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The bidirectional relationship between brain structure and physical activity: A longitudinal analysis in the UK Biobank

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ABSTRACT

Physical activity is a protective factor against brain atrophy, while loss of brain volume could also be a determinant of physical activity. Therefore, we aimed to explore the bidirectional association of physical activity with brain structures in middle-aged and older adults from the UK Biobank. Overall, 3027 participants (62.45 ± 7.27 years old, 51.3% females) had data at two time points. Hippocampal volume was associated with total (β=0.048, p_{FDR}=0.016) and household (β=0.075, p_{FDR}<0.001) physical activity. Global fractional anisotropy (β=0.042, p_{FDR}=0.028) was also associated with household physical activity. In the opposite direction, walking was negatively associated with white matter volume (β=-0.026, p_{FDR}=0.008). All these associations were confirmed by the linear mixed models. Interestingly, sports at baseline were linked to hippocampal and frontal cortex volumes at follow-up but these associations disappeared after adjusting for multiple comparisons (p_{all}>0.104). In conclusion, we found more consistent evidence that a healthier brain structure predicted higher physical activity levels than for the inverse, more established relationship.

1. Introduction

The proportion of adults aged 60 years and older will increase by over a billion by 2050. Consequently, several adaptations across all sectors of societies (e.g., health and social care) are urgently needed to adapt to and prevent the increasing prevalence of age-rated diseases (WHO, 2017).

Due to its multisystemic benefits, increasing physical activity levels is considered one of the most promising strategies to prevent diseases, improve quality of life, and reduce public health-care costs in older adults (Bull et al., 2020; Gopinath et al., 2018; Izquierdo et al., 2021). In contrast, the age-related decline in physical and mental capacity leads older adults to avoid physical activity, which results in higher rates of physical inactivity at these ages (Izquierdo et al., 2021). Altogether, the limited success in getting and keeping older adults physically active and the urgent need to increase physical activity levels at these ages emphasize the necessity of identifying factors that influence physical activity in older adults. In this line, previous studies observed that physical activity levels can be predicted by physical health indicators (e.g., physical functioning), other lifestyle behaviors (e.g., no smoking), or psychosocial factors (e.g., self-efficacy) (Koeneman et al., 2011). More recently, it has also been suggested that a healthier brain structure (e.g., gray/white matter volume) predicts a lower decline in physical activity levels in older people (Arnardottir et al., 2016; Hofman et al., 2022). In particular, we observed that larger total brain volume, gray matter volume, and white matter volume were associated with increased sports participation in older people from the Netherlands (Hofman et al., 2022). Similarly, Arnardottir et al. found that total brain volume was positively associated with physical activity levels in older adults from Iceland (Arnardottir et al., 2016). A possible explanation for this might be that a healthier brain structure results in a stronger behavioral control network, which positively affects the capacity to resist environments that tempt individuals to be physically inactive (Marteau and Hall, 2013). For instance, older adults with higher working memory or cognitive flexibility might be more able to plan or prioritize physical activity routines in their daily lives. This is a theorized control network

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associated with the prefrontal cortex that controls behavior and thought (Diamond, 2013).

Even when optimal levels are not achieved, physical activity is associated with healthier cognitive aging (Erickson et al., 2022), which suggests that the association between physical activity and brain structure might be bidirectional. Specifically, several studies have explored the association between physical activity and brain volumes, particularly in the hippocampus (Erickson et al., 2019, 2009). However, the literature remains still controversial. For instance, a systematic review, based on observational studies, suggested that physical activity is associated with larger brain volumes (i.e., less brain atrophy) (Domingos et al., 2021). In contrast, a recently published meta-analysis of experimental studies found no significant effect of exercise interventions on brain volume changes among older adults (Gogniat et al., 2021). Concerning white matter microstructure, a longitudinal study suggested that better maintenance of time spent walking over a decade was associated with slower deterioration in global microstructural features of white matter over time (Best et al., 2017b). Contrary, we recently observed that higher levels of physical activity were not associated with better white matter microstructure over time (Hofman et al., 2022).

Overall, studies examining the link between physical activity and brain structure are typically undertaken with the assumption of a unidirectional relationship between physical activity and brain structure, being lower levels of physical activity preceding or contributing to future brain atrophy. However, there remains the possibility of a bidirectional relationship. The confirmation of this bidirectionality might help to make policymakers more aware of the need for prioritizing effective interventions in this target group of older people. Additionally, exploring whether a higher volume in brain regions associated with executive function (e.g., frontal cortex) predicts more physical activity over time might shed light on the mechanisms linking brain structure with physical activity in older people. Therefore, this study aimed to investigate the bidirectional relationship between physical activity and brain structure, while considering potential differences between various physical activity domains and brain regions, in a cohort of older adults from the United Kingdom (UK).

2. Methods

2.1. Study design and participants

This study used data from a large community-based cohort of UK Biobank, which enrolled 502,507 individuals aged 40 and 69 years across the United Kingdom (UK) between 2006 and 2010. All UK Biobank participants provided written informed consent, and the North West Multi-Center Ethics Committee granted ethical approval. Brain imaging began in 2014 and is still ongoing. From 2018 onwards, participants were reinvited for a second brain scan within two years after their initial scan. The first time participants attended the MRI assessment center was considered the baseline. Information about physical activity was obtained during both imaging visits. In the current study, we included all 3027 participants who had complete brain imaging and physical activity data at both time points (as of July 7, 2021; see Figure 1).

2.2. Physical activity

Information on the levels of physical activity was obtained through a leisure-time physical activity self-reported questionnaire (Chudasama et al., 2019; Paudel et al., 2023). To assess the level of physical activity, respondents indicated the duration (i.e., less than 15 min, between 15 and 30 min, between 30 min and 1 h, between 1 and 1.5 h, between 1.5

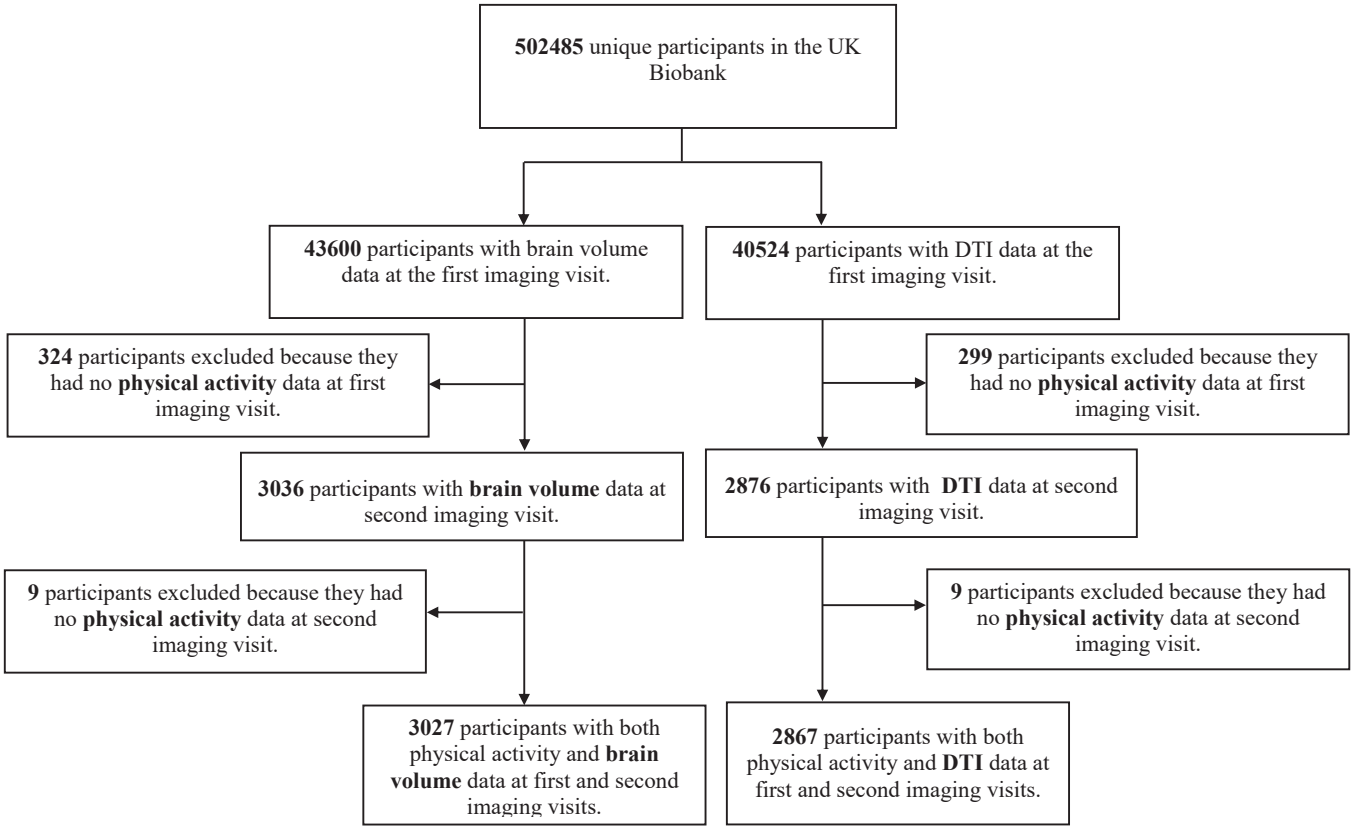

Fig. 1. Flow chart of participant inclusion (data available as of July 7, 2021). DTI= Diffusion tensor imaging. Participants at the second imaging visit are a subsample, which means they are not part of a drop-out.

and 2 h, between 2 and 3 h) and frequency (i.e., once in the last 4 weeks, 2–3 times in the last 4 weeks, once a week, 2–3 times a week, 4–5 times a week, every day) they engage in: walking (not as a means of transport), strenuous sports, other exercises (e.g., swimming, cycling, keep fit, bowling), light do-it-yourself (DIY) activities (e.g., pruning, watering the lawn), and heavy DIY activities (e.g., weeding, lawn mowing, carpentry, digging). A total household physical activity score was calculated by adding the hours of light DIY and heavy DIY. In addition, a total physical activity score was calculated by adding the hours of walking, strenuous sports, other exercises, and household activities. Since the activities listed under 'other exercises' varied substantially in terms of the form of exercise and their physical strain, we did not include this category in our domain-specific analyses.

2.3. Magnetic resonance imaging

Participants were scanned at three centers with identical Siemens Skyra 3 T scanners using a standard 32-channel head coil (Littlejohns et al., 2020). Overall, T1, T2 FLAIR, and DTI images were used in this analysis. Details on UKB preprocessing and quality control pipelines can be found (https://git.fmrib.ox.ac.uk/falmagro/UK_biobank_pipeline_v_1).

2.4. Image acquisition and processing

T1-weighted images were obtained using an MPRAGE sequence: TR=2000 ms, TE=2.0 ms, 208 sagittal slices, flip angle=8°, FOV=256 mm, matrix=256×256, slice thickness=1.0 mm (voxel size 1×1x1mm). T2-weighted FLAIR imaging was additionally acquired with 3D SPACE in the sagittal plane (resolution = 1.05×1 x 1 mm, field of view = 192×256×256 mm; inversion time = 1800 ms, repetition time = 5000 ms). Diffusion images were obtained using a spin-echo echo-planar sequence with 10 T2-weighted baseline volumes, 50b = 1000 s mm-2 and 50 b=2000 s mm-2 diffusion-weighted volumes, with 100 diffusion-encoding directions and 2 mm isotropic voxels.

Summary measures of brain structure (i.e., total brain volume, gray matter volume, white matter volume, white matter hyperintensity, hippocampal volume, frontal cortex volume, global fractional anisotropy [FA], global mean diffusivity [MD]) have been generated on behalf of UK Biobank (Alfaro-Almagro et al., 2018), and are available from UK Biobank upon data access application. Global brain volume measures were normalized for head size. Therefore, we did not adjust our analyses for other volumetric MRI measures such as intracranial volume. For a detailed description of the imaging protocol and pre-processing steps, please see **Appendix 1**.

2.5. Covariates

All models were adjusted for sex (Field 31); education, categorized as higher (college/university degree or other professional qualification) or lower (Field 6138) (Malik et al., 2021); ethnicity (Field 21000), categorized as white/non-white; and age and body mass index (BMI) when participants attended for the first time to the MRI assessment center (Field 21003 and Field 21001, respectively).

Fully adjusted models also included the following covariates assessed at baseline: diet quality (Fields 1309, 1319, 1289, 1299, 1448, 1438, 1468, 1458, 1329, 1339, 1408, 1418, 1428, 2654, 1349, 1359, 1369, 1379,1389, 3680), smoking status (Field 20116), and hypertension (Fields 4079–80), which were defined according to the LS7 score for ideal cardiovascular health (Malik et al., 2021). In addition, depression was defined by any of the ICD-10 codes (Field 41270) F32 (depressive episode), or F33 (recurrent depressive disorder). Cardiovascular disease was defined by any of the ICD-10 codes I20-I25 (coronary/ischaemic heart diseases), I46 (cardiac arrest), I48 (atrial fibrillation), I50 (heart failure), I60-I69 (cerebrovascular diseases) as well as algorithmically defined stroke outcomes (ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage; Fields 42006–42013) (Alaa et al., 2019). Diabetes was defined by ICD-10 codes E10–14 (Diabetes mellitus). Cancer was obtained from the cancer registry records and considering all ICD-10 cancer ('C') code entries (Field 40005, 40006, 40008, 40009), except C44 (other malignant neoplasms of skin) (Ong et al., 2018).

Lastly, dementia diagnosis was obtained from the algorithmically defined dementia outcomes (all-cause dementia, Alzheimer's disease, vascular dementia, frontotemporal dementia; Fields 42018–42025) or any of the ICD-10 diagnosis codes F00 (dementia in Alzheimer's disease), and F01 (vascular dementia). No participants were diagnosed with dementia when baseline and follow-up measures were obtained. Therefore, the dementia variable was not used as a confounder in this study.

2.6. Statistical analysis

Statistical analyses were performed using R version 4.2.1 (The R Foundation for Statistical Computing, Vienna, Austria). The bidirectional associations of total physical activity and domain-specific physical activity with brain tissue volumes and white matter microstructure were examined using a cross-lagged panel model approach using the Lavaan package (version 0.6–12) (Rosseel, 2012).

In these analyses, all associations were adjusted for each other: i.e., analyses are adjusted for the underlying associations of physical activity over time (autoregressive path, $\beta_{AR\text{-}PA}$), brain variables over time (autoregressive path, $\beta_{AR\text{-}MRI}$), the cross-sectional paths ($\beta_{CS\text{-}Baseline}$), and the prospective mutual associations that represent the bidirectional associations between physical activity and brain variables: the cross-lagged pathways $\beta_{CL\text{-}1}$ and $\beta_{CL\text{-}2}$. These path analyses generate standardized structural regression coefficients (i.e., per standard deviation change) that can be directly compared to assess the direction of the association between physical activity and brain structure (Hofman et al., 2022; Vitezova et al., 2015). To preserve all available data (missing data in baseline covariates $\leq$ 10%, except for diet quality: 20% and hypertension: 30%), we used maximum likelihood with robust standard errors (MLR) to fit the models, as implemented in Lavaan (Rosseel, 2012). This is a standard approach to prevent listwise deletion of participants with missing data (Rosseel, 2012).

According to the literature (Hofman et al., 2022), we assessed the associations between total physical activity and brain structure adjusted for age, sex, educational level, national origin, and BMI (model 1). In the second model, we additionally adjusted for other behaviors (i.e., diet quality and smoking) and diseases (i.e., hypertension, cancer cardiovascular diseases, diabetes, and depression). To adjust for multiple comparisons, we used false discovery rate based on the Benjamini-Hochberg method (Benjamini and Hochberg, 1995). We adjusted each pathway for a total of eight tests (i.e., 6 measures of brain volumes and 2 measures of white matter microstructure).

To test the robustness of the analyses to a specific statistical model, associations that showed a significant association after adjusting for multiple comparisons in the cross-lagged panel model were re-assessed by using linear mixed-effects models with random intercepts. Follow-up time in years after baseline measurement was used as the time variable. A more detailed description of the linear mixed-effects modeling approach can be found in **Appendix 2**. As both modeling types have strengths and limitations (Lucas, 2023), linear mixed-effects models were used to investigate the robustness of our findings (Lawlor et al., 2016). In particular, linear mixed-effects models do provide a more explicit measure of within-subject change, equivalent to a change score.

As a sensitivity analysis, we ran the models excluding those individuals who were less able to perform physical activity (defined as those who were by their doctor restricted in physical activity due to heart condition or chest pain felt during physical activity) (Field 6014–6015). In post-hoc exploratory analyses, we tested first whether the bidirectional significant associations differed between younger (< median age: 63 years) and older adults (>median age: 63 years), by performing multi-group analyses. In addition, we tested whether the

associations between physical activity and regions-of-interest volumes (i.e., hippocampus and frontal cortex), remained stable after adjusting for intracranial volume. Lastly, since people with lower hippocampal volume could have more difficulty recalling their physical activity levels and in turn, report it less accurately, we checked whether visual declaration memory, assessed by the Pairs Memory Test at the first imaging visit (Fawns-Ritchie and Deary, 2020), was associated with total physical activity at the same time point (accounting for age, age^2, sex, education, and intracranial volume).

3. Results

The mean age of the study population was 62.45 ± 7.27 years at baseline, and 64.78± 7.22 at follow-up (Table 1). In total, 51.3% of the participants were female, and the mean time between visit 1 and visit 2 was 2.1 years. At baseline, participants reported a total physical activity of 6.51 ± 5.88 h per week, of which walking was the most prevalent (2.45 ± 3.05 h per week). At follow-up, participants reported a total physical activity of 6.39 ± 5.95 h per week. Overall, participants decreased their physical activity levels at follow-up in all domains except for walking which increased (see **Table A.1**). The subsample of imaged participants had a healthier lifestyle and was less often diagnosed with chronic diseases than the non-imaged participants (Littlejohns et al., 2020). Notably, compared with the general population, participants of the UK Biobank were less likely to be obese, smoke, drink alcohol, and report health conditions (Fry et al., 2017).

Results of the cross-lagged models exploring the bidirectional association between brain structure variables and total physical activity are presented in Table 2, adjusting for age, sex, educational level, national origin, BMI, diet quality, smoking, hypertension, cancer, cardiovascular diseases, diabetes, and depression (model 2). Our results indicated that a lower burden of white matter hyperintensity (β=-0.040, p_{FDR}=0.016), and greater hippocampal volume (β=0.048, p_{FDR}=0.016) at baseline, were associated with higher total physical activity levels at follow-up. Results were similar for model 1 (including age, sex, educational level, ethnicity, and BMI; **Table A.2**). Only the association between hippocampal volume at baseline and total physical activity at follow-up was confirmed by linear mixed model (β=0.019, p=0.016) (**Table A.3**).

Fully adjusted associations of domain-specific physical activity and brain structure indicators are presented in Table 3 (model 2). Contrary to our hypothesis, higher levels of walking at baseline were negatively associated with white matter volume at follow-up (β=-0.026, p_{FDR}=0.008). This association was confirmed by linear mixed model (β=-0.016, p=0.001) (**Table A.3**). In line with our hypothesis, a positive association of strenuous sports with hippocampal volume (β=0.011, p=0.027) and frontal cortex volume (β=0.011, p=0.013) was observed. These associations disappeared after adjusting for multiple comparisons (p_{FDR}>0.1). Results were similar for model 1 (see **Table A.4**).

Brain structure at baseline was also associated with physical activity domains at follow-up. In particular, our results from our cross-lagged models indicated that larger hippocampal volume (β=0.075, p_{FDR}<0.001), frontal cortex volume (β=0.043, p_{FDR}=0.037), and global FA (β=0.042, p_{FDR}=0.028) were positively associated with higher household activities levels at follow-up (Table 3). Results were similar when using model 1 (**Table A.4**). The association of hippocampal volume (β=0.025, p=0.006) and Global FA (β=0.029, p=0.010) with household physical activity was confirmed by linear mixed model, while the association with frontal cortex volume and household physical activity was not (β=0.012, p=0.207).

Autoregressive coefficients are shown for total physical activity and physical activity domains in **Table A.5** and **Table A.6**, respectively. In addition, our most robust findings have been graphically described in Table 4.

In our sensitivity analyses, we observed results were similar when we excluded individuals who were less able to be physically active (defined as those whose doctors restricted physical activity due to heart conditions or chest pain felt during physical activity; **Table A.7**). Lastly, in post-hoc exploratory analyses, we observed that the association of hippocampal volume with total physical activity were moderated by age. In our stratified analyses, hippocampal volume was associated among those who were older (β=0.048, p=0.030), but not among those who were younger (β=0.035, p=0.097). All the associations that we found between physical activity variables and hippocampal and frontal cortex volumes remained similar after adjusting for intracranial volume in the models. Lastly, visual declaration memory was not associated with total physical activity at baseline (β=0.046, p>0.05).

Table 1
Study sample characteristics at baseline (n=3027).

	Mean/%	SD
Sex		
Women (%)	51.3	
Age, years	62.45	7.27
Education (%)		
Low	46.6	
High	53.4	
National Origin (%)		
British	94.9	
Other than British	5.1	
Body mass index, kg/m^2	26.27	4.18
Adherence to dietary guidelines (%)		
Poor	22.8	
Intermediate	76.4	
Optimal	0.8	
Hypertension (%)		
yes	11.8	
Cancer (%)		
yes	11.0	
Cardiovascular diseases (%)		
yes	8.7	
Diabetes (%)		
yes	3.1	
Depression (%)		
yes	2.9	
Smoking (%)		
Never	65.7	
Former	31.2	
Current	3.0	

Abbreviations: SD = Standard Deviation. no. =Number of participants.
*Note: 160 participants had no data on DTI but they were included in analyses of brain volume. Low education includes A levels/AS levels or equivalent, 0 levels/GCSEs or equivalent, CSEs or equivalent, and NVQ or HND or HNC or equivalent. High education includes college or university degree, and other professional qualifications (e.g., nursing, teaching).

4. Discussion

4.1. Main findings

This study aimed to explore the bidirectional relationship between physical activity and brain structure in a cohort of older adults from the UK. Overall, there seems to be a bidirectional association between physical activity and brain structure in middle-aged and older adults. However, we found more consistent evidence that a healthier brain structure predicted higher physical activity levels than for the inverse, more established relationship (higher physical activity predicted a healthier brain structure). Notably, the association between brain structure and physical activity levels seemed to be driven by household activities, which suggests people with a healthier brain structure are more able to deal with their active daily routines. This association is particularly relevant in older adults. In line with previous literature, we also observed that higher levels of strenuous sports predicted a lower decrease in hippocampal and frontal cortex volume over time, but this association disappeared after adjusting for multiple comparisons and needs to be confirmed by future studies. Lastly, there was a paradoxical,

Table 2
Bidirectional associations between total physical activity and brain structure based on cross-lagged panel models.

	Physical activity → Brain			Brain → Physical activity			Cross-sectional		Fit measures	
	$\beta_{CL\text{-}1}$	*p*	p_{FDR}	$\beta_{CL\text{-}2}$	*p*	p_{FDR}	$\beta_{CS\text{-}Baseline}$	*p*	CFI	RMSEA
Total physical activity										
Brain volumes (n=3027)										
Total brain volume	-0.000 (-0.010,0.009)	0.971	0.971	0.017 (-0.018,0.053)	0.343	0.457	0.016 (-0.018,0.043)	0.416	0.995	0.024
Gray matter volume	0.012 (0.001,0.022)	**0.033**	0.264	0.003 (-0.034,0.041)	0.866	0.866	0.003 (-0.026,0.030)	0.878	0.995	0.023
White matter volume	-0.012 (-0.028,0.004)	0.130	0.331	0.020 (-0.011,0.053)	0.208	0.333	0.022 (-0.015,0.055)	0.208	0.993	0.022
White matter hyperintensity	-0.012 (-0.030,0.006)	0.194	0.331	-0.040 (-0.075,-0.014)	**0.004**	**0.016**	-0.049 (-0.067,-0.013)	0.004	0.990	0.024
Hippocampus volume	-0.000 (-0.011,0.010)	0.968	0.971	0.048 (0.017,0.078)	**0.002**	**0.016**	0.005 (-0.027,0.035)	0.793	0.996	0.019
Frontal cortex volume	0.009 (-0.001,0.019)	*0.067*	0.268	0.025 (-0.006,0.057)	0.113	0.226	0.018 (-0.016,0.049)	0.322	0.994	0.025
White matter microstructure (n=2867)										
Global FA	0.008 (-0.005,0.021)	0.248	0.331	0.029 (-0.002,0.068)	*0.061*	0.163	0.017 (-0.016,0.045)	0.362	0.994	0.017
Global MD	0.011 (-0.006,0.026)	0.214	0.331	-0.008 (-0.048,0.029)	0.626	0.715	-0.024 (-0.048,0.029)	0.626	0.989	0.023

Abbreviations: DTI = Diffusion Tensor Imaging, FA=Fractional anisotropy, MD=Mean diffusivity. $\beta_{CL\text{-}1}$ = the cross-lagged path 1, where PA scores at time 1 predict MRI findings at time 2; $\beta_{CL\text{-}2}$ = the cross-lagged path 2, where MRI findings at time 1 predict PA scores at time 2. $\beta_{CS\text{-}Baseline}$ = the cross-sectional association between PA and MRI within time 1. *p* = Significant levels, CFI = comparative fit index, RMSEA = root mean square error of approximation. Statistically significant values are shown in bold ($p_{FDR} < 0.05$). Cross-lagged models were adjusted for age, sex, educational level, national origin, and body mass index, other behaviors (i.e., diet quality and smoking) and other diseases (i.e., hypertension, cancer cardiovascular diseases, diabetes, and depression).

Table 3
Bidirectional associations between physical activity domains and brain structure based on cross-lagged panel models (model 2).

	Physical activity → Brain			Brain → Physical activity			Cross-sectional		Fit measures	
	$\beta_{CL\text{-}1}$	*p*	p_{FDR}	$\beta_{CL\text{-}2}$	*p*	p_{FDR}	$\beta_{CS\text{-}Baseline}$	*p*	CFI	RMSEA
Walking										
Brain volumes (n=3027)										
Total brain volume	-0.011 (-0.020,-0.001)	**0.026**	0.104	0.041 (0.006,0.076)	**0.023**	0.184	-0.003 (-0.032,0.028)	0.883	0.996	0.022
Gray matter volume	0.007 (-0.004,0.017)	0.244	0.437	0.036 (-0.001,0.074)	*0.056*	0.224	-0.018 (-0.041,0.014)	0.339	0.996	0.021
White matter volume	-0.026 (-0.041,-0.010)	**0.001**	**0.008**	0.026 (-0.004,0.056)	0.090	0.236	0.013 (-0.022,0.046)	0.495	0.995	0.020
White matter hyperintensity	-0.013 (-0.030,0.005)	0.146	0.389	-0.020 (-0.049,0.006)	0.118	0.236	0.036 (-0.002,0.043)	0.070	0.913	0.057
Hippocampus volume	0.004 (-0.007,0.015)	0.502	0.564	0.015 (-0.015,0.043)	0.336	0.384	0.078 (0.011,0.035)	<0.001	0.939	0.063
Frontal cortex volume	0.005 (-0.005,0.015)	0.335	0.447	-0.003 (-0.032,0.026)	0.839	0.839	0.020 (-0.005,0.017)	0.307	0.949	0.057
White matter microstructure (n=2867)										
Global FA	0.004 (-0.010,0.018)	0.564	0.564	0.023 (-0.009,0.060)	0.152	0.243	0.061 (0.021,0.082)	0.001	0.996	0.014
Global MD	0.010 (-0.008,0.028)	0.273	0.437	-0.018 (-0.058,0.016)	0.270	0.360	-0.048 (-0.067,-0.009)	0.011	0.992	0.020
Strenuous sports										
Brain volumes (n=3027)										
Total brain volume	0.005 (-0.003,0.012)	0.255	0.510	0.015 (-0.021,0.052)	0.409	0.628	0.013 (-0.018,0.039)	0.459	0.995	0.021
Gray matter volume	0.000 (-0.008,0.008)	0.939	0.939	0.010 (-0.026,0.048)	0.550	0.628	-0.006 (-0.030,0.021)	0.726	0.996	0.022
White matter volume	0.009 (-0.002,0.020)	0.109	0.291	0.011 (-0.021,0.044)	0.481	0.628	0.026 (-0.008,0.058)	0.144	0.994	0.020
White matter hyperintensity	0.003 (-0.011,0.017)	0.693	0.924	-0.013 (-0.044,0.015)	0.336	0.628	-0.009 (-0.025,0.009)	0.372	0.990	0.023
Hippocampus volume	0.011 (0.001,0.019)	**0.027**	0.108	0.036 (0.004,0.070)	**0.027**	0.216	0.011 (-0.019,0.039)	0.497	0.997	0.017
Frontal cortex volume	0.011 (0.002,0.018)	**0.013**	0.104	0.023 (-0.009,0.058)	0.156	0.624	0.005 (-0.029,0.038)	0.793	0.994	0.023
White matter microstructure (n=2867)										
Global FA	0.001 (-0.012,0.014)	0.848	0.939	0.004 (-0.035,0.045)	0.801	0.801	-0.007 (-0.035,0.024)	0.709	0.995	0.015
Global MD	0.005 (-0.011,0.021)	0.551	0.882	0.018 (-0.018,0.064)	0.271	0.628	0.005 (-0.023,0.031)	0.781	0.990	0.021
Household activities										
Brain volumes (n=3027)										
Total brain volume	0.008 (-0.003,0.018)	0.147	0.588	-0.009 (-0.048,0.029)	0.634	0.689	0.023 (-0.014,0.051)	0.259	0.997	0.017
Gray matter volume	0.012 (-0.000,0.023)	*0.052*	0.416	-0.024 (-0.063,0.014)	0.215	0.344	0.014 (-0.021,0.040)	0.524	0.997	0.016
White matter volume	0.002 (-0.015,0.019)	0.829	0.829	0.007 (-0.028,0.043)	0.689	0.689	0.023 (-0.014,0.058)	0.228	0.997	0.015
White matter hyperintensity	-0.003 (-0.022,0.017)	0.781	0.829	-0.030 (-0.066,-0.000)	**0.046**	0.092	0.037 (-0.001,0.044)	0.065	0.903	0.056
Hippocampus volume	-0.005 (-0.015,0.005)	0.330	0.829	0.075 (0.038,0.107)	**<0.001**	**<0.001**	0.017 (-0.016,0.046)	0.354	0.999	0.007
Frontal cortex volume	0.002 (-0.008,0.013)	0.638	0.829	0.043 (0.009,0.077)	**0.014**	**0.037**	0.022 (-0.012,0.053)	0.218	0.996	0.019
White matter microstructure (n=2867)										
Global FA	0.001 (-0.010,0.013)	0.821	0.829	0.042 (0.013,0.081)	**0.007**	**0.028**	-0.019 (-0.048,0.016)	0.321	0.999	0.007
Global MD	0.004 (-0.011,0.018)	0.619	0.829	-0.013 (-0.056,0.025)	0.454	0.605	0.005 (-0.030,0.038)	0.816	0.993	0.017

Abbreviations: DTI = Diffusion Tensor Imaging, FA=Fractional anisotropy, MD=Mean diffusivity. $\beta_{CL\text{-}1}$ = the cross-lagged path 1, where PA scores at time 1 predict MRI findings at time 2; $\beta_{CL\text{-}2}$ = the cross-lagged path 2, where MRI findings at time 1 predict PA scores at time 2. $\beta_{CS\text{-}Baseline}$ = the cross-sectional association between PA and MRI within time 1. p_{FDR} = Significant levels, CFI = comparative fit index, RMSEA = root mean square error of approximation. Statistically significant values are shown in bold ($p_{FDR} < 0.05$). Cross-lagged models were adjusted for age, sex, national origin, educational level, body mass index, other behaviors (i.e., diet quality and smoking), and other diseases (i.e., hypertension, cancer cardiovascular diseases, diabetes, and depression).

Table 4
Graphical table summarizing the robustness of our findings across two different models.

	Cross-lagged panel models			Linear mixed-effect models	
	β	*p*	p_{FDR}	β	*p*
Physical activity → Brain					
Walking → White matter volume	-0.026	0.001	0.008	-0.016	0.001
Brain → Physical activity					
Hippocampus volume → total physical activity	0.048	0.002	0.016	0.019	0.016
Hippocampus volume → Household activities	0.075	<0.001	<0.001	0.025	0.006
Global FA→ Household activities	0.042	0.007	0.028	0.029	0.010

β= standardized beta value; Global FA= Global fractional anisotropy. p= significant level; p_{FDR}= significant level after adjusting for multiple comparisons.

yet consistent association between walking and a larger decrease in white matter volume that requires further investigation.

4.2. The association of brain structure with physical activity over time

A healthier brain structure predicted higher total physical activity levels over time, especially more household activities. Consistent with the current findings, we previously observed that healthier brain structure, in terms of larger brain volume(s) and better white matter integrity, was associated with more self-reported physical activity (i.e., sports and walking) in middle-aged and older adults from the population-based Rotterdam Study (Hofman et al., 2022). Interestingly, participants from the UK Biobank were on average healthier than those from the Rotterdam Study. For instance, in the present study, only 12% of the participants had hypertension vs. 65% in the Rotterdam Study. This is relevant because high blood pressure is a strong risk factor for global and regional brain atrophy in older adults (den Heijer et al., 2003; Raz et al., 2005). Together, these findings seem to suggest that older individuals with healthier brain structures, in terms of larger brain volume(s) and better white matter integrity, remain more physically active at follow-up, independent of other health outcomes such as hypertension. In addition, it is important to note that both studies included self-reports, which could have led to under- or overestimations of physical activity levels. However, our results are also consistent with those from (Arnardottir et al., 2016), who observed that higher grey and white matter volumes were associated with more objective total physical activity, assessed by accelerometers, in 352 older adults, even when adjusted for self-reported physical activity. Lastly, intervention studies have shown that those participants with a healthier brain structure, defined by larger brain volume, had better adherence to a structured physical activity intervention (Best et al., 2017a; Gujral et al., 2018). Altogether, previous and current results seem to indicate that brain structure predicts levels of daily movement over time in older adults independently of the physical activity tool (i.e., self-reported vs. objectively measured physical activity) or the structure of the physical activity practice (i.e., household activities or structured physical activity interventions). Therefore, future policies designed to keep older adults physically active might consider brain structure (an early indicator of cognitive decline) as a potential determinant of physical activity.

4.3. The association of physical activity levels with brain structure over time

This study found a borderline association of sports participation with hippocampal and frontal cortex volume in middle-aged and older adults. The hippocampus, a subcortical brain structure implicated in memory, spatial navigation, and other aspects of cognitive functioning, is structurally sensitive to exposure and engagement with novel experiences and environments (Rolls, 2010). It is therefore not surprising that the hippocampus is the most widely studied region consistently associated with physical activity across the lifespan (Erickson et al., 2022, 2019, 2011; Stillman et al., 2020, 2018; Urban-Wojcik et al., 2022). However, the majority of prior research on physical activity and the hippocampus relies mostly on animal models (Suzuki, 2016; van Praag et al., 1999) or clinical samples (Riggs et al., 2017), had a cross-sectional design (Urban-Wojcik et al., 2022), or explored the effect of a structured exercise intervention on hippocampal volume in late adulthood (Erickson et al., 2011; Firth et al., 2018). Interestingly, the only study that has previously explored the bidirectional relationship between unstructured physical activity (free time or self-selected free physical activity) and hippocampal volume in middle-aged and older adults did not observe an association (Hofman et al., 2022). Several factors could underlie these results. For instance, physical activity may be no longer beneficial in individuals whose brain structure has already deteriorated to a certain degree (Brown et al., 2019). In this sense, differences in the health status of participants from the UK Biobank and the Rotterdam Study might explain why we observed a small beneficial effect of physical activity only in the UK Biobank sample.

Surprisingly, higher levels of walking were associated with lower white matter volume at follow-up. Those results were not observed with white matter microstructure (i.e., global FA and global MD) but were consistent in our cross-lagged and linear mixed models. In our previous investigation in the Rotterdam Study, we also identified an unexpected association between lower white matter volume and more walks at follow-up, which was, however, in the opposite direction than the relationship observed in the present study. We can only speculate what may have caused these contradictory results. It is possible that several moderators, such as the cognitive demand of the walks, freely chosen by older people, could be clouding or confounding the association between walking and brain outcomes. In particular, several factors associated with more cognitively enriched walking (e.g., green vs. urban spaces, different vs. same route, walking in a group vs. alone) (O'Malley et al., 2018; O'Mara, 2021; Sudimac et al., 2022) could have influenced the relationship between walking and brain structure and should therefore be taken into account in future work. Another possible explanation could be that not only time dedicated to walking matters but also the walking speed. In this line, a recent systematic review gathered strong evidence indicating that slower gait speed predicts higher cognitive decline in older people (Marín-jiménez et al., 2022).

Different mechanisms may explain the relationship between physical activity and brain structure and vice versa. The analyses of different physical activity subtypes and in young versus old age groups support this idea. In particular, we found a weak borderline association between strenuous sports and hippocampal volume. A biological explanation could be that high-intensity activities, such as sports, are more likely to stimulate the release of neurotrophic factors and thereby increase brain volume, particularly in brain areas where adult neurogenesis occurs (Stillman et al., 2020). On the contrary, brain structure, including hippocampal volume, and global FA, was associated with housework in older people over time. One possible explanation could be that larger brain volumes indicate healthier older adults who were cognitively and/or physically better able to manage their daily lives and thus maintain an active lifestyle. Overall, our findings indicate that the type of physical activity should be considered when studying the (bidirectional) relationship between physical activity and brain health. Further studies are needed to explore the potentially different underlying pathways.

Several potential limitations should be noted. First, a highly selected sample of healthy participants from the UK was included in this study, which could affect both our findings and the generalizability of these to the general population. The imaging subsample has been shown to be healthier than the entire UK Biobank cohort, potentially underestimating associations between physical activity and brain structure

(Lyall et al., 2022). In addition, even though we excluded participants with neurogenerative diseases, it is possible that some participants at a preclinical stage remained in the analyses and may have influenced our results. Second, given that most participants were of Caucasian ethnicity and/or European ancestry, generalizability to other ethnicities needs to be addressed in future studies. Third, physical activity was self-reported using a questionnaire that has not been validated and which in turn could overestimate or underestimate the levels of physical activity. This issue could be particularly problematic for physical activity subdomains that do not have a clear start/end (e.g., household activities or walking), subdomains such as "other exercises" that include a broad set of heterogeneous activities (i.e., other exercises that could include from bowling to swimming), or people with reduced hippocampal volume and deficits in memory performance. Notably, we did not find an association between visual memory and total physical activity in our data. Fourth, the observational design limits inferences about causality, and residual confounding cannot be ruled out. Fifth, we caution against interpreting either the cross-lagged panel model or the linear mixed model as causal effects (Lucas, 2023). Both models take baseline measures into account and therefore limit the possibility of confounding effects, but these cannot be ruled out completely. Both statistical models represent slightly different approaches to model longitudinal effects. The cross-lagged panel model associates the outcome at follow-up with the predictor at baseline, while adjusting for baseline differences. The linear mixed model in contrast more explicitly models the change within subjects, equivalent to an ordinary least squares regression model with a change score as an outcome. The robustness of some physical activity-brain associations to the exact longitudinal model chosen supports the presence of longitudinal effects independent of a particular statistical modeling approach for these pathways (Lawlor et al., 2016). Sixth, although we studied a wide range of MRI metrics, future studies may complement our findings by exploring other types of structural (e.g., gyrification, fractal dimension, and cortical thickness) and microstructural (e.g., myelin water fraction, T1w/T2w ratio) measures that might reveal new insights into the bidirectional relationship between brain structure and physical activity. Lastly, we restricted our study to global brain structures and regions that are known to be plastic and therefore responsive to physical activity (e.g., hippocampus). We cannot exclude that there are different relationships between physical activity and other local brain structures. The strengths of the current study are the large sample size and the prospectively collected data across two-time points. Additionally, we used two established analysis methods to ensure that the reported results are robust.

4.4. Practical implications

In 2030, 499 million new cases of preventable major noncommunicable diseases and mental health conditions will occur globally if the prevalence of physical inactivity does not change (Santos and Willumsen, 2023). In this context, older adults have fewer opportunities to access safe, affordable, and appropriate physical activity programs, missing out on the physical, mental, and social health benefits of being active ("Global action plan on physical activity, 2018–2030: more active people for a healthier world," n.d.). Overall, we provided further evidence for the novel insight that, besides the known positive effect of physical activity on brain health, there is also a reverse effect of poorer brain health being a potential risk factor for low physical activity in middle-aged and older people. This new research might help policymakers prioritize the development of policy actions to promote and enable more middle-aged and older adults with potentially accelerated brain aging to be active.

5. Conclusions

There seems to be a bidirectional association between physical activity and brain structure in middle-aged and older adults. However, we found more consistent evidence that a healthier brain structure predicted higher physical activity levels than for the inverse, more established relationship (higher physical activity predicted a healthier brain structure). Notably, the association between brain structure and physical activity levels seemed to be driven by household activities, which suggests people with a healthier brain structure are more able to deal with their active daily routines. Further longitudinal studies are needed to disambiguate populations most affected by physical activity, the key stages to appreciate brain structure changes (e.g., cognitively normal vs. cognitively impaired), and the mechanisms that might explain why specific physical activity domains are differently associated with brain structure in middle-aged and older adults.

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CRediT authorship contribution statement

Alexander Neumann: Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing – review & editing. **Amy Hofman:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **María Rodriguez-Ayllon:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Meike W. Vernooij:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – review & editing. **Julia Neitzel:** Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

None.

Data availability

All data analyzed herein (including IDPs) were provided by UK Biobank under project reference 68400, subject to a data transfer agreement. Researchers can apply to use the UK Biobank data resource for health-related research in the public interest. A guide to access is available from the UK Biobank website (http://www.ukbiobank.ac.uk/register-apply/).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neurobiolaging.2024.03.001.

References

Alaa, A.M., Bolton, T., Angelantonio, E., di, Rudd, J.H.F., van der Schaar, M., 2019. Cardiovascular disease risk prediction using automated machine learning: a prospective study of 423,604 UK Biobank participants. PLoS One 14, e0213653. https://doi.org/10.1371/JOURNAL.PONE.0213653.

Alfaro-Almagro, F., Jenkinson, M., Bangerter, N.K., Andersson, J.L.R., Griffanti, L., Douaud, G., Sotiropoulos, S.N., Jbabdi, S., Hernandez-Fernandez, M., Vallee, E., Vidaurre, D., Webster, M., McCarthy, P., Rorden, C., Daducci, A., Alexander, D.C., Zhang, H., Dragonu, I., Matthews, P.M., Miller, K.L., Smith, S.M., 2018. Image processing and quality control for the first 10,000 brain imaging datasets from UK

Biobank. Neuroimage 166, 400–424. https://doi.org/10.1016/J.NEUROIMAGE.2017.10.034.
Arnardottir, N.Y., Koster, A., Domelen, D.R.V., Brychta, R.J., Caserotti, P., Eiriksdottir, G., Sverrisdottir, J.E., Sigurdsson, S., Johannsson, E., Chen, K.Y., Gudnason, V., Harris, T.B., Launer, L.J., Sveinsson, T., 2016. Association of change in brain structure to objectively measured physical activity and sedentary behavior in older adults: age, gene/environment susceptibility-Reykjavik Study. Behav. Brain Res. 296, 118–124. https://doi.org/10.1016/j.bbr.2015.09.005.
Benjamini, Y., Hochberg, Y., 1995. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing.
Best, J.R., Chiu, B.K., Hall, P.A., Liu-Ambrose, T., 2017a. Larger lateral prefrontal cortex volume predicts better exercise adherence among older women: evidence from two exercise training studies. J. Gerontol. A Biol. Sci. Med. Sci. 72, 804–810. https://doi.org/10.1093/gerona/glx043.
Best, J.R., Rosano, C., Aizenstein, H.J., Tian, Q., Boudreau, R.M., Ayonayon, H.N., Satterfield, S., Simonsick, E.M., Studenski, S., Yaffe, K., Liu-Ambrose, T., 2017b. Long-term changes in time spent walking and subsequent cognitive and structural brain changes in older adults. Neurobiol. Aging 57, 153–161. https://doi.org/10.1016/j.neurobiolaging.2017.05.023.
Brown, B.M., Peiffer, J., Rainey-Smith, S.R., 2019. Exploring the relationship between physical activity, beta-amyloid and tau: a narrative review. Ageing Res Rev. https://doi.org/10.1016/j.arr.2019.01.003.
Bull, F.C., Al-Ansari, S.S., Biddle, S., Borodulin, K., Buman, M.P., Cardon, G., Carty, C., Chaput, J.P., Chastin, S., Chou, R., Dempsey, P.C., Dipietro, L., Ekelund, U., Firth, J., Friedenreich, C.M., Garcia, L., Gichu, M., Jago, R., Katzmarzyk, P.T., Lambert, E., Leitzmann, M., Milton, K., Ortega, F.B., Ranasinghe, C., Stamatakis, E., Tiedemann, A., Troiano, R.P., van der Ploeg, H.P., Wari, V., Willumsen, J.F., 2020. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br. J. Sports Med. https://doi.org/10.1136/bjsports-2020-102955.
Chudasama, Y.V., Khunti, K.K., Zaccardi, F., Rowlands, A.V., Yates, T., Gillies, C.L., Davies, M.J., Dhalwani, N.N., 2019. Physical activity, multimorbidity, and life expectancy: a UK Biobank longitudinal study. BMC Med. 17, 1–13. https://doi.org/10.1186/S12916-019-1339-0/FIGURES/4.
den Heijer, T., Skoog, I., Oudkerk, M., de Leeuw, F.E., de Groot, J.C., Hofman, A., Breteler, M.M.B., 2003. Association between blood pressure levels over time and brain atrophy in the elderly. Neurobiol. Aging 24, 307–313. https://doi.org/10.1016/S0197-4580(02)00088-X.
Diamond, A., 2013. Executive Functions. https://doi. Org. /10. 1146/Annu. -Psych. -113011-143750 64, 135–168. https://doi.org/10.1146/ANNUREV-PSYCH-113011-143750.
Domingos, C., Pêgo, J.M., Santos, N.C., 2021. Effects of physical activity on brain function and structure in older adults: a systematic review. Behav. Brain Res. 402, 113061 https://doi.org/10.1016/J.BBR.2020.113061.
Erickson, K.I., Donofry, S.D., Sewell, K.R., Brown, B.M., Stillman, C.M., 2022. Cognitive aging and the promise of physical activity. https://doi. Org. /10. 1146/Annu. -clinpsy-072720-014213 18, 417–442. https://doi.org/10.1146/ANNUREV-CLINPSY-072720-014213.
Erickson, K.I., Prakash, R.S., Voss, M.W., Chaddock, L., Hu, L., Morris, K.S., White, S.M., Wójcicki, T.R., McAuley, E., Kramer, A.F., 2009. Aerobic fitness is associated with hippocampal volume in elderly humans. Hippocampus 19, 1030–1039. https://doi.org/10.1002/hipo.20547.
Erickson, K.I., Hillman, C., Stillman, C.M., Ballard, R.M., Bloodgood, B., Conroy, D.E., Macko, R., Marquez, D.X., Petruzzello, S.J., Powell, K.E., 2019. Physical activity, cognition, and brain outcomes: a review of the 2018 physical activity guidelines. Med Sci. Sports Exerc. https://doi.org/10.1249/MSS.0000000000001936.
Erickson, K.I., Voss, M.W., Prakash, R.S., Basak, C., Szabo, A., Chaddock, L., Kim, J.S., Heo, S., Alves, H., White, S.M., Wojcicki, T.R., Mailey, E., Vieira, V.J., Martin, S.A., Pence, B.D., Woods, J.A., McAuley, E., Kramer, A.F., 2011. Exercise training increases size of hippocampus and improves memory. Proc. Natl. Acad. Sci. USA 108, 3017–3022. https://doi.org/10.1073/pnas.1015950108.
Fawns-Ritchie, C., Deary, I.J., 2020. Reliability and validity of the UK Biobank cognitive tests. PLoS One 15, e0231627. https://doi.org/10.1371/JOURNAL.PONE.0231627.
Firth, J., Stubbs, B., Vancampfort, D., Schuch, F., Lagopoulos, J., Rosenbaum, S., Ward, P.B., 2018. Effect of aerobic exercise on hippocampal volume in humans: a systematic review and meta-analysis. Neuroimage 166, 230–238. https://doi.org/10.1016/J.NEUROIMAGE.2017.11.007.
Fry, A., Littlejohns, T.J., Sudlow, C., Doherty, N., Adamska, L., Sprosen, T., Collins, R., Allen, N.E., 2017. Comparison of sociodemographic and health-related characteristics of UK biobank participants with those of the general population. Am. J. Epidemiol. 186, 1026. https://doi.org/10.1093/AJE/KWX246.
Global action plan on physical activity 2018–2030: more active people for a healthier world [WWW Document], n.d. URL https://apps.who.int/iris/handle/10665/272722 (accessed 12.20.22).
Gogniat, M.A., Robinson, T.L., Miller, L.S., 2021. Exercise interventions do not impact brain volume change in older adults: a systematic review and meta-analysis. Neurobiol. Aging 101, 230–246. https://doi.org/10.1016/J.NEUROBIOLAGING.2021.01.025.
Gopinath, B., Kifley, A., Flood, V.M., Mitchell, P., 2018. Physical activity as a determinant of successful aging over ten years. Sci. Rep. 2018 8:1 8, 1–5. https://doi.org/10.1038/s41598-018-28526-3.
Gujral, S., McAuley, E., Oberlin, L.E., Kramer, A.F., Erickson, K.I., 2018. Role of brain structure in predicting adherence to a physical activity regimen. Psychosom. Med 80, 69–77. https://doi.org/10.1097/PSY.0000000000000526.
Hofman, A., Rodriguez-Ayllon, M., Vernooij, M.W., Croll, P.H., Luik, A.I., Neumann, A., Niessen, W.J., Ikram, M.A., Voortman, T., Muetzel, R.L., 2022. Physical activity levels and brain structure in middle-aged and older adults: a bidirectional longitudinal population-based study. Neurobiol. Aging. https://doi.org/10.1016/J.NEUROBIOLAGING.2022.10.002.
Izquierdo, M., Duque, G., Morley, J.E., 2021. Physical activity guidelines for older people: knowledge gaps and future directions. Lancet Healthy Longev. 2, e380–e383. https://doi.org/10.1016/S2666-7568(21)00079-9.
Koeneman, M.A., Verheijden, M.W., Chinapaw, M.J.M., Hopman-Rock, M., 2011. Determinants of physical activity and exercise in healthy older adults: a systematic review. Int J. Behav. Nutr. Phys. Act. 8. https://doi.org/10.1186/1479-5868-8-142.
Lawlor, D.A., Tilling, K., Smith, G.D., 2016. Triangulation in aetiological epidemiology. Int J. Epidemiol. 45, 1866–1886. https://doi.org/10.1093/IJE/DYW314.
Littlejohns, T.J., Holliday, J., Gibson, L.M., Garratt, S., Oesingmann, N., Alfaro-Almagro, F., Bell, J.D., Boultwood, C., Collins, R., Conroy, M.C., Crabtree, N., Doherty, N., Frangi, A.F., Harvey, N.C., Leeson, P., Miller, K.L., Neubauer, S., Petersen, S.E., Sellors, J., Sheard, S., Smith, S.M., Sudlow, C.L.M., Matthews, P.M., Allen, N.E., 2020. The UK Biobank imaging enhancement of 100,000 participants: rationale, data collection, management and future directions. Nat. Commun. 2020 11:1 11, 1–12. https://doi.org/10.1038/s41467-020-15948-9.
Littlejohns, T.J., Holliday, J., Gibson, L.M., Garratt, S., Oesingmann, N., Alfaro-Almagro, F., Bell, J.D., Boultwood, C., Collins, R., Conroy, M.C., Crabtree, N., Doherty, N., Frangi, A.F., Harvey, N.C., Leeson, P., Miller, K.L., Neubauer, S., Petersen, S.E., Sellors, J., Sheard, S., Smith, S.M., Sudlow, C.L.M., Matthews P.M., Allen N.E., 2020. The UK Biobank imaging enhancement of 100,000 participants: rationale, data collection, management and future directions. Nat Commun. 26;11(1):2624. doi: 10.1038/s41467-020-15948-9.
Lucas, R.E., 2023. Why the cross-lagged panel model is almost never the right choice. Adv. Methods Pract. Psychol. Sci. 6. https://doi.org/10.1177/25152459231158378/ASSET/IMAGES/LARGE/10.1177_25152459231158378-FIG7.JPEG.
Lyall, D.M., Quinn, T., Lyall, L.M., Ward, J., Anderson, J.J., Smith, D.J., Stewart, W., Strawbridge, R.J., Bailey, M.E.S., Cullen, B., 2022. Quantifying bias in psychological and physical health in the UK Biobank imaging sub-sample. Brain Commun. 4. https://doi.org/10.1093/BRAINCOMMS/FCAC119.
Malik, R., Georgakis, M.K., Neitzel, J., Rannikmäe, K., Ewers, M., Seshadri, S., Sudlow, C. L.M., Dichgans, M., 2021. Midlife vascular risk factors and risk of incident dementia: Longitudinal cohort and Mendelian randomization analyses in the UK Biobank. Alzheimer'S. Dement. 17, 1422–1431. https://doi.org/10.1002/ALZ.12320.
Marín-jiménez, N., Cruz-león, C., Perez-bey, A., Conde-caveda, J., Grao-cruces, A., Aparicio, V.A., Castro-piñero, J., Cuenca-garcía, M., 2022. Predictive validity of motor fitness and flexibility tests in adults and older adults: a systematic review. J. Clin. Med 11. https://doi.org/10.3390/JCM11020328/S1.
Marteau, T.M., Hall, P.A., 2013. Breadlines, brains, and behaviour. BMJ 347. https://doi.org/10.1136/BMJ.F6750.
O'Malley, M., Innes, A., Wiener, J.M., 2018. How do we get there? Effects of cognitive aging on route memory. Mem. Cogn. 46, 274–284. https://doi.org/10.3758/S13421-017-0763-7/TABLES/2.
O'Mara, S., 2021. Biopsychosocial functions of human walking and adherence to behaviourally demanding belief systems: a narrative review. Front Psychol. 12. https://doi.org/10.3389/FPSYG.2021.654122.
Ong, J.S., An, J., Law, M.H., Whiteman, D.C., Neale, R.E., Gharahkhani, P., MacGregor, S., 2018. Height and overall cancer risk and mortality: evidence from a Mendelian randomisation study on 310,000 UK Biobank participants. Br. J. Cancer 2018 118:9 118, 1262–1267. https://doi.org/10.1038/s41416-018-0063-4.
Paudel, S., Ahmadi, M., Phongsavan, P., Hamer, M., Stamatakis, E., 2023. Do associations of physical activity and sedentary behaviour with cardiovascular disease and mortality differ across socioeconomic groups? A prospective analysis of device-measured and self-reported UK Biobank data. Br. J. Sports Med 0, bjsports-2022, 105435. https://doi.org/10.1136/BJSPORTS-2022-105435.
Raz, N., Lindenberger, U., Rodrigue, K.M., Kennedy, K.M., Head, D., Williamson, A., Dahle, C., Gerstorf, D., Acker, J.D., 2005. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. Cereb. Cortex 15, 1676–1689. https://doi.org/10.1093/CERCOR/BHI044.
Riggs, L., Piscione, J., Laughlin, S., Cunningham, T., Timmons, B.W., Courneya, K.S., Bartels, U., Skocic, J., de Medeiros, C., Liu, F., Persadie, N., Scheinemann, K., Scantlebury, N., Szulc, K.U., Bouffet, E., Mabbott, D.J., 2017. Exercise training for neural recovery in a restricted sample of pediatric brain tumor survivors: a controlled clinical trial with crossover of training versus no training. Neuro Oncol. 19, 440. https://doi.org/10.1093/NEUONC/NOW177.
Rolls, E.T., 2010. A computational theory of episodic memory formation in the hippocampus. Behav. Brain Res. 215, 180–196. https://doi.org/10.1016/J.BBR.2010.03.027.
Rosseel, Y., 2012. Lavaan: An R package for structural equation modeling. J. Stat. Softw. 48, 1–36. https://doi.org/10.18637/jss.v048.i02.
Santos, A.C., Willumsen, J., 2023. The cost of inaction on physical inactivity to public health-care systems: a population-attributable fraction analysis. Lancet Glob. Health 11, e32–e39. https://doi.org/10.1016/S2214-109X(22)00464-8.
Stillman, C.M., Esteban-Cornejo, I., Brown, B., Bender, C.M., Erickson, K.I., 2020. Effects of Exercise on brain and cognition across age groups and health states. Trends Neurosci. https://doi.org/10.1016/j.tins.2020.04.010.
Stillman, C.M., Uyar, F., Huang, H., Grove, G.A., Watt, J.C., Wollam, M.E., Erickson, K.I., 2018. Cardiorespiratory fitness is associated with enhanced hippocampal functional connectivity in healthy young adults. Hippocampus 28, 239–247. https://doi.org/10.1002/hipo.22827.
Sudimac, S., Sale, V., Kühn, S., 2022. How nature nurtures: amygdala activity decreases as the result of a one-hour walk in nature. Mol. Psychiatry 27. https://doi.org/10.1038/S41380-022-01720-6.

Suzuki, W.A., 2016. How body affects brain. Cell Metab. 24, 192–193. https://doi.org/10.1016/j.cmet.2016.07.022.

Urban-Wojcik, E.J., Lee, S., Grupe, D.W., Quinlan, L., Gresham, L., Hammond, A., Charles, S.T., Lachman, M.E., Almeida, D.M., Davidson, R.J., Schaefer, S.M., 2022. Diversity of daily activities is associated with greater hippocampal volume. Cogn. Affect Behav. Neurosci. 22, 75–87. https://doi.org/10.3758/S13415-021-00942-5/TABLES/3.

van Praag, H., Christie, B.R., Sejnowski, T.J., Gage, F.H., 1999. Running enhances neurogenesis, learning, and long-term potentiation in mice. Proc. Natl. Acad. Sci. USA 96, 13427–13431. https://doi.org/10.1073/pnas.96.23.13427.

Vitezova, A., Voortman, T., Zillikens, M.C., Jansen, P.W., Hofman, A., Uitterlinden, A.G., Franco, O.H., Kiefte-de Jong, J.C., 2015. Bidirectional associations between circulating vitamin D and cholesterol levels: the Rotterdam Study. Maturitas 82, 411–417. https://doi.org/10.1016/J.MATURITAS.2015.08.005.