0.056441)	-0.0648037 (0.0868811)	0.184169 (0.0887083)	-0.0546 (0.1045)	0.0411433 (0.138721)	-0.063098 (0.10013)

Supplementary Table 2: Summary of the eight glioma GWAS cohorts.

Study series	Centre	Sampling	Cases	Controls
FRE	Groupe Hospitalier Pitié-Salpêtrière Paris	Patients with glioma were selected through the Service de Neurologie Mazarin, Groupe Hospitalier Pitié-Salpêtrière Paris. Individuals from the SU.VI.MAX (Supplementation en Vitamines et MineralesAntioXydants) study were used as controls.	1,423	1,190
GER	University of Bonn	Comprised of patients who had undergone surgery between 1996 and 2008 for glioma at the Department of Neurosurgery, University of Bonn Medical Center. Control subjects were taken from three population studies: KORA (Co-operative Health Research in the Region of Augsburg); POPGEN (Population Genetic Cohort) and the Heinz Nixdorf Recall study.	846	1,310
GICC	GLIOGENE Consortium	Comprised of glioma cases and controls that were selected through Brigham and Women's Hospital (Boston, Massachusetts), Case Western Reserve University (Cleveland, Ohio), Columbia University (New York, New York), the Danish Cancer Society Research Centre (Copenhagen, Denmark), the Gertner Institute (Tel Hashomer, Israel), Duke University (Durham, North Carolina), the University of Texas MD Anderson Cancer Center (Houston, Texas), Memorial Sloan Kettering Cancer Center (New York, New York), the Mayo Clinic (Rochester, Minnesota), NorthShore HealthSystem (Chicago, Illinois), Umeå University (Umeå, Sweden), the University of California, San Francisco (San Francisco, California), the University of Southern California (Los Angeles, California), and the Institute of Cancer Research (London, United Kingdom). Cases had newly diagnosed glioma, and controls had no personal history of central nervous system tumors at the time of selection for the studies.	4,572	3,286
MDA	The University of Texas M.D. Anderson Cancer Center	Cases were ascertained between 1990 and 2008 through the MD Anderson Cancer Center, Texas. Controls were taken from the Cancer Genetic Markers of Susceptibility studies.	1,175	2,236
GliomaScan (NIH)	National Cancer Institute	Cases were newly diagnosed glioma (ICDO-3 codes 9380-9480 or equivalent), and controls were cancer-free.	1,653	2,725
UCSF-Mayo	Mayo Clinic	Comprised of Mayo cases, UCSF cases, and Mayo Clinic Biobank control data.	1,519	804
UCSF	University of California, San Francisco	Cases were adults with newly diagnosed, histologically confirmed glioma. Population-based cases who were diagnosed between 1991 and 2009 and who were residing in the six San Francisco Bay area counties were ascertained using the Cancer Prevention Institute of California's early-case ascertainment system. Clinic-based cases who were diagnosed between 2002 and 2012 were recruited from the UCSF Neuro-oncology Clinic, regardless of their place of residence. From 1991 to 2010, population-based controls from the same residential area as the population-based cases were identified using random digit-dialling and were frequency matched to population-based cases for age, gender and ethnicity. Between 2010 and 2012, all controls were selected from the UCSF general medicine phlebotomy clinic. Clinic-based controls were matched to clinic-based glioma cases for age, gender and ethnicity.	677	3,940
UK	INTERPHONE	Cases were ascertained through the INTERPHONE study. Controls were selected from the 1958 Birth Cohort.	631	2,699
Total			12,496	18,190

Supplementary Table 3: MR estimates between multi-SNP risk scores of 25(OH)D synthesis (rs12785878 and rs10741657) and all glioma, GBM and non-GBM glioma using the IVW and MLE methods.

	IVW method				**MLE method**			
	β	**SE(β)**	**OR (95% CI)**	***P* value**	**β**	**SE(β)**	**OR (95% CI)**	***P* value**
All glioma	0.207	0.161	1.23 (0.90-1.69)	0.197	0.200	0.117	1.22 (0.97-1.54)	0.086
GBM	-0.509	0.315	0.60 (0.32-1.11)	0.106	-0.514	0.225	0.60 (0.38-0.93)	0.023
Non-GBM	0.090	0.338	1.09 (0.56-2.12)	0.789	0.088	0.242	1.09 (0.68-1.75)	0.716

IVW, inverse-variance weighted; MLE, maximum likelihood estimation; SE, standard error; OR, odds ratio; CI, confidence interval; GBM, glioblastoma.

Supplementary Table 4: MR estimates between multi-SNP risk scores of 25(OH)D metabolism (rs2282679 and rs6013897) and all glioma, GBM and non-GBM glioma using the IVW and MLE methods.

	IVW method				**MLE method**			
	β	**SE(β)**	**OR (95% CI)**	***P* value**	**β**	**SE(β)**	**OR (95% CI)**	***P* value**
All glioma	0.088	0.382	1.09 (0.52-2.31)	0.817	0.090	0.271	1.09 (0.64-1.86)	0.741
GBM	-0.391	0.464	0.68 (0.27-1.68)	0.400	-0.392	0.330	0.68 (0.35-1.29)	0.234
Non-GBM	0.368	0.503	1.44 (0.54-3.87)	0.464	0.369	0.357	1.45 (0.72-2.91)	0.301

IVW, inverse-variance weighted; MLE, maximum likelihood estimation; SE, standard error; OR, odds ratio; CI, confidence interval; GBM, glioblastoma.

Supplementary Table 5: MR estimates between multi-SNP risk scores of 25(OH)D levels (excluding rs12785878, which has been associated with non-European status) and all glioma, GBM and non-GBM glioma using the IVW and MLE methods.

	IVW method				**MLE method**			
	β	**SE(β)**	**OR (95% CI)**	***P* value**	**β**	**SE(β)**	**OR (95% CI)**	***P* value**
All glioma	0.215	0.161	1.24 (0.90-1.70)	0.183	0.209	0.115	1.23 (0.98-1.55)	0.069
GBM	-0.666	0.319	0.51 (0.27-0.96)	0.037	-0.668	0.220	0.51 (0.33-0.80)	0.003
Non-GBM	0.285	0.344	1.33 (0.68-2.61)	0.407	0.285	0.244	1.33 (0.83-2.14)	0.242

IVW, inverse-variance weighted; MLE, maximum likelihood estimation; SE, standard error; OR, odds ratio; CI, confidence interval; GBM, glioblastoma.