Beneficial effects of physical activity on brain health are partly mediated by a reduction in cardiovascular risk factors

Supplemental materials

Results

Model selection for the association between physical activity and global neuroimaging values

We assessed the linearity of the association between physical activity and neuroimaging global values by using models with polynomial terms of different orders. The physical activity-term was modelled with a polynomial of degree from *1* to *n+1* where *n* is the best-fit degree. Different model types were considered to estimate the best fit model of GM volume and cerebral glucose metabolism. The candidate models were tested from the simplest to the most complex. A model type was kept as a potential candidate when likelihood ratio test (i.e., polynomial of degree *n* vs. polynomial of degree *n-1*) and physical activity-term coefficients were significant using t-statistic ($P<0.05$). Candidate models were compared using the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) according to Burnham criteria.[1] When interpretations were not straightforward, the ratio likelihood test was preferred to test whether the more complex model was significantly better at capturing the data than the simpler model.

As depicted in eTable 1, GM volume is linearly associated with physical activity. The quadratic term coefficient ($\hat{c}_2$) and the p-value of the likelihood ratio test were not significant, and the AIC/BIC of the linear model was the lowest.

On the other hand, for glucose metabolism, the linear association was significant but the quadratic term coefficient (ĉ2) did not reach significance and the AIC/BIC ratio was very small. This suggests that the association between glucose metabolism and physical activity was better described by a linear association. However, the p-value of the likelihood ratio test was significant, suggesting that the quadratic model cannot be completely rejected. Therefore, for glucose metabolism, results should be interpreted with caution, and this even more as AIC and BIC tend towards divergent conclusions (probably because BIC penalizes model complexity more heavily).

FDG-PET data uncorrected for partial volume effects

We replicated our main analyses with PVE-uncorrected cerebral glucose metabolism. As depicted in eTable 3, higher physical activity was associated with higher PVE-uncorrected cerebral glucose metabolism (eFigure 2). However, none of the cardiovascular risk factors (i.e. insulin and BMI) previously found to be associated with physical activity were associated with PVE-uncorrected cerebral glucose metabolism (eTable 4).

Role of other lifestyle factors

To further investigate whether other lifestyle factors drive the association between physical activity and brain integrity, we analyzed whether physical activity was associated with other lifestyle factors available in our cohort (i.e., The Mediterranean Diet Adherence Screener (MEDAS) questionnaire,[2] assessing adherence to the Mediterranean diet, and the Lifetime Cognitive Activity questionnaire,[3] evaluating participation in cognitive activities). As depicted in eTable 5, physical activity was associated with adherence to the Mediterranean diet, but not with cognitive activity.

Results from the multiple linear regression models testing the association between physical activity and the neuroimaging measures remained unchanged when adding these additional lifestyle factors (eTable 6). This suggests that the associations previously highlighted are specific to physical activity.

We further assessed whether other lifestyle factors could influence the associations between physical activity and the AD-sensitive regions (eTable 6).

When adherence to the Mediterranean diet was added as a covariate, the association between physical activity and glucose metabolism in the precuneus was not significant anymore. However, as adherence to the Mediterranean diet was not directly associated with glucose metabolism in the precuneus, it seems unlikely that diet mediates the association.

eReferences

e1. Burnham KP, Anderson DR. Multimodel inference: Understanding AIC and BIC in model selection. *Sociol Methods Res*. 2004;33(2):261-304. doi:10.1177/0049124104268644

e2. Schröder H, Fitó M, Estruch R, et al. A Short screener is valid for assessing mediterranean diet adherence among older spanish men and women. *J Nutr*. 2011;141(6):1140-1145. doi:10.3945/jn.110.135566

e3. Wilson RS, Barnes LL, Bennett DA. Assessment of lifetime participation in cognitively stimulating activities. *J Clin Exp Neuropsychol*. 2003;25(5):634-642. doi:10.1076/jcen.25.5.634.14572

eTables and eFigures

eTable 1 Model comparison for the associations between physical activity and global neuroimaging values.

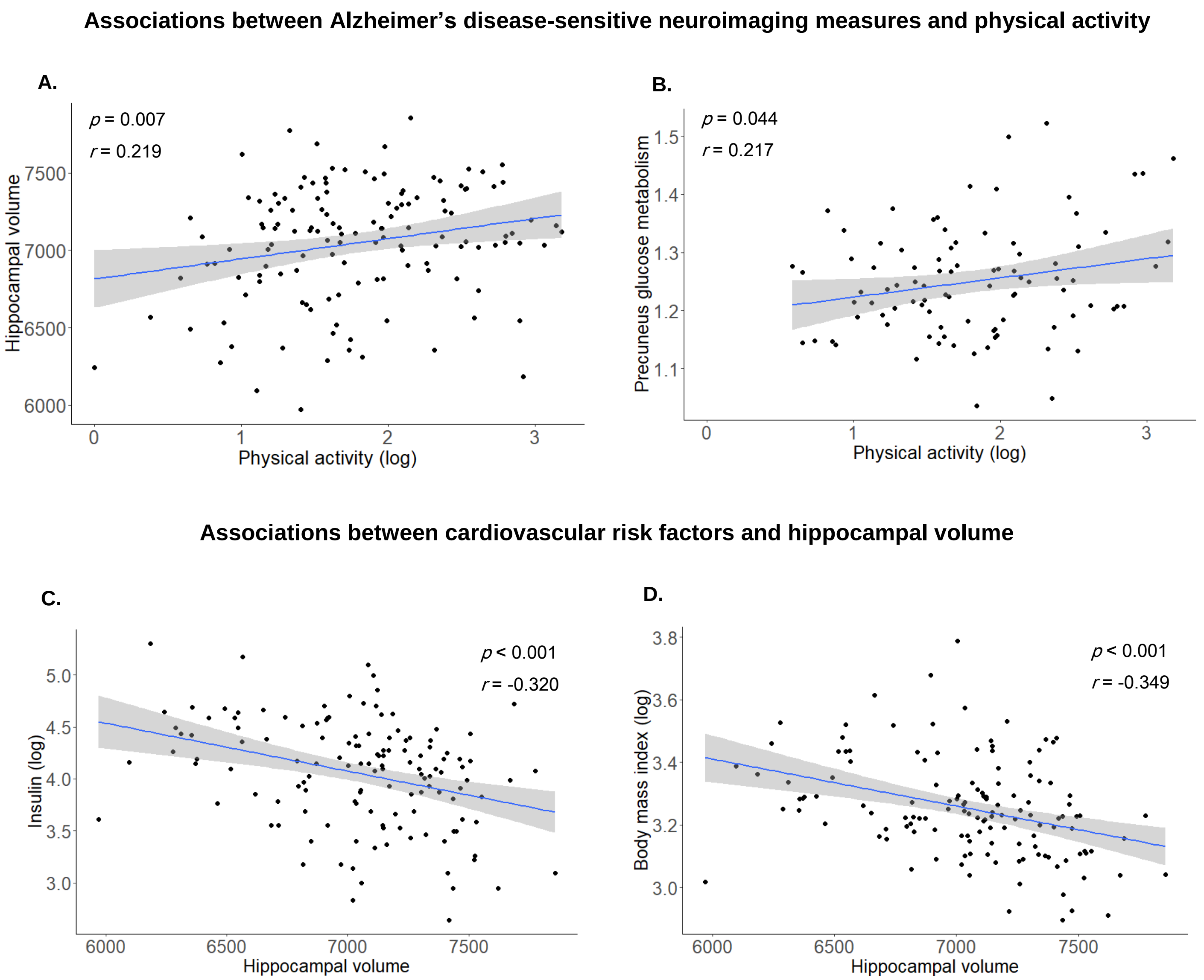
Neuroimaging global values	**Model**	**t-test of each coefficient (ĉ) for Physical activity *p*-value**				**LRT *p*-value**	**AIC**	**BIC**
		$\hat{c}_1$	$\hat{c}_2$	$\hat{c}_3$	$\hat{c}_4$			
GM volume	m_l	0.030*	-	-	-	-	3082.970	3100.357
	m_2	0.807	0.821	-	-	0.816	3084.916	3105.201
Cerebral glucose metabolism	m_1	0.019*	-	-	-	-	-224.237	-209.106
	m_2	0.157	0.056	-	-	0.048*	-226.154	-208.501

Models represented are m^1 = linear model; m^2 = quadratic model. Model written in red is the selected model.
All regressions are adjusted for age, sex and education. **P* > 0.05, ***P* > 0.01, ****P* < 0.001. Abbreviations: GM = gray matter; LRT = likelihood ratio test; AIC = Akaike information criterion; BIC = Bayesian information criterion.

eTable 2 Multiple linear regressions between cardiovascular risk factors and physical activity or gray matter volume

		Physical activity					**GM volume**				
		b	**Std. Error**	**ß**	**t Value**	**p Value**	**b**	**Std. Error**	**ß**	**t Value**	**P Value**
Cardiovascular risk factors	**Covariates**										
Insulin	Age, sex, education, hypo-glycaemia treatment	-0.199	0.067	-0.249	-2.956	0.004**	-15270.0	3870.1	-0.306	-3.946	<0.001***
Total Cholesterol	Age, sex, education, hypo-cholesterol treatment	0.027	0.132	0.015	0.205	0.838					
HDL Cholesterol	Age, sex, education, hypo-cholesterol treatment	0.040	0.046	0.067	0.871	0.386					
SBP	Age, sex, education, high blood pressure treatment	-2.781	2.562	-0.089	-1.085	0.280					

**P* > 0.05, ***P* > 0.01, ****P* < 0.001. Abbreviations: GM = gray matter; HDL Cholesterol = high density lipoprotein cholesterol; SBP = systolic blood pressure.



eFigure 1 Associations between physical activity, neuroimaging values, and cardiovascular risk factors. Physical activity is associated with hippocampal (A) neuroimaging values of gray matter volume, and precuneus (B) glucose metabolism. Hippocampal gray matter volume is associated with insulin (C) and body mass index (D). Raw data (i.e., unadjusted) are plotted. Solid lines represent estimated regression lines and shaded areas represent 95% confidence intervals. Statistical values were obtained using multiple linear regressions controlling for age, sex, and education. Physical activity, insulin and body mass index values are log-transformed.

eTable 3 Multiple linear regressions between physical activity and global neuroimaging values

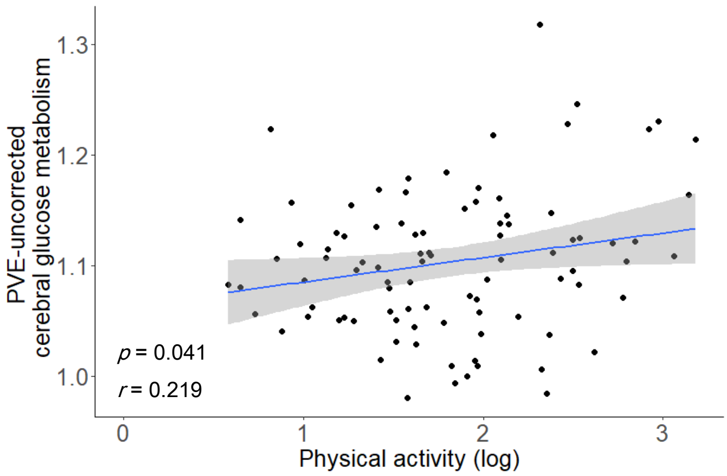
		Physical activity				
Global FDG-PET using PVE-uncorrected SUVr	**Covariates**	**b**	**Std. Error**	**ß**	***t* Value**	***p* Value**
Cerebral glucose metabolism	Age, sex, education	0.023	0.011	0.219	2.072	0.041 *
Cerebral glucose metabolism	Age, sex, education, insulin	0.024	0.011	0.227	2.105	0.038*
Cerebral glucose metabolism	Age, sex, education, BMI	0.025	0.011	0.240	2.235	0.028*

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. Abbreviations: FDG = ^{18}F-fluorodeoxyglucose; PET = positron emission tomography; PVE = partial volume effect; SUVR = Standardized uptake value ratio.

eTable 4 Multiple linear regressions between cardiovascular risk factors and global neuroimaging values

		Insulin					BMI				
Global neuroimaging values	**Covariates**	**b**	**Std. Error**	**ß**	***t* Value**	***p* Value**	**b**	**Std. Error**	**ß**	***t* Value**	***p* Value**
PVE-uncorrected cerebral glucose metabolism	Age, sex, education	0.001	0.014	0.006	0.060	0.953	0.034	0.048	0.077	0.702	0.485

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. Abbreviations: PVE = partial volume effect; BMI = body mass index.



eFigure 2 Associations between physical activity and global neuroimaging values. Physical activity and global neuroimaging values of partial volume effect- (PVE) uncorrected cerebral glucose. Raw data (i.e., unadjusted) are plotted. Solid lines represent estimated regression lines and shaded areas represent 95% confidence intervals. Statistical values were obtained using general linear models controlling for age, sex, and education. Physical activity values are log-transformed. Abbreviations: PVE = partial volume effect.

eTable 5 Multiple linear regressions between physical activity and other lifestyle factors

		Physical activity				
Lifestyle factors	**Covariates**	**b**	**Std. Error**	**ß**	***t* Value**	***p* Value**
Mediterranean diet adherence	Age, sex, education	0.069	0.026	0.232	2.663	0.009**
Cognitive activity	Age, sex, education	0.011	0.018	0.054	0.577	0.565

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

eTable 6 Multiple linear regressions between physical activity and neuroimaging values or cardiovascular risk factors correcting for other lifestyle factors

		Physical activity				
Global neuroimaging values	**Covariates**	**b**	**Std. Error**	**ß**	***t* Value**	***p* Value**
GM volume	Age, sex, education	6900.768	3149.087	0.174	2.191	0.030*
	Age, sex, education, Mediterranean diet adherence	7017.768	3246.796	0.177	2.161	0.033*
	Age, sex, education, cognitive activity	7037.1	3156.5	0.177	2.228	0.028*
Glucose metabolism	Age, sex, education	0.028	0.012	0.247	2.383	0.019*
	Age, sex, education, Mediterranean diet adherence	0.028	0.012	0.243	2.272	0.026*
	Age, sex, education, cognitive activity	0.028	0.012	0.245	2.331	0.022*
AD-signature regions						
Hippocampal volume	Age, sex, education	127.828	47.025	0.219	2.718	0.007**
	Age, sex, education, Mediterranean diet adherence	142.649	48.148	0.245	2.963	0.004**
	Age, sex, education, cognitive activity	131.002	46.945	0.225	2.791	0.006**
Precuneus glucose metabolism	Age, sex, education	0.033	0.016	0.217	2.045	0.044*
	Age, sex, education, Mediterranean diet adherence	0.032	0.017	0.213	1.950	0.054
	Age, sex, education, cognitive activity	0.032	0.016	0.215	2.005	0.048*

$^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. Abbreviations: GM = Gray matter; AD = Alzheimer's disease.