Supplemental Materials

Hypothalamic Gliosis is Associated With Multiple Cardiovascular Disease Risk Factors

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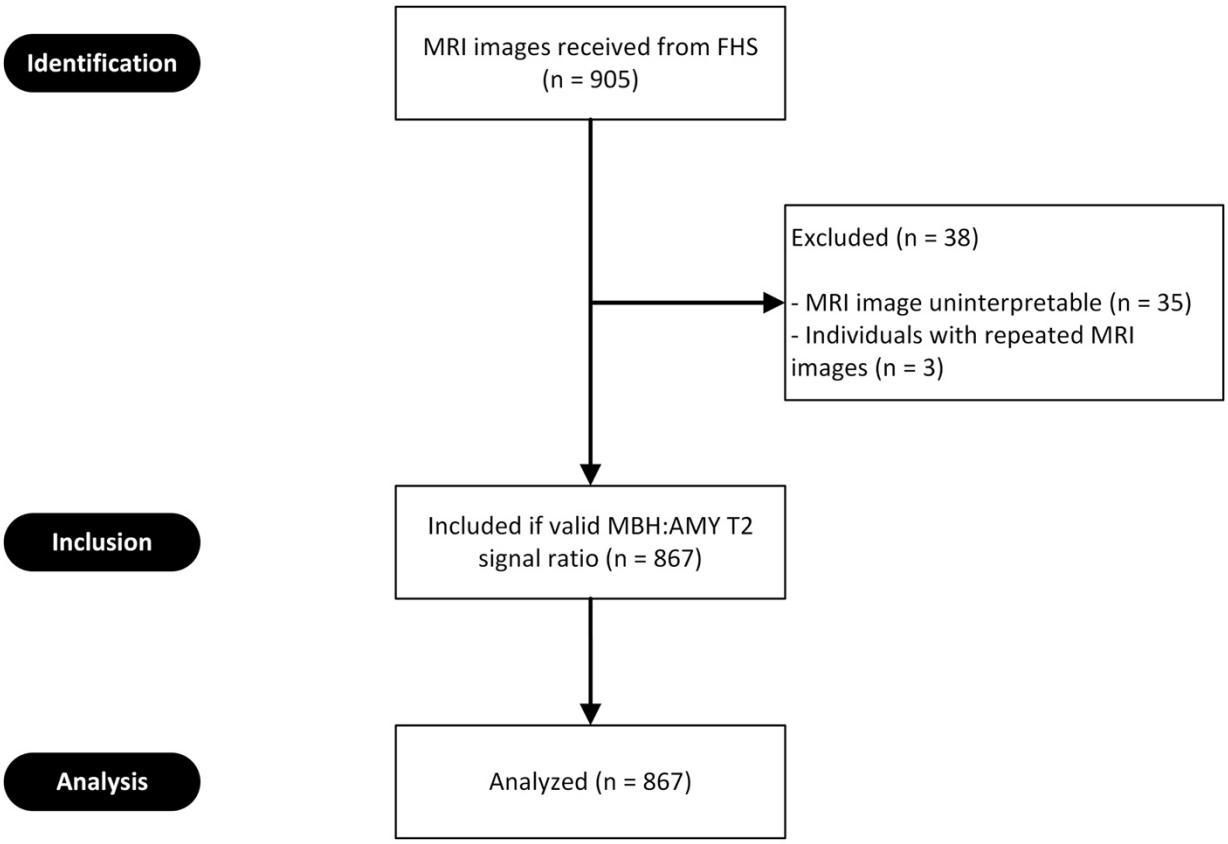
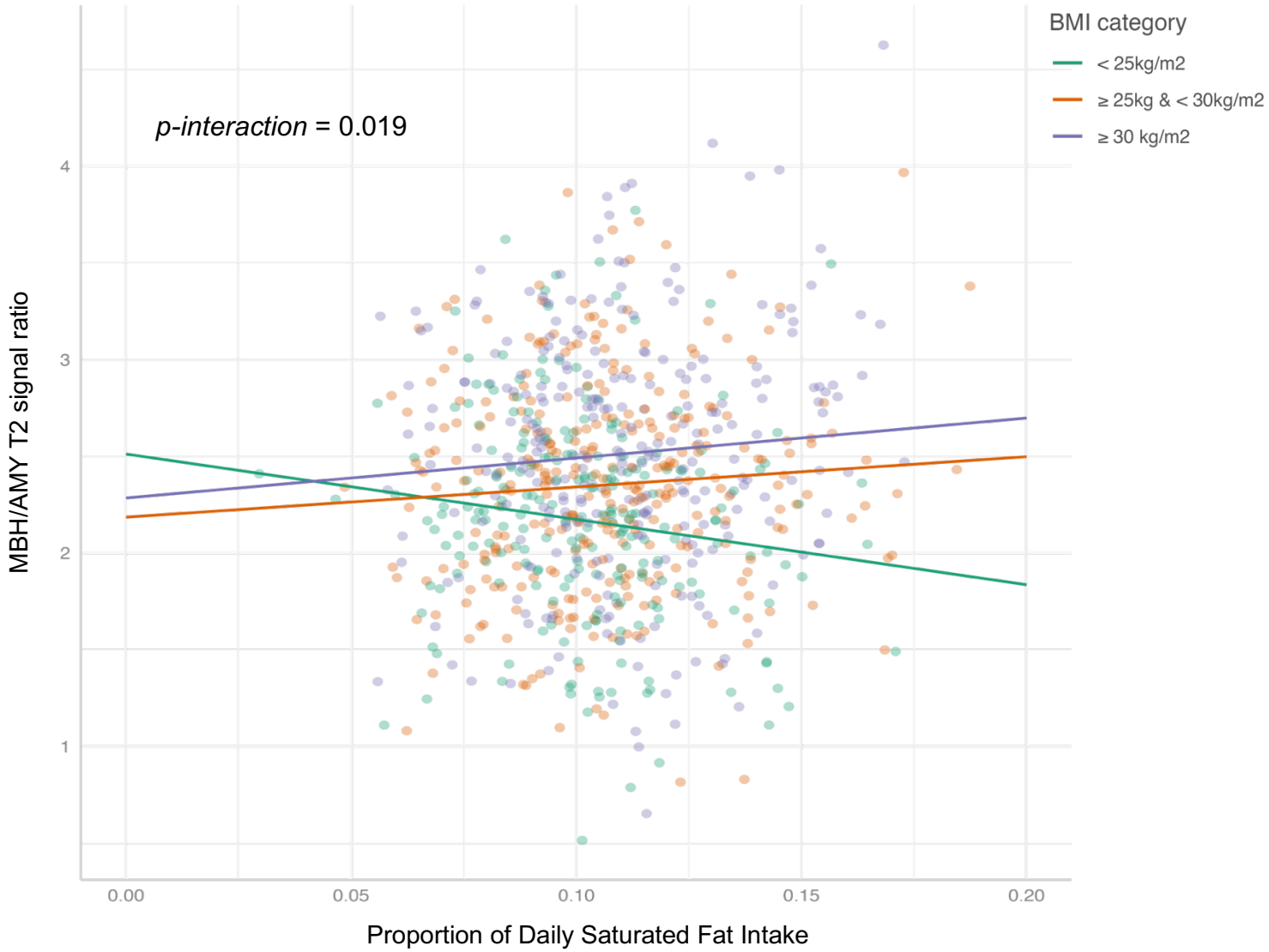
Figure S1. Flow chart describing inclusion and exclusion criteria for the study population



MRI, magnetic resonance imaging; FHS, Framingham Heart Study; MBH, mediobasal hypothalamus; AMY, amygdala.

Figure S2. Adjusted marginal effects model of the association of MBH/AMY T2 signal ratio and the proportion of daily saturated fat intake stratified by BMI category (<25 kg/m^2; ≥25 kg/m^2 & <30 kg/m^2; ≥30 kg/m^2)



The marginal effects model was conducted using a linear regression model adjusting for age, sex, and time interval between dietary exposures and MRI and including an interaction term for BMI category*saturated fat. The sample size of each BMI category was 231, 305, and 278, respectively. MBH/AMY T2 signal ratios were natural logarithm-transformed.

Table S1. Covariates included in each model by cardiovascular risk factor and coronary heart disease outcomes.

	BMI	HDL-C	LDL-C	ln(Triglycerides)	HTN	DM	MetS	CHD
Model 1	Age, sex	Age, sex	Age, sex	Age, sex	Age, sex	Age, sex	Age, sex	Age, sex
Model 2	Model 1 + Smoking	Model 1 + Smoking	Model 1 + Smoking	Model 1 + Smoking	Model 1 + Smoking	Model 1 + Smoking	Model 1 + Smoking	Model 1 + Smoking
Model 3	Model 2 + Diabetes treatment	Model 2 + Lipid treatment	Model 2 + Lipid treatment	Model 2 + Lipid treatment	Model 2 + Lipid treatment	Model 2 + Hypertension	Model 2 + Physical activity	Model 2 + Lipid treatment
Fully adjusted	NA	Model 3 + BMI	Model 3 + BMI	Model 3 + BMI	Model 3 + BMI	Model 3 + BMI	NA	Model 3 + BMI

BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HTN, hypertension; DM, diabetes mellitus; MetS, metabolic syndrome; CHD, coronary heart disease

Table S2. T2 signal ratio odds ratios & 95% CIs by cardiovascular disease risk factor and coronary heart disease outcomes.

T2 signal ratio predictor and model		Hypertension		Diabetes mellitus		Metabolic syndrome		Coronary heart disease	
		Coefficient [95%CI]	*P* value	Coefficient [95%CI]	*P* value	Coefficient [95%CI]	*P* value	Coefficient [95%CI]	*P* value
MBH/AMY	Model 1*	1.36 [1.17, 1.57]	<0.001	1.24 [0.95, 1.61]	0.11	1.34 [1.15, 1.57]	<0.001	0.75 [0.49, 1.15]	0.19
	Model 2†	1.36 [1.17, 1.57]	<0.001	1.24 [0.95, 1.61]	0.12	1.34 [1.14, 1.57]	<0.001	0.73 [0.47, 1.14]	0.17
	Model 3‡	1.36 [1.17, 1.58]	<0.001	1.14 [0.87, 1.49]	0.34	1.33 [1.13, 1.56]	<0.001	0.71 [0.45, 1.12]	0.14
	Fully adjusted§	1.23 [1.05, 1.44]	0.0088	1.01 [0.77, 1.33]	0.93	…	…	0.69 [0.44, 1.08]	0.11
MBH/PUT	Model 1*	1.24 [1.08, 1.43]	0.0030	1.39 [1.07, 1.81]	0.015	1.35 [1.15, 1.58]	<0.001	0.99 [0.67, 1.47]	0.96
	Model 2†	1.25 [1.08, 1.44]	0.0028	1.37 [1.06, 1.79]	0.018	1.34 [1.15, 1.57]	<0.001	0.97 [0.65, 1.45]	0.89
	Model 3‡	1.24 [1.07, 1.43]	0.0040	1.30 [1.00, 1.69]	0.051	1.34 [1.14, 1.57]	<0.001	0.97 [0.65, 1.44]	0.87
	Fully adjusted§	1.13 [0.97, 1.31]	0.12	1.19 [0.91, 1.56]	0.21	…	…	0.95 [0.64, 1.42]	0.81
PUT/AMY	Model 1*	0.99 [0.86, 1.14]	0.88	0.81 [0.62, 1.05]	0.11	0.90 [0.77, 1.05]	0.18	0.82 [0.55, 1.23]	0.35
	Model 2†	0.99 [0.86, 1.14]	0.85	0.82 [0.63, 1.06]	0.12	0.91 [0.78, 1.05]	0.20	0.85 [0.57, 1.26]	0.41
	Model 3‡	1.00 [0.86, 1.15]	0.95	0.81 [0.63, 1.05]	0.12	0.90 [0.78, 1.05]	0.20	0.84 [0.56, 1.25]	0.39
	Fully adjusted§	1.02 [0.88, 1.18]	0.83	0.83 [0.63, 1.09]	0.18	…	…	0.83 [0.55, 1.25]	0.37

Results are from multiple logistic regression models. MRI-assessed T2 signal ratios were natural logarithm transformed and used as model predictors: MBH/AMY (primary), MBH/PUT (positive control), and PUT/AMY (negative control). ORs and 95% CIs are presented as the change in odds for the outcome per a 1 SD difference in T2 signal ratio.

MBH, mediobasal hypothalamus; AMY, amygdala; PUT, putamen; OR, odds ratio, CI, confidence interval.

* Model 1 adjusted for age and sex.

† Model 2 adjusted for model 1 covariates plus smoking.

‡ Model 3 adjusted for model 2 covariates plus lipid treatment for hypertension and CHD models, hypertension status for diabetes mellitus models, or physical activity index for metabolic syndrome models.

§ Fully adjusted model includes model 3 covariates plus BMI.

Table S3. T2 signal ratio odds ratios & 95% CIs by continuous cardiovascular risk factor outcomes, adjusting for time between MRI assessment and health exam.

T2 signal ratio predictor and model		BMI		HDL-C		LDL-C		Ln(Triglycerides)	
		Coefficient [95%CI]	*P* value	Coefficient [95%CI]	*P* value	Coefficient [95%CI]	*P* value	Coefficient [95%CI]	*P* value
MBH/AMY	Model 1*	22.1 [15.9, 28.2]	<0.001	-47.1 [-67.3, -27.0]	<0.001	18.2 [-16.5, 52.8]	0.30	1.2 [0.6, 1.7]	<0.001
	Model 2†	22.1 [15.9, 28.2]	<0.001	-47.1 [-67.3, -26.9]	<0.001	17.7 [-16.9, 52.4]	0.32	1.1 [0.6, 1.7]	<0.001
	Model 3‡	21.4 [15.4, 27.5]	<0.001	-46.1 [-66.1, -26.1]	<0.001	21.5 [-11.4, 54.4]	0.20	1.1 [0.6, 1.7]	<0.001
	Fully adjusted§	…	…	-20.8 [-40.0, -1.6]	0.034	12.5 [-21.2, 46.3]	0.47	0.5 [-0.0, 1.0]	0.076
MBH/PUT	Model 1*	13.0 [8.6, 17.3]	<0.001	-34.7 [-48.8, -20.6]	<0.001	-1.8 [-25.9, 22.2]	0.88	0.9 [0.5, 1.3]	<0.001
	Model 2†	13.2 [8.9, 17.5]	<0.001	-34.1 [-48.2, -20.0]	<0.001	-1.0 [-25.1, 23.1]	0.94	0.9 [0.5, 1.2]	<0.001
	Model 3‡	12.5 [8.2, 16.8]	<0.001	-32.8 [-46.7, -18.8]	<0.001	3.3 [-19.6, 26.3]	0.78	0.8 [0.5, 1.2]	<0.001
	Fully adjusted§	…	…	-18.1 [-31.4, -4.8]	0.0079	-2.8 [-26.1, 20.5]	0.81	0.5 [0.1, 0.8]	0.012
PUT/AMY	Model 1*	-2.8 [-7.7, 2.1]	0.26	15.0 [-0.8, 30.8]	0.063	17.3 [-9.4, 44.0]	0.20	-0.4 [-0.8, 0.0]	0.077
	Model 2†	-3.1 [-8.0, 1.8]	0.22	14.2 [-1.7, 30.0]	0.080	16.1 [-10.7, 42.8]	0.24	-0.4 [-0.8, 0.1]	0.10
	Model 3‡	-2.6 [-7.4, 2.3]	0.30	12.9 [-2.8, 28.6]	0.11	12.4 [-13.1, 37.9]	0.34	-0.3 [-0.8, 0.1]	0.12
	Fully adjusted§	…	…	9.8 [-4.7, 24.4]	0.19	13.5 [-11.9, 38.9]	0.30	-0.3 [-0.7, 0.1]	0.20

Results are from multiple linear regression models. MRI-assessed T2 signal ratios were natural logarithm transformed and used as model predictors: MBH/AMY (primary), MBH/PUT (positive control), and PUT/AMY (negative control). Coefficient and confidence intervals represent the estimated change in outcome per 1 unit difference in the natural logarithm-transformed T2 signal ratio.

BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ln(Triglycerides), natural logarithm transformed fasting triglycerides; MBH, mediobasal hypothalamus; AMY, amygdala; PUT, putamen.

* Model 1 adjusted for age, sex, and interval between health examination and MRI assessment.
† Model 2 adjusted for model 1 covariates plus smoking.
‡ Model 3 adjusted for model 2 covariates plus diabetes treatment for BMI model or lipid treatment for HDL-C, LDL-C, and natural log-transformed triglycerides models.
§ Fully adjusted model includes model 3 covariates plus BMI, when appropriate.

Table S4. T2 signal ratio odds ratios & 95% CIs by cardiovascular risk factor and coronary heart disease outcomes, adjusting for time between MRI assessment and health exam.

T2 signal ratio predictor and model		Hypertension		Diabetes mellitus		Metabolic syndrome		Coronary heart disease	
		Coefficient [95%CI]	*P* value	Coefficient [95%CI]	*P* value	Coefficient [95%CI]	*P* value	Coefficient [95%CI]	*P* value
MBH/AMY	Model 1*	1.4 [1.2, 1.6]	<0.001	1.2 [0.9, 1.6]	0.12	1.3 [1.1, 1.6]	<0.001	0.7 [0.5, 1.1]	0.18
	Model 2†	1.4 [1.2, 1.6]	<0.001	1.2 [0.9, 1.6]	0.12	1.3 [1.1, 1.6]	<0.001	0.7 [0.5, 1.1]	0.17
	Model 3‡	1.4 [1.2, 1.6]	<0.001	1.1 [0.9, 1.5]	0.34	1.3 [1.1, 1.6]	<0.001	0.7 [0.4, 1.1]	0.10
	Fully adjusted§	1.2 [1.1, 1.4]	0.0088	1.0 [0.8, 1.3]	0.94	…	…	0.7 [0.4, 1.1]	0.081
MBH/PUT	Model 1*	1.2 [1.1, 1.4]	0.0027	1.4 [1.1, 1.8]	0.011	1.4 [1.2, 1.6]	<0.001	1.0 [0.7, 1.4]	0.88
	Model 2†	1.2 [1.1, 1.4]	0.0024	1.4 [1.1, 1.8]	0.013	1.4 [1.2, 1.6]	<0.001	1.0 [0.6, 1.4]	0.82
	Model 3‡	1.2 [1.1, 1.4]	0.0036	1.3 [1.0, 1.7]	0.043	1.3 [1.1, 1.6]	<0.001	0.9 [0.6, 1.4]	0.72
	Fully adjusted§	1.1 [1.0, 1.3]	0.11	1.2 [0.9, 1.6]	0.20	…	…	0.9 [0.6, 1.4]	0.68
PUT/AMY	Model 1*	1.0 [0.9, 1.1]	0.85	0.8 [0.6, 1.0]	0.087	0.9 [0.8, 1.0]	0.15	0.8 [0.6, 1.2]	0.37
	Model 2†	1.0 [0.9, 1.1]	0.82	0.8 [0.6, 1.0]	0.10	0.9 [0.8, 1.0]	0.17	0.9 [0.6, 1.3]	0.43
	Model 3‡	1.0 [0.9, 1.1]	0.92	0.8 [0.6, 1.0]	0.11	0.9 [0.8, 1.0]	0.17	0.8 [0.6, 1.3]	0.41
	Fully adjusted§	1.0 [0.9, 1.2]	0.83	0.8 [0.6, 1.1]	0.17	…	…	0.8 [0.6, 1.3]	0.39

Results are from multiple logistic regression models. MRI-assessed T2 signal ratios were natural logarithm transformed and used as model predictors: MBH/AMY (primary), MBH/PUT (positive control), and PUT/AMY (negative control). ORs and 95% CIs are presented as the change in odds for the outcome per a 1 SD difference in T2 signal ratio.

MBH, mediobasal hypothalamus; AMY, amygdala; PUT, putamen; OR, odds ratio, CI, confidence interval.

* Model 1 adjusted for age, sex, and interval between health examination and MRI assessment.

† Model 2 adjusted for model 1 covariates plus smoking.

‡ Model 3 adjusted for model 2 covariates plus lipid treatment for hypertension and CHD models, hypertension status for diabetes mellitus models, or physical activity index for metabolic syndrome models.

§ Fully adjusted model includes model 3 covariates plus BMI.

Table S5. Adjusted prospective associations of self-reported dietary exposures and T2 signal ratio outcomes (N=814).

	MBH/AMY T2 signal ratio		MBH/PUT T2 signal ratio		PUT/AMY T2 signal ratio	
Predictor*	Coefficient [95% CI]	*P* value	Coefficient [95% CI]	*P* value	Coefficient [95% CI]	*P* value
Total fat	0.04 [-0.02, 0.11]	0.19	0.03 [-0.07, 0.13]	0.57	0.01 [-0.07, 0.10]	0.76
Total carbohydrates	-0.04 [-0.09, 0.01]	0.15	-0.08 [-0.16, 0.00]	0.04	0.04 [-0.03, 0.11]	0.25
Total protein	0.09 [-0.04, 0.22]	0.19	0.16 [-0.03, 0.35]	0.10	-0.06 [-0.23, 0.11]	0.50
Fructose	-0.03 [-0.22, 0.17]	0.78	-0.02 [-0.30, 0.26]	0.89	-0.01 [-0.27, 0.24]	0.93
Sucrose	-0.08 [-0.20, 0.04]	0.19	-0.2 [-0.38, -0.02]	0.025	0.10 [-0.06, 0.27]	0.21
Total saturated fat	0.12 [-0.04, 0.29]	0.14	0.18 [-0.07, 0.42]	0.15	-0.05 [-0.27, 0.17]	0.63
Total sugar	-0.02 [-0.08, 0.05]	0.63	-0.04 [-0.13, 0.05]	0.44	0.02 [-0.07, 0.10]	0.70

T2 signal ratios were natural log-transformed. All models were adjusted for age, sex, and time interval between dietary exposures and MRI.

* Predictors were calculated as proportions of total caloric intake.